1. Neuroanatomical bases of motivational and cognitive control: A focus on the medial and lateral prefrontal cortex.

Jérôme Sallet, Rogier B. Mars, René Quilodran, Emmanuel Procyk, Michael Petrides, and Matthew F.S. Rushworth

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Understanding the neural mechanisms of control regulation requires delineating specific functional roles for individual neural structures, and consequently their functional relationships. Higher-order control over behavior has traditionally been seen as the function of the prefrontal cortex (PFC). Models of various aspects of control, including top-down processing, decision making, and performance monitoring focus primarily on two subdivisions of the PFC, namely the dorsolateral prefrontal cortex (DLPFC) and the medial frontal cortex, particularly the anterior cingulate cortex (ACC). Within these frameworks, DLPFC is allocated a role in the maintenance of representations of goals and means to achieve them in order to bias processes that depend on posterior brain areas\textsuperscript{58}, while medial frontal areas, again especially ACC, participate in performance monitoring, action evaluation and detection of events that indicate the need for behavioural adaptation and
action re-valuation

Furthermore different hierarchical levels of cognitive control are thought to be supported by different prefrontal subdivisions.

One example is the conflict model proposed by Cohen et al. This model posits that the ACC tracks evidence for a need to increase cognitive control and sends this information to the DLPFC which then exerts control over the processes occurring in posterior brain areas. The ACC-DLPFC interactions can be direct or indirect. A related model proposed by Brown and Braver also posits that the activity of the ACC regulates the activity of structures involved in implementing cognitive control. A rather different model, based on the principles of reinforcement learning, proposed by Holroyd and Coles ascribes to the ACC a role in action selection in response to a dopaminergic teaching signal. For simplicity's sake these models either supposed the existence of a homogenous ACC and DLPFC, or else they are focussed on, sometimes undetermined, subdivisions of these two regions. Furthermore, most models have emphasized a unidirectional flow of information between the structures; in some cases, however, the direction emphasized is from the ACC to the DLPFC, while in other cases it is from the DLPFC to the ACC.

A feature of these computational models is that they often do not consider all aspects of the underlying neuro-anatomy. Moreover, a more detailed analysis of the connections between these brain areas may be of extreme importance to the functionality of models. Indeed as suggested by Passingham et al. each cytoarchitectonic area has a unique connectivity pattern that is likely to be related to its function. Thus paying careful attention to the details of the anatomical properties of networks may facilitate the identification of functional subdivisions within each area, which may in turn generate a clearer understanding of integrated system function. In this chapter we will review neuroanatomical data concerning two key nodes in cognitive and motivational control.
models, the ACC and the DLPFC. Our aim is to review neuro-anatomical data related to these two regions in the hope it may help improve our understanding of control networks and how structures within these networks are interacting. Furthermore, we will discuss the degree of correspondence in the anatomy of these areas in the human brain and the monkey brain, a model on which much of our knowledge is based.

**Cytoarchitecture of ACC and DLPFC**

Despite being commonly used neither the term ACC nor the term DLPFC correspond to a unique cortical area. They refer to a collection of areas (or subareas) with distinct cytoarchitectonic properties and connectivity profiles.

The abbreviation ACC is commonly used to refer the cytoarchitectonic areas 24 and 32 (Fig. 1.1a). Based on cytoarchitectural properties, or quantification of neurotransmitter receptors, it has been proposed that the ACC in monkeys extends to the middle of the dorsal bank of the cingulate sulcus, or that it lies just dorsally to the bottom of the cingulate sulcus. Vogt et al. consider that most of the cortex on the dorsal bank of the cingulate sulcus belongs to the adjacent medial frontal cortex. Area 32 is located rostrally to area 24. Petrides and Pandya proposed that the latter area extended caudally and formed, on the dorsal bank of the cingulate sulcus, a transition area between the ACC and the medial prefrontal cortex. One can also find some disagreement about the nature of the cingulate cortex. While Petrides and Pandya distinguished an agranular (area 24) and granular ACC (area 32), others considered area 32 to be dysgranular, and argued that area 24, or at least the area 24c subdivision was dysgranular in nature. Such discrepancies in
interpretation have also been associated with debate concerning the number of subdivisions of the ACC. Depending on the study, the ACC (area 24) contains from 4 to 9 subdivisions\textsuperscript{55,88}. According to Vogt et al. area 24 can be divided into an anterior division, the ACC, and a posterior division, that they refer to as the midcingulate cortex (MCC)\textsuperscript{88}. The ACC then corresponds to area 24a, b and c; the MCC corresponds to subdivisions 24a’, b’, c’, and d.

