1 Neuroanatomical Basis 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

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,[58] while medial frontal areas, again especially ACC, participate in performance monitoring, action evaluation and detection of events that indicate the need for behavioral adaptation and action revaluation.[75,76] Furthermore different hierarchical levels of cognitive control are thought to be supported by different prefrontal subdivisions.[4,46,47,68]

One prominent example of framework of control is the conflict model proposed by Cohen et al.[15] 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[11] or indirect.[15] 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.[14] A rather different model, based on the principles of reinforcement learning has been proposed by Holroyd and Coles and ascribes to the ACC a role in action selection[37,38] in response to a dopaminergic teaching signal.[38] For simplicity's sake these models either supposed the existence of a homogenous ACC and DLPFC, or else they are focused 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,[11,14,15] while in other cases it is from the DLPFC to the ACC.[38]

A feature of these computational models is that they often do not consider all aspects of the underlying neuroanatomy of these cortical regions. However, a more detailed analysis of the connections between these brain areas may be of extreme importance to the functionality of models. Indeed, as Passingham et al. suggest, each cytoarchitectonic area has a unique connectivity pattern that is likely to be related to its function.[65] 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 review neuroanatomical data concerning two key nodes in cognitive and motivational control models, the ACC and the DLPFC. Our aim is to review neuroanatomical data related to these two regions in the hope that it may help improve our understanding of control networks and how structures within these networks are interacting. Furthermore, we 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

Though both terms are commonly used, neither ACC nor DLPFC corresponds to a unique cortical area. They refer to a collection of areas (or subareas) with distinct cytoarchitectonic properties and connectivity profiles.

The abbreviation ACC commonly refers to cytoarchitectonic areas 24 and 32 (figure 1.1a). Based on cytoarchitectural properties and 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,[53,54,61,88] or lies just ventrally to the bottom of the cingulate sulcus.[12,20,87] Vogt et al. consider that most of the cortex on the dorsal bank of the cingulate sulcus belongs to the adjacent medial frontal cortex.[87] Area 32 is located rostrally to area 24. Petrides and Pandya proposed that the latter area extended caudally to form, on the dorsal bank of the cingulate sulcus, a transition area between the ACC and the medial prefrontal cortex.[68] Some disagreement also exists over 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,[8] or at least the area 24c subdivision,[20] was dysgranular. Similar discrepancies also exist concerning the number of subdivisions of the ACC. Various studies find from four to nine subdivisions[54,87] in ACC area 24. Vogt et al. divide area 24 into an anterior division (the ACC) and a posterior division, which they call the midcingulate cortex (MCC).[87] The ACC then corresponds to areas 24a, b, and c; the MCC corresponds to subdivisions 24a′, b′, c′, and d.

