

# Is the rostro-caudal axis of the frontal lobe hierarchical?

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**Abstract** | The frontal lobes in the brain are a component of the cerebral system that supports goal-directed behaviour. However, their functional organization remains controversial. Recent studies have reported rostro-caudal distinctions in frontal cortex activity based on the abstractness of action representations. In addition, some have proposed that these differences reflect a hierarchical organization, whereby anterior frontal regions influence processing by posterior frontal regions during the realization of abstract action goals as motor acts. However, few have considered whether the anatomy and physiology of the frontal lobes support such a scheme. To address this gap, this Review surveys anatomical, neuroimaging, electrophysiological and developmental findings, and considers the question: could the organization of the frontal cortex be hierarchical?

## Cognitive control

Also termed executive function, cognitive control allows flexible behaviour by guiding thought and action based on goals, plans and intentions.

## Double dissociation

When two experimental manipulations have different effects on two dependent variables (for example, on the left and right hemisphere or on the medial and lateral prefrontal cortex).

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Defining the functional organization of the frontal lobes remains a significant challenge for cognitive neuroscience. The frontal cortex (FIG. 1) has long been associated with higher cognitive functions and cognitive control<sup>1–8</sup>. Moreover, it is commonly assumed that spatially distinct portions of the prefrontal cortex (PFC) support qualitatively distinct cognitive control functions<sup>9–11</sup>. However, despite the frontal cortex having been the focus of a considerable amount of research, it has not been easy to distinguish separate frontal regions in terms of their functional properties. Although neuropsychological studies of patients with frontal lobe lesions have demonstrated large-scale distinctions in function between each hemisphere, and between lateral and medial PFC<sup>12</sup>, they have revealed few examples of double dissociations for tasks or cognitive functions<sup>5</sup> (but see REF. 13). Moreover, many neuroimaging studies report frontal activation across a diverse range of tasks and paradigms<sup>14</sup>. Likewise, single-unit recording experiments have revealed that frontal neurons are highly flexible, capable of changing their tuning properties as task demands change<sup>15</sup>.

However, recent experiments have provided initial support for a functional organizing principle along the rostro-caudal axis of the frontal lobes that is based on a hierarchy of action control<sup>16–19</sup>. To understand why actions might be processed hierarchically by the brain, consider the act of making a sandwich. The overall goal ('make a sandwich') is abstract in that it does not specify what particular sequence of movements is necessary to make the sandwich given one's current situation. But this abstract goal can be broken down into more

specific subgoals, like slicing bread or spreading mayonnaise, and each of these subgoals can be further broken down into more specific sub-subgoals, and so forth. One can continue to decompose the task until it is expressed as a unique series of motor actions. Unlike the abstract goal of making a sandwich, these final motor acts are highly specific. Thus, a traditional idea is that control of action may involve selecting and maintaining goals at multiple levels of abstraction, from general task goals at higher levels ('make a sandwich') to concrete motor responses at the lowest levels<sup>20–24</sup>. A more contentious hypothesis to emerge from cognitive neuroscience is that this hierarchy of action control is instantiated along a rostro-caudal gradient in the frontal cortex, whereby neurons in more-anterior regions of the frontal lobe process abstract action goals (like deciding to make a sandwich), and those in more-posterior regions process more-concrete information about action that is closer to the actual motor output<sup>7,16,18,19,25–43</sup>. However, it should be noted that abstraction has been defined somewhat differently across these experiments<sup>25,27</sup> (BOX 1).

Moreover, some researchers have suggested that frontal regions along the rostro-caudal axis interact with one another hierarchically<sup>17,19,35,37</sup>; they propose that there is a dominance relationship whereby higher, more-anterior regions influence processing in lower, more-posterior regions to a greater extent than vice versa. If such a processing hierarchy indeed exists, it would be reasonable to assume that systematic rostro-caudal patterns would be evident in the anatomy and physiology of the frontal cortex.

**Domain (stimulus/input domains)**

A type of information, such as spatial versus verbal versus object-related information. Domains are often associated with independent or modular input systems.

**Action rule**

A type of knowledge that specifies how to behave given a particular state. A stimulus-to-response mapping is a simple rule.

This Review surveys functional and anatomical studies for differences along the rostral-caudal axis of the frontal lobes. First, we evaluate neural recording, neuropsychological and functional imaging data that support a rostral-caudal gradient of function, focusing on possible regional differences in the response to different levels of abstraction. Then we consider whether the rostral-caudal anatomy of the frontal lobes, including its intrinsic connectivity, also supports this gradient. Finally, we consider how these data support and/or constrain the hypothesis that the rostral-caudal functional organization is hierarchical, and discuss what evidence would be required to demonstrate this hierarchical architecture.

**A rostral-caudal axis processing gradient**

Neurons in the frontal cortex possess a number of properties that are useful for cognitive control<sup>6,44</sup>. Specifically, they can integrate multiple sources and domains of input<sup>45,46</sup>, sustain information in the face of distraction<sup>47</sup>, acquire and represent action rules<sup>8,48,49</sup>, and change their tuning properties depending on whether a stimulus is task relevant or not<sup>15</sup>. Although all neurons in areas that lie anterior to the motor cortex possess these properties to varying degrees, there is evidence for

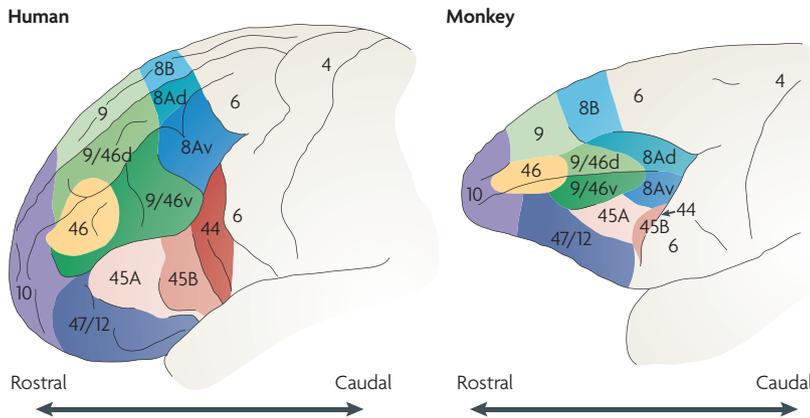
regional differences in their instantiation, particularly with respect to domain generality (see [Supplementary information S1 \(box\)](#)) and rule representation. These putative functional differences are currently the primary evidence for theories regarding a rostral-caudal hierarchical architecture to the frontal cortex. In the following section, we focus on the evidence for and against a gradient in ‘rule abstraction’ along the rostral-caudal axis of the frontal lobe.