While most of these debates have concerned the nature of ACC in the macaque similar debates can be had concerning the identity of the human ACC. The problem becomes even more complex due to the presence of an additional sulcus, dorsal to the cingulate sulcus, the paracingulate sulcus\textsuperscript{85}. This sulcus is only present in 30-60% of cases\textsuperscript{30} and, when present, shows highly variable morphology across individuals\textsuperscript{85}. The morphology of the paracingulate sulcus affects the extent of areas 24 and 32 and is suggested to be related with performance in cognitive demanding tasks\textsuperscript{31}. One hypothesis proposed to explain the inter-individual differences in sulcal anatomy is that it reflects differences in the connectivity between dorsal ACC and DLPFC\textsuperscript{31}. As in monkeys one can distinguished several subdivisions of the area 24 and a similar organization has been proposed\textsuperscript{63,87} (Fig. 1.1a).

The DLPFC is also a heterogenous region (Fig 1.1b). In monkeys, it is located within the principal sulcus and extends dorsally. Based on cytoarchitectonic properties one can distinguish multiple areas: areas 8A and 8B, area 9, area 46. Some authors proposed even further subdivisions. They include transition areas around the lip of the principal sulcus and subdivisions with respect to the position of in the principal sulcus. Those areas are labelled
area 9/46 dorsal and ventral\textsuperscript{68,69} and a distinction is often made between area 46 ventral and dorsal\textsuperscript{3,7}. Finally, area 8 is subdivided into area 8A, located at the level of the genu of the arcuate sulcus, and area 8B dorsally to it.

As is immediately apparent, the human lateral prefrontal cortex is more folded than the monkey one (Fig. 1.1b). Instead of one sulcus (the principal sulcus), there are 3: the superior frontal sulcus, the complex intermediate frontal sulcus and the inferior frontal sulcus\textsuperscript{71}. The inferior frontal sulcus is suggested to be the ventral boundary of the DLPFC. Despite this discrepancy between humans and monkeys, Petrides and Pandya proposed than the organization of the DLPFC is similar\textsuperscript{69}.

**Connectivity of ACC and DLPFC**

*Medio-lateral prefrontal cortex connectivity in monkeys*

Before discussing DLPFC-ACC connectivity, it is important to underline the fact that a perfect description of the relationships between cingulate cytoarchitectonic areas and connectivity patterns is difficult to make. Indeed, in the literature most of the tracers injected in the cingulate cortex targeted either the cingulate gyrus (area 24a, b) or the rostral/caudal cingulate motor areas (rCMA, cCMA). rCMA and cCMA are cingulate subregions defined by their projections to the primary motor area (M1), the spinal cord and their excitability\textsuperscript{52,59,74}. In the interest of clarity we will consider the portion of area 24 that includes all the cingulate motor areas as the posterior ACC (pACC). Area 24 rostral to pACC will be referred to as the rostral ACC (rACC). Connectivity of area 32 will be considered separately.
A number of models of control emphasize interactions between ACC and DLPFC\textsuperscript{12,15}. Surprisingly, the emphasis put on the ACC-DLPFC functional relationships in fact relies on relatively weak anatomical connections (Fig 1.2). For instance pACC receives roughly 20 to 40 times more projections from the preSMA and cCMA than from area 46\textsuperscript{37}, and area 46 projects more to medial prefrontal areas (areas 8B, 9) than to rCMA\textsuperscript{81}. Note that the rACC also receives projections from the DLPFC\textsuperscript{7,73}. The ACC also projects back to the DLPFC. Despite a lack of fully quantitative data, it seems that the anterior part of area 24 (and area 32) project more to the principal sulcus than its caudal part\textsuperscript{51}.