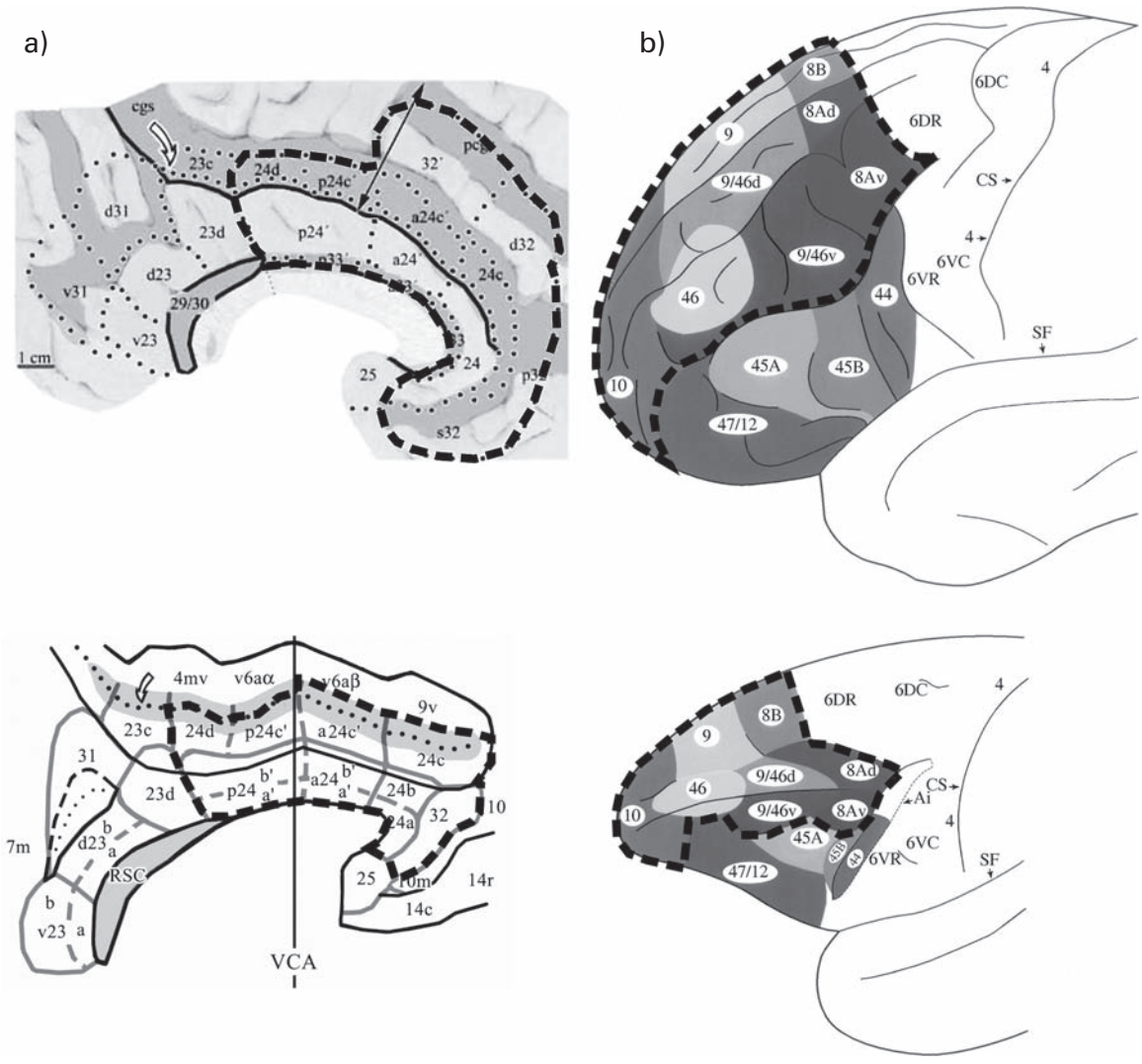


Figure 1.1
Cartography of medial and lateral prefrontal cortex. (a) Cytoarchitecture maps of human (top) and monkey (bottom) medial prefrontal cortex (adapted from Vogt et al.[83,87] by permission of Oxford University Press). (b) Cytoarchitecture maps of human (top) and monkey (bottom) lateral prefrontal cortex (adapted from Petrides and Pandya[69]). 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.

Although most of these debates have concerned the nature of ACC in the macaque, similar debates concern the human ACC. The presence of an additional sulcus known as the paracingulate sulcus, dorsal to the cingulate sulcus, further complicates the problem.[84] This sulcus is present in only 30 to 60% of cases[29] and, when present, shows highly variable morphology across individuals.[84] The morphology of the paracingulate sulcus affects the extent of areas 24 and 32 and is suggested to be related to performance in demanding cognitive tasks.[30] One hypothesis explaining the interindividual differences in sulcal anatomy is that they reflects differences in the connectivity between dorsal ACC and DLPFC.[30] As in monkeys, several subdivisions of the area 24 can be distinguished, and a similar organization has been proposed[63,86] (figure 1.1a).

The DLPFC is also a heterogenous region (figure 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, including transition areas around the lip of the principal sulcus and subdivisions based on the position in the principal sulcus. Those areas are labeled area 9/46 dorsal and ventral,[68,69] and a distinction is often made between area 46 ventral and dorsal.[3,7] Finally, area 8 is subdivided into area 8A, located at the level of the genu of the arcuate sulcus, and area 8B dorsal to it.

As is immediately apparent, the human lateral prefrontal cortex is more folded than that of the monkey (figure 1.1b). Instead of one sulcus (the principal sulcus), there are three: the superior frontal sulcus, the complex intermediate frontal sulcus, and the inferior frontal sulcus.[70] 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 similar organization of the DLPFC.[69]

Connectivity of ACC and DLPFC

Mediolateral Prefrontal Cortex Connectivity in Monkeys

Before discussing DLPFC-ACC connectivity, it is important to underline the fact that it is difficult to perfectly describe the relationships between cingulate cytoarchitectonic areas and connectivity patterns. 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.[51,59,73] In the interest of clarity, we consider the portion of area 24 that includes all the cingulate motor areas as the pos-

terior ACC (pACC). Area 24 rostral to pACC is referred to as the rostral ACC (rACC). Connectivity of area 32 is considered separately.