**Abstract rule representations in frontal cortex.** The frontal cortex is often proposed to support learning, storage and/or retrieval of rules for behaviour. An action rule specifies the relationship between a condition of the system (one of the simplest being an encounter with a perceptual stimulus), an action and an anticipated outcome<sup>2,8,48,49</sup>. For example, a conditional stimulus–response association — such as a saccade to the left in response to a high tone — would be a simple rule that specifies a concrete motor function. However, rules can also be more abstract in that they do not specify a particular action, but a class of action rules. Thus, in the above example, a more abstract rule might specify whether the saccade direction is cued by a tone or by a colour, without specifying the direction itself. As described later, growing evidence suggests that when rules are more abstract, the execution of these rules depends on more-anterior portions of the frontal cortex<sup>17,19,25,29,40,50</sup>.

The caudal frontal cortex (specifically the dorsal premotor (PMd) corresponding to area 6, see FIG. 1) contains neurons that are associated with and, as lesions studies have shown, necessary for the execution of simple action rules<sup>42,51–58</sup>. PMd neurons increase their firing to response-relevant cues during the course of training, and this increase mirrors behavioural learning curves<sup>56</sup>. Lesioning the PMd following training results in a loss of the ability to select responses on the basis of previously learnt rules<sup>51,59–62</sup>.

Neurons in the more-rostrally located lateral PFC (that is, area 45, area 46 and area 9/46) (FIG. 1) also demonstrate concrete rule selectivity<sup>45,48,63–69</sup>. However, lesioning the mid-dorsolateral PFC after rule learning does not impair performance on simple response-selection tasks. Rather, in non-human primates PFC lesions prevent the acquisition of new rules<sup>62,70</sup>. Moreover, cue-specific PFC firing decreases as the rules are acquired. Functional MRI (fMRI) studies in humans have shown a similar pattern in PFC activation during simple rule learning<sup>71,72</sup>.

The distinction between PFC and PMd activity is often interpreted as dissociating the learning from the execution of rules, but it could also be explained in terms of differences in the capacity of PFC and PMd to execute abstract versus concrete action rules. Specifically, during the course of learning, monkeys often adopt abstract strategies, like shifting to a new response after receiving negative feedback but sticking to the same response after positive feedback. Animals that adopt this ‘win-stay, lose-shift’ strategy acquire arbitrary associations between a cue and a response faster than animals that do not. Notably, such a strategy



**Figure 1 | Cytoarchitectonic divisions of the human and monkey frontal lobe.**

Rostral and caudal axes are labelled and the numbers represent the update by Petrides and Pandya<sup>120</sup> of the Brodmann<sup>151</sup> and Walker cytoarchitecture maps. Several investigators have created maps of the frontal cortex based on morphological criteria such as the gross characteristics of cells, the arrangement of these cells in cortical layers, and gross characteristics of myelin in the cortex (for examples see REFS 152, 153). However, area boundaries differ significantly between maps. For example, in the lateral prefrontal cortex, Brodmann’s area 9 is extensive and area 46 does not exist<sup>152</sup>, whereas Walker includes area 46 and a much more restricted area 9 (REF. 153). Another issue concerns the correspondence between maps of monkey and human cortex. Indeed, a comparison between Brodmann’s monkey and human cortex maps reveals seemingly significant differences; for example, the human map includes area 46, but the monkey map does not<sup>151,152</sup>. Likewise, in Walker’s map of the monkey cortex, area 46 is far more extensive than that depicted in Brodmann’s map of the human cortex. To resolve these discrepancies, Petrides and Pandya<sup>10,120,121</sup> performed an extensive comparison of the architecture of the frontal cortex between monkeys and humans. This revealed that both in monkeys and humans, areas 9 and 46 are in the mid-dorsolateral sector of the lateral prefrontal cortex. Also, in both species, area 9 lies dorsal to area 46. However, in humans, area 9 encircles area 46 caudally, which is not the case in monkeys. This caudal portion of area 9 in humans is similar to the caudal portion of area 46 in monkeys. This led Petrides and Pandya to create a new label, area 9/46, which they divided into a dorsal portion (area 9/46d) and a ventral portion (area 9/46v). The nomenclature they put forth in their maps is used in this Review. Figure is reproduced, with permission, from REF. 10 © (2002) Wiley-Blackwell.

**Box 1 | Different types of abstraction of frontal lobe representations**

Studies that have distinguished regional differences along the rostral-caudal axis of the frontal lobe based on abstraction have used different definitions of abstraction (see REFS 25,27). These definitions are not mutually exclusive, but it is important to review their characteristics.

**Domain generality**

A domain-general neuron can encode information across input domains. For example, if a neuron fires to any cue that indicates a leftward joystick movement, regardless of whether the response-relevant dimension of the cue is its location on the screen (spatial domain) or its object identity (object domain; for example, is the cue a picture of an animal versus a tool?), then this is a domain-general neuron.

**Relational integration**

A first order of relational complexity could involve assigning a property to an item (“What is the colour?”). A second order might involve drawing relations between concrete properties (“Do the colours match?”). A third order could involve evaluating relations among relations, such as verifying the analogy ‘pilot is to airplane as captain is to ship’. As increasing numbers of independent dimensions of stimuli are related to one another in order to determine a response, a relation becomes more abstract<sup>2,30,31,43,50,95,97,135,136</sup>.

**Temporal abstraction**

In the example of making a sandwich, the goal ‘make a sandwich’ is relevant for longer than the goal ‘slice bread’. In general, as action goals become more abstract, the timescale of action that they govern increases. Thus, timescale is an important variable in a system that maintains action goals at different levels of abstraction. The extent to which goals (like making a sandwich) are maintained over longer temporal gaps — whereas more concrete goals (like slicing bread and spreading mayonnaise) are being updated — is referred to as temporal abstraction.

**Policy abstraction**

The goal ‘make a sandwich’ is an abstraction over more specific subgoals, like slicing bread versus heating up a tortilla wrap, depending on the context of the sandwich in question. Policy is the relationship between the state of a system, an action, and an anticipated outcome. Policy abstraction refers to the degree to which a given goal representation forms a generalization over lower-level goal representations<sup>27,137–139</sup>. In this sense, policy abstraction relates directly to rule complexity. A simple rule linking a stimulus and a response is a first order policy. For example, learning that a red cue means ‘press button 1’ and a blue cue means ‘press button 2’ would be a first order policy. However, assume one also learns that a square means ‘press 1’ and a circle means ‘press 2’. What does one press in response to a red circle? In this case, an additional rule is necessary to determine whether the colour or shape rules are relevant in the current context. Such a meta-rule, linking the context to a relevant set of first order rules, would be a second order policy. Adding additional contingencies will progressively result in more abstract policy.

does not specify what response the animal should make to a particular stimulus, but rather indicates a class of rules by which a response should be selected given the most recent response, cue and feedback. Thus, one interpretation of the dissociation between PFC and PMd activity during rule learning is that both areas execute rules, but that these rules differ in their level of abstraction. The PMd executes the specific arbitrary association between a stimulus and a response, whereas the PFC executes higher-order strategies, such as the win-stay, lose-shift strategy. This strategy becomes obsolete once the arbitrary associations have been learnt; thus, PFC lesions have little effect after learning. Consistent with this interpretation, lateral PFC neurons fire selectively to win-stay, lose-shift strategies (regardless of the specific response that is selected)<sup>73</sup>, and lesions of the lateral PFC prevent the application of such strategies<sup>70</sup>.