[Fig. 1.2 around here]

This last result suggests that the connectivity patterns between the ACC and the DLPFC differ between cytoarchitectonic areas. Labelled cells often formed clusters and are not evenly distributed across the entire area. Note that the clustering organization of connections may reflect a modular organization of the prefrontal cortex\textsuperscript{50}. For instance area 8B but not area 8A, projects to the rACC\textsuperscript{64,72}. However area 8A is interconnected with pACC and receives afferents from rACC\textsuperscript{1,40,90}. The efferents from area 8A to pACC are limited to two separate clusters, one just anterior to rCMA and one adjacent to the ventral cCMA, that are then defined as cingulate eye field rostral and caudal respectively\textsuperscript{90}. Note that no projection in the cingulate sulcus was found after an injection of isotope specifically in the ventral subdivision of area 8A\textsuperscript{72}. Area 8A and 8B also present different connectivity patterns with other areas of the DLPFC. They are both connected with each other, and with areas 10, 9, 9/46d. However only the rostral part of area 8A is connected with area 46d while area 8B is connected with area 46v\textsuperscript{64,72}. 
ACC receives projections from areas 10, 9, 46 and 9/46d \cite{6,7,43,59,60,72,73,86}. But even within one cytoarchitectonic territory the projections are not even. For instance the connectivity of the ACC with the medial part of areas 9 and area 8B is stronger than with their lateral parts. Indeed while area 8B and the medial area 9 project to both the sulcal and gyral part of the rostral ACC, the lateral part of area 9 only projects to the rostral cingulate sulcus \cite{6,60,72}. The dorsal part of area 46 receives projection from area 32, rACC and pACC, but only the ventral part of area 46 receives afferent inputs, from pACC \cite{1,7}. The projections from area 10 to the ACC are principally targeting the cingulate gyrus and are reported to be organized in columnar manner \cite{73}. Area 10 projections to the cingulate sulcus area are restricted to its more rostral part \cite{73}. Note that only the rACC and area 32 projects back to area 10; no projection from pACC to the frontopolar cortex has been reported \cite{1,6,86}. Finally rACC (at the depth of the cingulate sulcus) and pACC (only the more ventral subdivision) project to 9/46v \cite{66}; only pACC receives inputs from area 9/46v \cite{78}.

This overview of the medio-lateral prefrontal connectivity shows the expected interconnectivity between the different areas but also highlights the complexity of the connection patterns. Consistent with this, a meta-analysis of prefrontal cortex connectivity based on the COCOMAC database (http://cocomac.org/) reveals that the ACC and DLPFC do not simply correspond to two different entities \cite{3} (Fig. 1.2). Instead a cluster analysis suggested that one can consider the medial part of area 9, the cingulate sulcus (24c) and part of the cingulate gyrus (area 24b) as a dorsomedial prefrontal cortex whereas areas 24a and 32 form part of a ventromedial prefrontal cortex. On the lateral surface areas 8A, 46d, lateral part of area 9 formed the dorsolateral cluster.

*Microarchitecture of the medio-lateral prefrontal cortex connectivity*
Not merely the presence of connections, but also their laminar distribution pattern is important. Indeed, it may reflect some key functional properties of the network\textsuperscript{9,17,26,83}. A simplified approach is to consider terminations that principally target layer IV as driving or feedforward projections. Terminations that principally target supragranular (layers I to III) or infragranular layers (layers V and VI) are considered as modulating or feedback projections, respectively. A similar logic could be applied depending on the localization of the cell bodies of efferent projections. If the majority of the cells bodies are found in the supragranular layers or in the infragranular layers, the projections are feedforward or feedback respectively. This hierarchical organization originally proposed for the visual system has been also proposed for the prefrontal cortex\textsuperscript{20}.