A number of models of control emphasize interactions between ACC and DLPFC.[11,14] Surprisingly, the emphasis on the ACC-DLPFC functional relationships in fact relies on relatively weak anatomical connections (figure 1.2). For instance, pACC receives roughly 20 to 40 times more projections from the preSMA and cCMA than from area 46,[36] and area 46 projects more to medial prefrontal areas (areas 8B, 9) than to rCMA.[80] Note that the rACC also receives projections from the DLPFC,[7,72] and the ACC projects back to the DLPFC. Despite a lack of fully quantitative data, the anterior part of area 24 (and area 32) seems to project more to the principal sulcus than its caudal part.[50]

This last result suggests that the connectivity patterns between the ACC and the DLPFC differ between cytoarchitectonic areas. Labeled cells often form 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.[49] For instance, area 8B but not area 8A projects to the rACC.[64,71] However, area 8A is interconnected with pACC and receives afferents from rACC.[1,39,89] 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.[89] Note that no projection in the cingulate sulcus was found after an injection of isotope specifically in the ventral subdivision of area 8A.[71] Areas 8A and 8B also present different connectivity patterns with other areas of the DLPFC. They are connected to each other as well as to areas 10, 9, and 9/46d; however, only the rostral part of area 8A is connected with area 46d, whereas area 8B is connected with area 46v.[64,71]

ACC receives projections from areas 10, 9, 46, and 9/46d.[6,7,42,59,60,71,72,85] 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 8B is stronger than that with their lateral parts. Indeed, while area 8B and 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.[6,60,71] 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.[1,7] The projections from area 10 to the ACC principally target the cingulate gyrus and are reported to be organized in columnar manner.[72] Area 10 projections to the cingulate sulcus area are restricted to its more rostral part.[72] Note that only the rACC and area 32 project back to area 10; no projection from pACC to the frontopolar cortex has been reported.[1,6,85] Finally, rACC (at the depth of the cingulate sulcus) and pACC (only the more ventral subdivision) project to 9/46v[66]; only pACC receives inputs from area 9/46v.[77]