PFC neurons generally fire in response to more-abstract action rules. For example, PFC neurons fire selectively based on stimulus identity and location when these features are response relevant, but their firing is less likely to depend on which motor response is associated with those cues than that of PMd neurons<sup>53,74</sup>. Likewise, during the performance of sequential actions (such as making a familiar sequence of joystick movements in response to a visual cue or sequence of cues), the activity of neurons in pre-PMd (area 8) and caudal portions of PFC (area 9/46) during the delay period (that is, the time between stimulus and response) is tuned for the full sequence of responses to be performed, rather than for the identity of the first response. For example, an individual cell in caudal PFC will fire in response to a cue indicating that a sequence of ‘push-push-pull-pull’ movements must be made but not in response to a cue indicating the sequence ‘push-pull-push-pull’, even though both sequences start with a push movement<sup>75–78</sup>. Moreover, PFC cells (those in area 9/46) can encode a category of sequences, rather than a specific sequence. For example, these cells will fire in advance of the push-push-pull-pull and pull-pull-push-push sequences even though these differ in terms of their specific movements<sup>77</sup>. Thus, PFC neurons can maintain an abstract sequential movement plan, rather than individual movements.

However, under certain circumstances, the PMd can also represent abstract rules<sup>69</sup>. Monkeys learnt to respond depending on whether a presented stimulus did or did not match a target stimulus. This response rule is abstract because the response is determined based on the relationship (match–non-match) between two stimuli and can be generalized to new items. PMd firing was selective for the match–non-match rule and this rule-selectivity was stronger in PMd than in PFC<sup>69</sup>. Two potential explanations have been given to reconcile this result with those reported in the broader literature on abstraction and PMd<sup>69,79</sup>. First, extensive training on the task could have reduced control demands and permitted transfer of the rule to PMd from PFC through automation. Second, although the task involved making generalizations about the perceptual input, or context, of the response, it also involved a simple mapping to a concrete response rather than to a class of actions. Nevertheless, the PFC might not be required to represent all types of abstraction but only particularly abstract classes or courses of action.

Data from human studies, mostly using fMRI, have been broadly consistent with the distinctions in the degree of abstraction during action decisions between PMd (area 6), pre-PMd (areas 6 and 8) and lateral PFC (area 9/46) that have been suggested by studies on non-human primates. Simple conditional-motor and response-selection tasks activate PMd and pre-PMd (area 8)<sup>74,80–85</sup>, but activation in PMd and pre-PMd can be distinguished on the basis of their respective association with motor execution or preparation versus attentional or memory processing during movement selection<sup>74,82,86</sup>. At a more abstract level, switching between two tasks<sup>87–90</sup> or making a response based on an abstract rule<sup>91</sup> is

## Semantic

Conceptual knowledge, beliefs and facts about the world. In the verbal domain, semantic refers to word meanings.

## Phonology (phonological)

The sound structure of a word in terms of the smallest sound units that distinguish different words in a language.

## Repetition priming

Facilitated processing of a stimulus upon repetition, which happens even following an extended delay.

associated with activation in more-anterior lateral PFC regions (area 45 and area 9/46) along the middle and inferior frontal gyrus.

At the most anterior extent of the PFC, the frontopolar cortex (FPC) has been consistently associated with ‘meta-level’ control processing<sup>43,92</sup>. Specifically, the human FPC is activated when one has to coordinate two simultaneously ongoing tasks by generating and maintaining subgoals<sup>93,94</sup>, when one must relate the outcomes of different simple perceptual or semantic comparison problems<sup>95–97</sup>, when one must monitor the results of episodic-memory retrieval with respect to task goals<sup>98–100</sup>, and when one must determine when to shift attention from ‘external’ information (for example, a perceptual stimulus) to ‘internal’ information (for example, information held in working memory)<sup>101</sup>. Also consistent with the hypothesis that the FPC can maintain and monitor a higher-order task goal (such as ‘make a sandwich’) while lower-order processes are ongoing, FPC activity has been shown to follow a more sustained, lower-frequency pattern of signal change relative to more-posterior frontal regions<sup>100,102,103</sup>. Hence, the FPC is associated with higher-order control functions that supervise or integrate ongoing processing in other, lower-order cognitive or motor processes<sup>43,92</sup>.

To summarize, across a range of studies, there are relative distinctions between PMd, pre-PMd, mid-lateral PFC and FPC in the degree of abstraction of the action representations that they process. But do these distinctions together form a gradient?

**Evidence for a functional gradient along the dorsal rostral-caudal axis.** The strongest evidence to date for a functional gradient along the rostral-caudal axis of the frontal lobes comes from human fMRI studies in which the level of abstraction of response selection was progressively varied in each individual participant. One ground-breaking study demonstrated that as the contextual information required to select a response progressively became more abstract and remained relevant over a longer temporal interval, fMRI activation moved from PMd to area 44 to the mid-dorsolateral PFC (area 46; FIG. 2a)<sup>19</sup>. Another study demonstrated that as conditions were added to an action rule (so that a more abstract action decision constituted a generalization over more lower-order action decisions (that is, policy abstraction; see BOX 1)), PMd (area 6), pre-PMd (area 8), mid-dorsolateral PFC (area 9/46) and FPC (area 10) were successively activated<sup>16</sup> (FIG. 2b). A third study demonstrated that as individual finger-press responses, short sequences of responses or a sequence of response sequences were initiated (that is, more abstract response chunks), activation was evident in PMd, area 44 and the mid-ventrolateral area (area 45), respectively<sup>18</sup>. Thus, the consistent pattern across these experiments suggests a rostral-caudal gradient in which caudal PFC regions are engaged for concrete action decisions that are closer in time and more directly related to choosing a specific motor response, and anterior PFC regions seem to guide behaviour over longer lags and at more abstract levels of action contingency.

Interestingly, a recent experiment has provided evidence for interactions between parallel rostral-caudal gradients along lateral and medial frontal cortex as more-abstract motivational factors are taken into consideration during cognitive control<sup>104</sup>. Specifically, the pre-supplementary motor area (in the medial frontal cortex) and the pre-PMd and/or caudal PFC (approximately areas 44 and 45; in the lateral frontal cortex) were associated with cues that indicated individual trials as having high or low stakes. By contrast, area 9/46 (in the lateral frontal cortex) and the dorsal anterior cingulate cortex (in the medial frontal cortex) were associated with cues indicating a general low or high stakes environment regardless of the status of a particular trial. Intriguingly, effective connectivity analysis indicated that the activation in lateral PFC could be explained by the activation in medial PFC, suggesting that motivational factors computed by medial frontal regions may upregulate neural activity in lateral frontal regions that support control at different levels of abstraction.