As is the case for the presence of the projections, their laminar patterns are also heterogenous. The afferents to rACC (area 24a, b) from area 9 are distributed through the different cortical layers\textsuperscript{1}. But rACC afferents from the principal sulcus are denser in supragranular layers than in the infragranular layers\textsuperscript{1,86}. The same pattern is observed in pACC\textsuperscript{51,86}. However rACC efferences to both area 46 and area 9 are distributed over all cortical layers with a lower density in area IV\textsuperscript{1}. Note that cingulate (area 32) projections to DLPFC originated mainly in the deep layers, layer V and VI\textsuperscript{5}.

A quantitative analysis of connectivity analogous to that applied in interpretation of the neuroanatomy of the visual system\textsuperscript{9,83} might potentially be applied to the study of the prefrontal cortex. Nevertheless the data available concerning ACC-DLPFC connectivity suggest that ACC may modulate DLPFC activity (feedback projections), while the DLPFC may drive ACC activity (feedforward projections). One can go a step further and try to understand how these two structures are interacting at a synaptic level.
At a more microscopic level, the literature is principally concerned with the intrinsic connectivity, i.e. the intra-areal connectivity, of the DLPFC or the ACC each in isolation\textsuperscript{22,23,33,34,61,75}. In a recent experiment Medalla and Barbas addressed the issue of the medio-lateral prefrontal connectivity at a synaptic level\textsuperscript{57}. They injected tracers in areas 32 and 46 and examined the labelled axon terminals in layers I-III of area 9. Both areas predominantly formed single synapses on the spines of spiny dendrites of excitatory cells. However, area 32 had more synapses with inhibitory neurons in area 9 than area 46 had, and the nature of inhibitory neurons receiving afferents from those two pathways was also different. Although the majority of synaptic boutons were of a small size, those from area 32 were bigger than those from area 46 suggesting the synapses had a higher efficacy. The interneurons receiving projections from area 32 are thought to be involved in the enhancement of the signal to noise ratio (calbindin positive cells, or CB cells), or in the enhancement of signals (calretinin positive cells, or CR cells) in highly cognitive demanding situations.

\textit{Medio-lateral prefrontal cortex connectivity in humans}

Our knowledge of connectivity patterns comes principally from studies on animal models. The recent development of the Diffusion Tensor Imaging (DTI) method enables investigation of connectivity in the human brain\textsuperscript{44}. There is a strong similarity in the results obtained with classic labelling (injection of tracers) and DTI\textsuperscript{18,79}. Apart from methods assessing structural connections, functional connectivity and effective connectivity, as assessed using functional magnetic resonance imaging (fMRI), provide another route that could be used to obtain information about the connectivity of the human brain. Functional connectivity is thought to
reflect temporal correlations between areas; effective connectivity refers to the influence of one neural system over another\textsuperscript{80}. Although these can be modulated by polysynaptic connections, patterns of effective and functional connectivity have often been related to direct anatomical connections\textsuperscript{29}.

A recent DTI study in humans confirmed the heterogeneity of the cingulate cortex (Fig. 1.3a). They reported that the ACC could be divided into different regions on the basis of their probability of interconnection with the rest of the brain\textsuperscript{10}. One cluster corresponded to the supracallosal part of the cingulate gyrus (cluster 7), one is likely to include area 32 (cluster 2). Three other clusters correspond to different regions of the cingulate sulcus and paracingulate sulcus. The caudal clusters have been suggested to be the cingulate motor areas (clusters 4 and 5).

Studies of cingulate functional connectivity at rest revealed that ACC activity is correlated with DLPFC activity but again emphasized that parts of the ACC are differently correlated with the DLPFC\textsuperscript{35,53}. The most striking result of a recent study by Margulies et al.\textsuperscript{53} is the difference between ventral and dorsal cingulate regions (Fig. 1.3b). Unfortunately it is difficult to distinguish from the results presented in their study with which different DLPFC regions ACC activity correlates. Nevertheless the caudal ACC (x=5, y=14, z=42, MNI space) did not correlate with the frontopolar cortex while the more anterior ACC did. Two patterns of functionally connectivity with the DLPFC could be observed for anterior regions at coordinates [5 25 36], [5 34 28], and regions at coordinates [5 42 21], [5 47 11]. The two most anterior regions are unlikely to contain the cingulate motor areas and showed less
correlation with the middle frontal gyrus. Note that the cCMA showed also less correlation with the DLPFC than rCMA. Furthermore the DLPFC region showing correlation with cCMA activity was more posterior [-30 37 32] than the one [-28 44 32] for which correlation was observed with rCMA activity.