**Evidence for a functional gradient along the ventral rostral-caudal axis.** The studies described above focused primarily on dorsolateral frontal gradients (FIG. 2a). However, there is also evidence for a rostral-caudal gradient of abstraction along the ventrolateral frontal cortex<sup>105</sup>. Activation in rostral ventrolateral PFC (areas 47 and 45) has been distinguished from that in caudal ventrolateral PFC (areas 45 and 44) based on semantic (abstract) versus phonological (closer to an articulated response, that is, a motor response) processing<sup>106–110</sup>. Further, multiple lines of evidence suggest that anterior (area 47) and mid-ventrolateral PFC (area 45) are dissociable based on the degree of specificity at which retrieval from memory is conducted<sup>16,111,112</sup>, going from abstract semantic retrieval to post-retrieval decision processing.

A recent repetition priming experiment has provided more direct evidence of a ventrolateral PFC gradient of abstraction<sup>113</sup>. Participants were presented with pictures of everyday objects and required to make one of two semantic decisions — judgment on size (“Is the object bigger than a 13-inch box?”) or composition (“Is the object made of an organic substance?”) — and then indicate their choice with a finger-press response. The items were subsequently repeated and subjects were asked to make either the same judgment or a different judgment. Thus, this experiment permitted independent estimation of repetition priming at the item (semantic), task (decision) and response levels. Consistent with a rostral-caudal gradient of item processing along ventrolateral PFC, these three levels were associated with priming effects in rostral ventrolateral PFC (area 47), mid-ventrolateral PFC (area 45) and pre-PMv (areas 44 and 6)/PMd (area 6), respectively (FIG. 2c). Hence, a gradient of abstraction seems evident along ventrolateral PFC. Given the rostral-caudal connectivity of the frontal cortex (see later), the existence of two distinct functional pathways, both emanating from the FPC (area 10), seems reasonable.

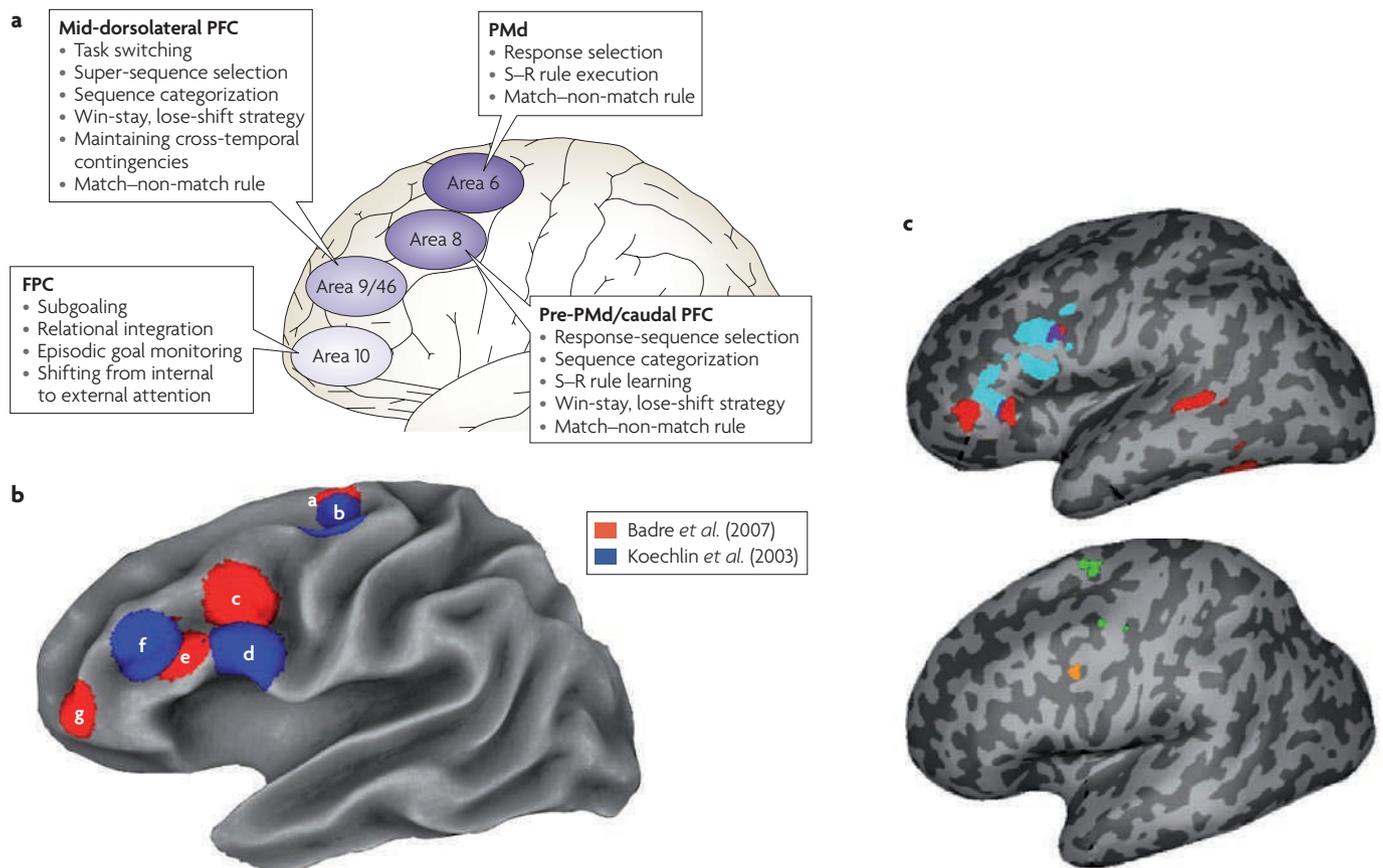
**Structural equation modelling**

A statistical approach for testing proposed causal relationships between variables.

However, what distinguishes this ventral gradient from the dorsal gradient discussed previously remains an open question. One speculative hypothesis is that the ventral frontal gradient could be involved in the processing of context, retrieving or selecting relevant information that is being processed by ventral-pathway perceptual and memory systems, in order to comprehend the environment in a goal-relevant way. By contrast, the dorsal-frontal gradient could be more directly involved in the planning and execution of actions. However, whatever theoretical account will ultimately emerge to explain the difference between dorsal and ventral rostro-caudal gradients, it will probably derive partially from functional distinctions between dorsal and ventral frontal cortex<sup>9,32,114–116</sup>.

**Are the functional gradients hierarchical?**

Beyond a gradient of abstraction, do neurons in rostral regions influence the activity of neurons in caudal regions more than caudal regions influence rostral regions? Although this hypothesis is both contentious and preliminary, there is some evidence for a rostral-to-caudal flow of control. One study<sup>19</sup> used structural equation modelling to show that activation in anterior frontal regions accounted for variance in activation in caudal regions but not vice versa. Another line of experiments<sup>117,118</sup> demonstrated that the functional connectivity between a domain-general, anterior PFC/FPC region and domain-sensitive regions in caudal frontal cortex changed depending on whether a spatial or verbal working memory task was being performed. Moreover,

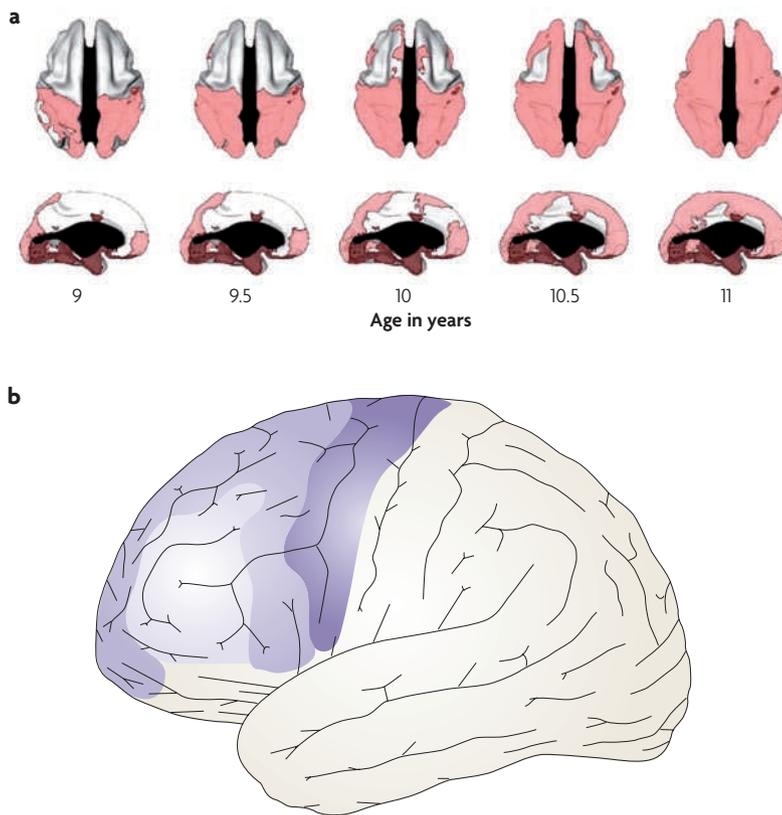


**Figure 2 | Functional gradients along the rostro-caudal axis.**

**a** | Summary of experimental findings from functional MRI (fMRI) studies and monkey electrophysiology along the rostro-caudal gradient. Across studies, there seems to be a trend for more-rostral regions to support more-abstract action rules. Anatomical locations of effects are approximate. **b** | Comparison of results from two fMRI studies showing functional gradients along the rostro-caudal axis of the human frontal lobe. Explicitly testing a rostro-caudal functional gradient, Koechlin *et al.*<sup>19</sup> (shown in blue) and Badre *et al.*<sup>16</sup> (shown in red) demonstrated highly convergent activation along a dorsal gradient from dorsal premotor cortex (PMd) (**a,b**; ~BA 6) to prePMd (**c,d**; ~BA 8) to mid-dorsolateral prefrontal cortex (PFC) (**e,f**; ~BA 9/46) to frontopolar cortex (**g**; ~BA 10), as cognitive control was required at progressively abstract levels. Although different forms of abstraction were tested — temporal abstraction in Koechlin *et al.*<sup>19</sup> and policy abstraction in Badre *et al.*<sup>16</sup> (see BOX 1) — the activation

patterns observed in these two experiments were highly convergent. **c** | Race *et al.*<sup>113</sup> aimed to locate a gradient of abstraction along the ventrolateral PFC by assessing repetition priming (that is, a reduction in signal change) at the stimulus (semantic), task (decision) and response levels. They showed that areas 44 and 8 (shown in orange) in caudal ventrolateral PFC showed repetition priming at the response level, that is, the signal change in these areas diminished when a motor response was repeated, regardless of the stimulus or decision associated with it. Area 45 (shown in blue) revealed repetition priming at the decision level even if the subsequent response differed. And area 47 (shown in red) demonstrated priming when the same item was encountered (semantic priming), regardless of the subsequent decision or response. These priming effects indicate a rostral-to-caudal gradient of decreasing abstraction. Part **b** is reproduced, with permission, from REF. 16 © (2007) MIT Press. Part **c** is reproduced, with permission, from REF. 113 © (2009) MIT press.

Box 2 | Development of the frontal lobes along the rostro-caudal axis



Changes in myelination and in synaptic density continue beyond infancy well into adulthood<sup>140–142</sup>, and are the primary markers of brain development in children. Important differences along the rostro-caudal axis of the frontal lobe can be seen during grey matter development throughout childhood and early adolescence. With some lamina-dependent variation<sup>143</sup>, synaptic density throughout the neocortex and subcortical structures increases sharply initially, followed by a slow decline, resulting in a skewed inverted U-shaped pattern of change in cortical thickness<sup>140,144–147</sup>. However, the ages at which grey matter changes progress differ substantially between brain regions<sup>148</sup>. Of particular interest, longitudinal data suggest that in the frontal lobes grey matter maturation progresses slowly from caudal to rostral regions, that is, from motor cortex to dorsal premotor (PMd) to area 9/46 during early childhood through to adolescence<sup>143,149</sup>.

The frontopolar cortex (area 10) seems to diverge from a linear caudal-to-rostral developmental trajectory<sup>143,149</sup>. A recent longitudinal study<sup>143</sup> reported that lateral and medial frontopolar cortical areas mature early, around the same time as the supplementary and premotor cortices (areas 6/8). This is followed by maturation of the interposed lateral prefrontal cortex regions (areas 9/46, 47 and 45); see part a of the figure, which shows the age at which different areas reach their peak cortical thickness (pink). Thus, the overall pattern of development is not a linear progression from caudal to rostral, but rather comprises a centrifugal pattern with the most rostral and caudal frontal regions developing first (see see part b of the figure, in which early maturing areas are indicated by darker colours).