Not only at rest, but also during the performance of a variety of tasks are the ACC and DLPFC co-activated. Paus and Koski’s meta-analysis of positron emission tomography (PET) studies revealed that supracallosal cingulate cortex activations, more precisely area 24c and 32, were very often associated with activation in the middle frontal cortex. In addition, they distinguished within this supracallosal activity a caudal cingulate region (y<10) in which activations co-occurred more frequently with activations in the precentral gyrus and the medial frontal gyrus than the rostral cingulate region (y>10) did.

For modelling purposes one is probably more interested in effective connectivity than in structural connectivity. Not only co-activation but also interactions have been reported between rCMA and the middle frontal gyrus peaking at (44, 30, 24) while subjects were performing a flanker task. According to Kouneiher et al., interaction between these two regions is related to motivational control, rather than cognitive control. Caudal paracingulate activity predicting behavioral adaptation did not interact with the middle frontal gyrus activity associated with behavioral adjustments.

In summary, resting state functional connectivity confirmed the existence of networks linking the ACC to the DLPFC. They also confirmed the fact that different regions of the ACC are communicating with different regions of the DLPFC (see Fig. 1.3b). Task related activity in fMRI and PET functional studies suggested that a network centered around rCMA and middle frontal gyrus (area 46 and 9/46) is of particular interest.
Beyond the ACC or the DLPFC

We principally focused in this chapter on the ACC and the DLPFC; however we are aware that motivational and cognitive control processes do not simply rely on these two regions. For instance, noadrenergic (NA) and dopaminergic (DA) systems are two systems playing a critical role in cognitive control\(^2,16,39\) (see Chapter 3, this volume).

The locus coeruleus and its two modes of response (tonic/phasic) are proposed to induce alternation between explorative and exploitative behaviors. This structure projects to the entire neocortex and receives projections back from the rACC and adjacent medial prefrontal areas, but not the lateral prefrontal areas\(^2\). The interactions between ACC, DLPFC and the DA system are quite complex. The DA has direct (mesocortical pathway), and indirect influences on the ACC and DLPFC via the striatum (nigrostriatal pathway) or the thalamus (nigrothalamocortical pathway)\(^36,42,91,92\).

The conflict monitoring model developed by Cohen et al. focuses on the effect of DA on the DLPFC, while the model developed by Holroyd and Coles is centered on DA inputs to the ACC\(^16,39\). Nevertheless both of them implied the involvement of the direct mesocortical pathway. While both ACC and DLPFC receive direct DA afferents, there is a regional difference in the origin of the inputs\(^92\). Similarly ACC and DLPFC send sparse projections to the midbrain DA nuclei with a similar spatial organization\(^32\). The DLPFC receives more afferents from more lateral DA midbrain nuclei, the distribution of ACC afferents originates more in the medial midbrain nuclei. The topographic segregation of DLPFC and ACC projections is more obvious in the caudal part of the midbrain nuclei while they tend to overlap more anteriorly.
This anatomical compartmentalization could reflect a functional compartmentalization. Indeed in recent study Brischoux et al. found some functional differences between dorsal and ventral VTA in rats\textsuperscript{14}, and along a dorso-ventral axis in monkeys DA midbrain nuclei\textsuperscript{56}. Some DA cells discharge preferentially for positive outcome related events\textsuperscript{14,28,56,82} but some DA cells discharge also, or preferentially for negative events\textsuperscript{14,56}. Earlier studies also reported functional heterogeneity in VTA/SN cells. Not only were cells found that discharged to visual or outcome related events but also cells that discharged to arm or mouth movement\textsuperscript{24,62}. Finally, although often described as relatively independent systems, it has been shown that non DA and DA VTA cells projects to the LC\textsuperscript{19} and LC cells are also projecting to the VTA\textsuperscript{27}. Furthermore stimulation of VTA cells induces discharge of LC cells\textsuperscript{19}.