This developmental pattern is significant for models of frontal lobe function, particularly those that seek to understand how a hierarchical architecture might develop in the frontal cortex (for examples see REFS 26, 27, 150). In general, because different frontal regions mature at different rates, the state of each region (as defined by its inputs) is distinct during synaptic pruning. This temporal differentiation in maturation could provide a basis for functional differences along the rostro-caudal axis. However, the centrifugal pattern, and consequently the early maturation of the 'top' and 'bottom' extremes of the hierarchy, means that the development of area 9/46 may be shaped by both higher-order and lower-order influence. The significance of such maturation in lateral prefrontal cortex remains to be understood. Part a of the figure is reproduced, with permission, from REF. 143 © (2008) Society for Neuroscience.

patients with rostral PFC damage showed intact activation in the domain-specific caudal frontal regions, but functional connectivity in the task-related networks was disturbed relative to controls<sup>119</sup>. Thus, the influence of rostral PFC on caudal PFC may help the coordination of lower-order regional networks.

Crucially, however, these results do not provide strong evidence for a processing hierarchy. In particular, the asymmetry and direction of influence that a hierarchical gradient would predict have only recently been directly tested<sup>17</sup>. And, indeed, it is unlikely that rostral frontal regions pass control through interposed frontal regions in order to influence motor cortex in all cases and for all tasks. For example, at least one result demonstrated that lesions in the monkey periarculate region, including areas 6 and 8, impair performance on various conditional motor tasks, but do not impair performance in a task that engages the more-rostral mid-dorsolateral PFC<sup>42</sup>. Thus, although there is evidence for rostro-caudal differences in the degree of abstraction during control tasks, additional evidence, including lesion and anatomical evidence, is needed to support a direct dominance relationship from rostral to caudal PFC.

Anatomy along the rostro-caudal axis

Clues as to the rostro-caudal organization of the frontal lobe can be derived from its anatomical organization<sup>35</sup> and its development (BOX 2). As mentioned earlier, hierarchical processing architectures are characterized by a dominance relationship from higher to lower levels. Notably, such a dominance relationship should not be confused with serial stages of processing or a direct temporal flow of processing: in a hierarchical architecture, goals at different levels of abstraction could be represented in parallel in different areas and could be updated dynamically depending on control demands at each level of abstraction. Thus, a dominance hierarchy should be reflected in a rostral-to-caudal influence of processing in the frontal cortex and a characteristic pattern of cortico-cortical connections linking regions from the FPC to the motor cortex. Similarly, projections to and from the primary and unimodal association cortex outside of the frontal lobe should reflect differing degrees of abstraction along the purported rostro-caudal gradient: higher frontal cortex regions should receive more integrated, cross-domain sensory input than lower regions. Here, we consider the extent to which the anatomical evidence supports such an organization.

To consider the anatomical organization of the frontal cortex, one must be precise regarding the boundaries of areas that are proposed to be anatomically distinct. Here, we use the nomenclature put forth by Petrides and Pandya<sup>10,120,121</sup> (FIG. 1). A key modification that Petrides and Pandya have made to the original cortex maps of Brodmann and Walker is the inclusion of a new area, that they refer to as area 9/46, and its division into dorsal (area 9/46d) and ventral (area 9/46v) portions (FIG. 1). In this scheme, the fMRI evidence for a dorsal rostro-caudal frontal gradient<sup>16,19</sup> has identified several anatomically distinct lateral PFC regions along the rostral-caudal axis: rostral PFC (area 10), mid-dorsolateral PFC (areas

46 and 9/46), pre-PMd and PMd (area 6/8). Thus, we consider the anatomy of each of these regions in terms of their intrinsic organization and connectivity.

**Intrinsic organization.** Barbas and Pandya<sup>122</sup> proposed that the difficulty with defining PFC areas can be obviated if the cerebral cortical architecture is considered in the theoretical framework of cortical laminar organization proposed by Sanides<sup>123</sup>. In this framework, the cerebral cortex evolved from two primordial parts: the hippocampal archicortex (on the mediodorsal line) and the olfactory paleocortex (on the basoventral line). Thus, the frontal cortex could be viewed as a set of areas showing gradual changes in architectonic organization in these two major cortical lines. Careful study of the PFC anatomy in rhesus monkeys led to several important observations<sup>124</sup>. First, areas differ in their degree of differentiation, and progressively more differentiated areas are more laminated (that is, cells are organized into cortical layers). In the basoventral line, increased differentiation proceeds from caudal orbitofrontal cortex (areas 25, 13, 14 and 12) to area 10, to rostral area 46, to caudal area 46 and finally to ventral area 8 (FIG. 3). In the mediodorsal line, increased differentiation proceeds from ventromedial prefrontal cortex (areas 24, 25, 32 and 14) to medial areas 9 and 10, to lateral areas 9 and 10, to rostral 46, to caudal area 46 and finally to dorsal area 8 (FIG. 3). Relevant to this Review, rostral PFC areas 10, 9 and 46 are less differentiated than more-caudal PFC areas 46 (later renamed area 9/46) and 8.

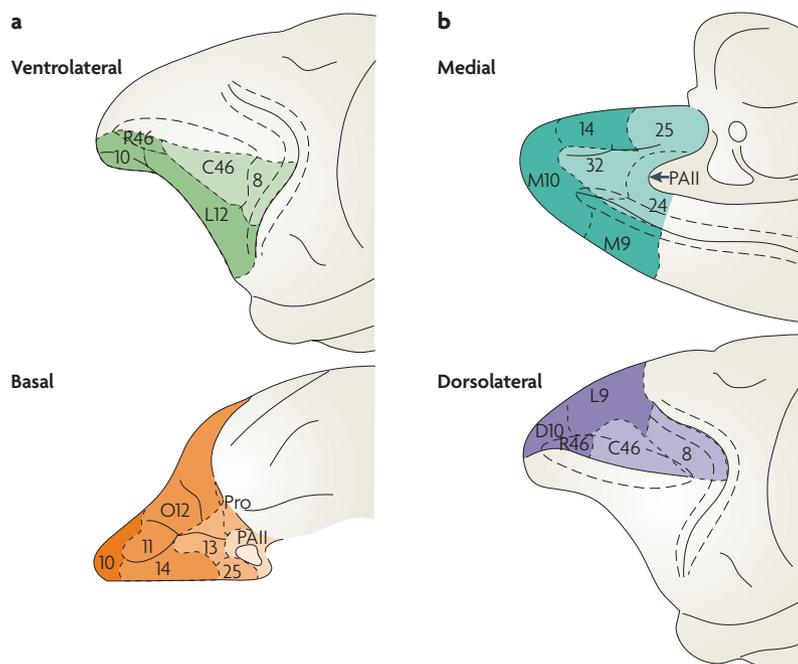
In a cortical line each frontal area projects to an area that is more architectonically differentiated and to one that is less differentiated. For example, rostral area 46 projects to area 10, which is less differentiated, and to area 8, which is more differentiated. However, it has been noted<sup>124,125</sup> that areas with well-developed laminar differentiation (such as area 8 or caudal area 46) have a restricted number of connections — mostly to neighbouring regions — whereas areas that have less laminar differentiation (such as area 10) have widespread connections to other areas. Thus less-differentiated areas such as those in rostral PFC (areas 10, 9 and 46) have more diffuse projections and are well situated to be at the top of a hierarchy. By contrast, more differentiated areas such as those in caudal PFC (areas 9/46 and 8) have more intrinsic connections and are well situated to be lower in a hierarchy.