Altogether the topographic segregation of mesocortical projections and the heterogeneity of DA cell activities may have to be taken into account in refining models of cognitive control. More specifically, the existence of VTA cells encoding either appetitive or aversive cues may need to be implemented in models such as those proposed by Holroyd and Coles\textsuperscript{39}.

Conclusion

Our intention was to propose some comments on computational models of control on the basis of a review of neuroanatomical data. Reviewing this literature reveals not only the huge amount of work that has been done but also the huge amount of work that remains to be done. There is still discussion about the identities of the principal subdivisions of the macaque brain, the most frequently used model for understanding the architecture of the
human brain, and quantitative analysis of prefrontal cortex connectivity remains largely to be done. Nevertheless we suggest, on the basis on anatomical connectivity studies in monkeys and functional and effective connectivity studies in humans that models of cognitive control might incorporate more precisely descriptions of regions than just “ACC” and “DLPFC”.
Outstanding questions

• What is the detailed topography of medio-lateral prefrontal connections, both at meso- and microscopic levels?

• What, if any, is the correspondence between the primate and the rat medial prefrontal cortex and dorsolateral prefrontal cortex?
Further reading

A comprehensive volume for more detailed reviews of cingulate structures and functions.

This book gives a nice overview of the major fiber pathways in the primate brain.

The first comprehensive overview of diffusion MRI techniques and their applications.
References


hierarchical rank and indicates the operation of a distance rule. J Neurosci 20:3263-3281.


Figure captions

**Figure 1.1** Cartography of medial and lateral prefrontal cortex. (a) Cytoarchitecture maps of human (top) and monkey (bottom) medial prefrontal cortex; adapted from Vogt et al.\(^\text{84,88}\). (b) Cytoarchitecture maps of human (top) and monkey (bottom) lateral prefrontal cortex; adapted from Petrides and Pandya\(^\text{70}\). The dashed lines on the left and right figures correspond to the boundaries of the ACC and DLPFC, respectively. VCA = vertical line through the anterior commissure.

**Figure 1.2** Connectivity of medial and lateral prefrontal cortex. (a) Schematic representation of the intra and interconnections between cytoarchitectonic areas of medial and lateral prefrontal cortex (b) Clustering of prefrontal areas based on their connectivity patterns, adapted from Averbeck and Seo\(^3\). (c) Profile of inputs characterizing the 5 clusters illustrated in (b). The y axis corresponds to the proportion of the connections. The top row represents the prefrontal interconnections; the bottom row corresponds to connections with extraprefrontal systems, adapted from Averbeck and Seo\(^3\). Note that DMPFC-DLPFC interconnections represent only between 20-30% of their prefrontal connections; connections that are themselves a subset of the total connections of these clusters.

**Figure 1.3.** Connectivity-based parcellation and functional connectivity at rest of the human cingulate cortex. (a) Connectivity-based parcellation of human ACC, adapted from Beckmann et al.\(^\text{11}\). The ACC (/MCC) corresponds to clusters 2, 3, 4, 5 and part of cluster 7. (b) Functional connectivity at rest of cingulate regions, adapted from Margulies et al.\(^\text{53}\). Positive correlations \(p < 0.05\), corrected of different cingulate regions, or seeds (represented on the
medial view) are shown in black on cortical surface maps for superior (s3, s4, s5, s6, s7) and inferior seeds (i3, i6). Inferior seeds are located 5 mm from the corpus callosum starting at $y = -10$ mm and spaced 10 mm apart along the curve parallel to the corpus callosum. Superior seeds are located 15 mm from the corpus callosum along the radial axis from each of the first seven inferior seeds.
Figure 1.1
Figure 1.2
Figure 1.3

(a) CMAc, CMAr

(b) Clusters 1 to 9 with brain sections labeled s3 to s7 and i3 to i6, showing significance level p < 0.05, corrected.