**Afferent and efferent projections in the frontal cortex.** When considering whether the frontal cortex is hierarchically organized, one could assess whether its anatomical organization adheres to general contiguity and asymmetry principles. Consider regions A, B and C, with region A at the top of the hierarchy and region C at the bottom. According to a contiguity principle, regions A and B, and regions B and C are contiguous and so should have reciprocal projections. For non-contiguous regions, an asymmetry principle should apply. Thus, region A can also project to region C but region C would not necessarily project back to region A. In other words, the hierarchy hypothesis predicts that there should be fewer long-range inputs from caudal regions to rostral regions and, conversely, more inputs from rostral regions to caudal regions. In the model of frontal hierarchy that we are assessing, rostral PFC (area 10) would lie at the top of the hierarchy, the lower level would be mid-dorsolateral PFC (area 9/46) and the lowest level the premotor cortex (area 6/8). Based on anatomical studies, we review the connectivity of each of these sectors below and summarize the findings in FIG. 4.

With regard to the rostral PFC, Petrides and Pandya performed a detailed analysis of the brain of a rhesus monkey<sup>126</sup> and found that area 10 projects caudally to dorsal frontal areas 9, 46, 8 and 6; to ventral frontal areas 47/12 and 45; and to medial and orbital frontal areas 24, 25, 32, 14 and 11 (tracer injection sites included lateral, medial and orbital areas).

In the mid-dorsolateral PFC, anatomical studies of areas 9/46d and 9/46v in two rhesus monkeys<sup>127</sup> revealed rostral projections from area 9/46d terminating in areas 9, 46 and 10. Caudal projections from area 9/46d terminated in lateral frontal areas 8Ad and 6d and medial frontal area 24. From area 9/46v, rostral projections were found terminating in areas 46 and 10, and caudal projections terminating in lateral frontal areas 8Av, 44, 45b and 6v, and in orbitofrontal areas 11 and 13.

Importantly, both area 9/46d and area 9/46v project rostrally to area 10, but their projections remain segregated (dorsal and ventral, respectively). Moreover, there are no direct connections between area 9/46v and area 9/46d. This potential independence is intriguing

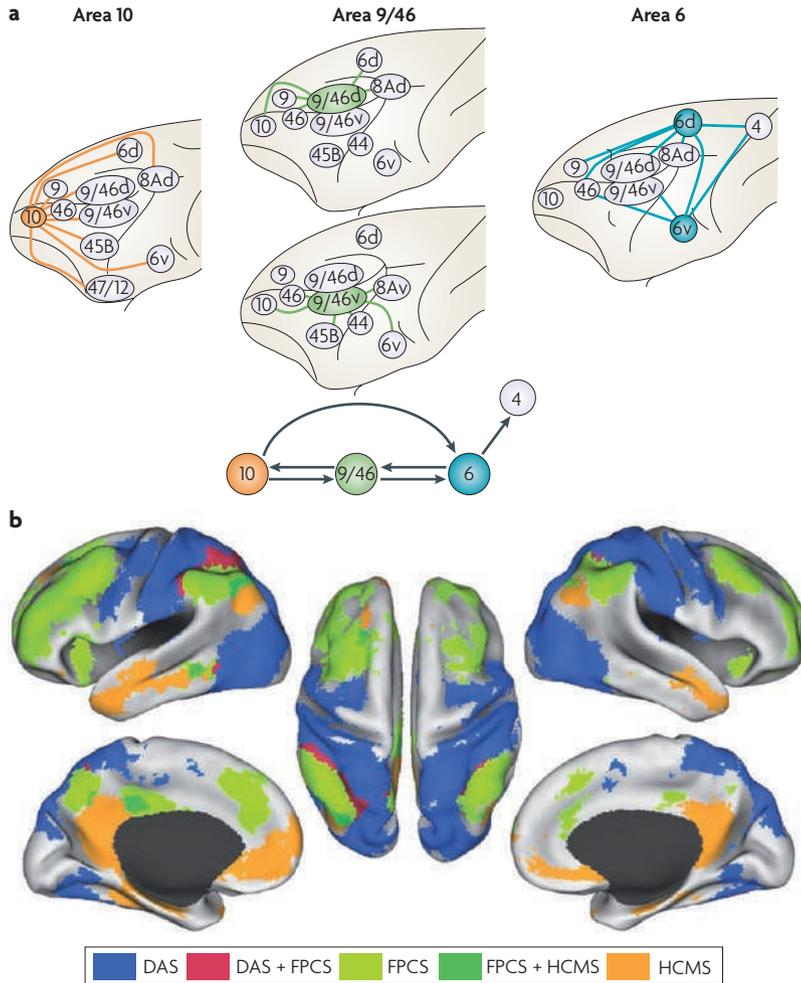


**Figure 3 | Architectonic stages of the prefrontal cortex.** Diagrams showing the architectonic stages in the basoventral (a) and mediodorsal (b) prefrontal cortices. Each of these two broad cortical regions shows a gradient of laminar organization (for example, differentiation) from the most anterior to more-posterior portions of the frontal cortex. This axis of differentiation proceeds in a direction from the least-differentiated (anterior frontal regions such as area 10 and rostral area 46) to the most-differentiated cortex (posterior frontal regions such as caudal areas 46 and 8). Figure is modified, with permission, from REF. 124 © (1989) Wiley.

considering the functional evidence, discussed earlier, for distinct dorsal and ventral rostro-caudal gradients. Finally, there are no direct projections from area 9/46 to primary motor cortex; all cortico-cortical connections in the frontal cortex pass through the premotor cortex. Thus, there is no direct influence of the PFC on the primary motor cortex.

The lateral premotor cortex (area 6) is divided into a dorsal region (containing a representation of the trunk) and a ventral region (representing the neck, head and

face). One study found that in rhesus monkeys, the dorsal premotor cortex (area 6d) is connected with other dorsal frontal regions and the primary motor cortex<sup>128</sup>. Specifically, the dorsal premotor cortex (area 6d) reciprocally projects to areas 46, 9, 9/46d and 8 above the principal sulcus. The ventral premotor cortex (area 6v) reciprocally projects to both dorsal and ventral PFC regions as well as to the primary motor cortex. Specifically, area 6v projects to areas 46 and 9/46v and to area 6d. Interestingly, no efferent projections from area 6 to FPC (area 10) were found.



**Figure 4 | Rostro-caudal connectivity of the frontal cortex.** **a** | Intrinsic connections of the lateral prefrontal cortex (PFC; top) and a schematic summary of the connections of the principal frontal regions (area 10, shown in orange; area 9/46, shown in green; and area 6, shown in blue) that are proposed to be part of a rostro-caudal functional gradient based on functional studies (bottom). Area 4 depicts the primary motor cortex. **b** | Results from Vincent *et al.*<sup>130</sup> showing that spontaneous activity in regions along the rostro-caudal axis of the prefrontal cortex (PFC) and in parietal and medial frontal cortex is correlated with activity in the frontopolar cortex (shown in light green). Also depicted in the figure is the spatial relationship of these regions to two other networks: the dorsal attention system (DAS) and the hippocampal-cortical memory system (HCMS), which were identified using visual motion area MT+ and the hippocampus as seeds, respectively. Importantly, these data provide evidence that the activities in regions of the frontal cortex that in other experiments were associated with control at increasing levels of abstraction are correlated with each other (and thus are part of a coherent rostro-caudal functional network, that is, the frontoparietal control system (FPCS)) but not with activity in other regions of the frontal cortex (that is, areas in the DAS and HCMS). Part **b** is reproduced, with permission, from REF. 130 © (2008) The American Physiological Society.

*Afferent and efferent projections outside the frontal cortex.* Based on their anatomical studies, Petrides and Pandya<sup>126</sup> made the crucial observation that area 10 (as well as area 9) does not project to the parietal cortex, the inferotemporal cortex or the visual areas of occipital cortex. Thus, they note, areas 9 and 10 do not directly interact with ventral visual pathways for object processing or dorsal visual pathways for spatial processing. By contrast, more-caudal areas of lateral PFC, such as area 9/46 (and areas 8A, 8B and 45), have massive, bidirectional projections with these areas<sup>9</sup>.

Generally consistent with this and other perspectives<sup>36</sup>, Botvinick<sup>26</sup> constructed a connectionist model of sequential behaviour with a ladder-like architecture that is similar to this pattern of connectivity. Specifically, input and output layers communicated directly with lower layers but indirectly (through the lower layers) with higher layers. During learning, this architecture acquired more abstract representations in the higher layers. Hence, although having a structurally arrayed hierarchical organization is not a requirement for the control of complex sequential behaviour<sup>129</sup>, when such an architecture exists, the same action can be represented at different levels of abstraction.

*Functional connectivity in the frontal cortex.* The basic anatomy reviewed here suggests that regions in the frontal cortex are not ‘fully connected’ in the sense that every region connects to every other region directly. Rather, there are constraints in frontal connectivity that follow contiguity and asymmetry principles. Specifically, adjacent regions along the rostro-caudal axis are connected to one another but do not project to more-rostral regions beyond those immediately adjacent, as in the specific case of area 6 (see FIG. 4). In addition, dorsal and ventral rostro-caudal gradients are only connected at the highest and lowest levels (areas 10 and 6, respectively), but not in the ‘middle’ (between areas 9/49d and 9/46v). But do these distinct rostro-caudal tracts form coherent functional systems, as would be required by a special rostro-caudal processing architecture such as a hierarchy?

A recent study<sup>130</sup> used an analysis of spontaneous fluctuations in BOLD activity to characterize the functional system that includes the FPC (area 10). This technique relies on the correlations among low-frequency BOLD changes that exist in the absence of an overt task, and has been a fruitful, ‘task-free’ approach of defining ensembles of regions that form a functional system<sup>131–134</sup>.

## Seeding

A step in functional connectivity analysis whereby a region of interest is defined to which connectivity of all other regions is estimated.

Seeding the FPC yielded a network that included the full dorsal-frontal gradient (areas 10, 9/46, 8 and 6) (FIG. 4) and that was distinct from networks acquired using the hippocampus or visual motion area MT+ as seeds. The network also included regions of medial frontal cortex, anterior insula, the head of the caudate nucleus and anterior inferior parietal lobule. Thus, a hierarchical architecture of the frontal cortex would not necessarily mean that this system is independent from the rest of the brain or is the only source of top-down signals. Rather, it must ultimately be understood as a component of a broader functional system, such as the fronto-parietal control system<sup>130</sup>.

## Conclusions and future directions

The evidence discussed in this Review supports two new insights about frontal organization. First, neurons in progressively rostral regions of the frontal cortex seem distinguished by their ability to support more-abstract representations and more-complex rules. Second, regions arrayed along dorsal and ventral rostro-caudal gradients act as coherent functional networks, along with regions of parietal and lateral temporal cortex. Is the rostro-caudal axis of the frontal lobe organized hierarchically? The results reviewed here suggest that the frontal cortex could, indeed, support such an architecture. Progressively rostral frontal lobe regions seem capable of supporting increasingly abstract neural representations and complex action rules. Such a differentiation would be essential in a hierarchical system, where 'higher' levels must maintain their state independent of the state of lower level processors or moment-to-moment changes in the environment. Moreover, the anatomical and functional connectivity data suggest that the rostro-caudal axis (that is, area 10 to area 9/46 to area 8 to area 6) forms a coherent functional network with longer connections, such as those from areas 10 to 6, being unidirectional. Again, such an arrangement is an important

precondition for a dominance hierarchy arrayed along the frontal cortex.

Crucially, although a hierarchical organization might require both of these features of frontal organization, these features do not, by themselves, require that the organization be hierarchical; they could be consistent with other architectures as well. So, additional research is required to provide definitive evidence for a hierarchy. However, a recent study in patients with focal damage due to stroke in the frontal cortex provides, perhaps, the strongest evidence to date for an asymmetric anterior to posterior dominance relationship<sup>17</sup>. In particular, these patients were impaired at making action decisions at a level of abstraction that was dependent on whether their damage was in pre-PMd (caudal, more concrete) or mid-DLPFC (more rostral, more abstract). Moreover, they were impaired on all tasks requiring more-abstract but not less-abstract action decisions. Importantly, the sites of damage among patient groups corresponded precisely to the foci identified for these levels of abstraction in healthy controls undergoing fMRI while performing this task<sup>16</sup>. This asymmetric pattern of deficits provides evidence of a rostral-to-caudal flow of processing during action control. However, it remains crucial to test whether perturbations in neural processing, such as due to stroke, asymmetrically influence processing in intact regions that are caudal but not rostral to the site of perturbation.

Broadly, the data reviewed here suggest that there are important regional distinctions along the rostro-caudal axis of the frontal lobe and that these regions act as a coherent functional network. These repeatable empirical phenomena demand an explanation, and hierarchy is one intriguing possibility. Whether it is hierarchy or some other scheme that explains the functional organization along the rostro-caudal axis of the frontal lobe, characterizing processing architecture is fundamental to our understanding of frontal lobe function.

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## FURTHER INFORMATION

D. Badre's homepage: <http://www.cog.brown.edu/research/badrelab/index.html>

M. D'Esposito's homepage: <http://bic.berkeley.edu/despolab>

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