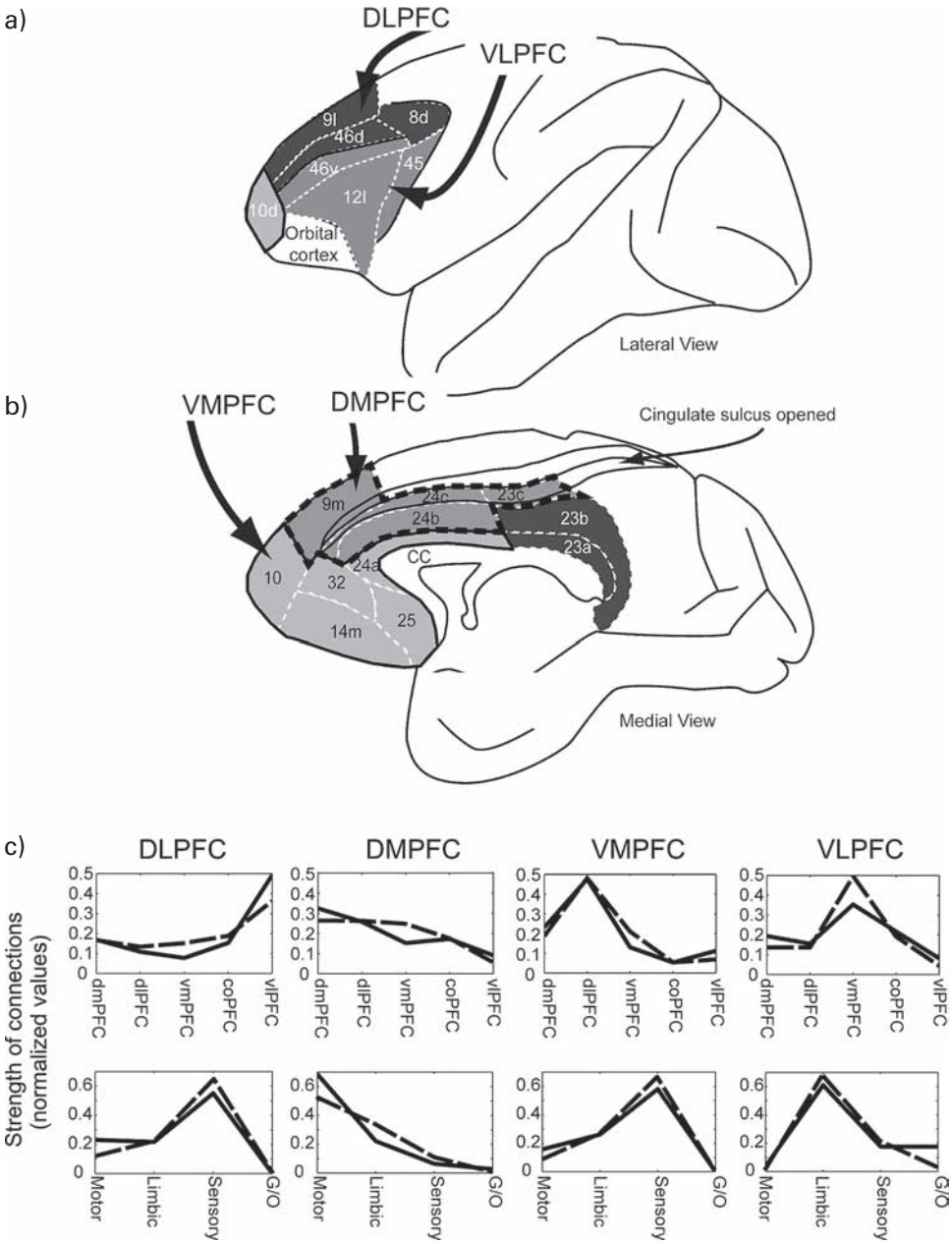


Figure 1.2
Connectivity of medial and lateral prefrontal cortex. (a,b) Lateral (a) and medial (b) view of macaque prefrontal areas. Clustering of prefrontal areas based on their connectivity patterns (adapted from Averbeck and Seo[3]). (c) Profile of inputs characterizing the five clusters illustrated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

This overview of the mediolateral 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[3] (figure 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, and the lateral part of area 9 form the dorsolateral cluster.

Microarchitecture of Mediolateral 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.[9,16,25,82] 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 V and VI) layers 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 cell 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 proposed for the prefrontal cortex as well.[19]

As is the case for the presence of the projections, their laminar patterns are also heterogenous. The afferents to rACC (areas 24a, b) from area 9 are distributed throughout the different cortical layers.[1] But rACC afferents from the principal sulcus are denser in supragranular layers than in the infragranular layers.[1,85] The same pattern is observed in pACC.[50,85] However, rACC efferences to both areas 46 and 9 are distributed over all cortical layers with a lower density in area IV.[1] Note that cingulate (area 32) projections to DLPFC originate mainly in the deep layers, layer V and VI.[5]

A quantitative analysis of connectivity analogous to that applied in interpreting the neuroanatomy of the visual system[9,82] 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, that is, the intra-areal connectivity, of the DLPFC or the ACC

each in isolation.[21,22,32,33,61,74] In recent experiments, Medalla and Barbas addressed the issue of the mediolateral prefrontal connectivity at a synaptic level.[56,57] In a first experiment they injected tracers in areas 32 and 46 and examined the labeled axon terminals in layers I through III of area 9.[56] 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 small, 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 demanding cognitive situations. In their subsequent experiment Medalla and Barbas also investigated area 32 connectivity with area 10.[57] Area 32 is also connected with area 10; however, some features of the pathway were distinct from the one that links area 32 and area 46. For instance, area 32 projections largely target the area 10 excitatory cells. This suggests that, instead of enhancing inhibition, area 32 enhances excitatory activities in area 10. These results highlight the importance not only of inferring the existence of connections, but also of understanding the nature of these connections.

Mediolateral 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.[43] There is a strong similarity between the results obtained with classic labeling (injection of tracers) and those obtained with DTI.[17,78] Apart from methods assessing structural connections, functional connectivity and effective connectivity, as assessed using functional magnetic resonance imaging (fMRI), provide another route to 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.[79] Although these can be modulated by polysynaptic connections, patterns of effective and functional connectivity have often been related to direct anatomical connections.[28]

A recent DTI study in humans confirmed the heterogeneity of the cingulate cortex (figure 1.3a). The study reported that the ACC could be divided into different regions on the basis of their probability of interconnection with the rest of the brain.[10] One cluster corresponded to the supracallosal part of the cingulate gyrus (cluster 7), and one is likely to include area 32 (cluster 2). Three other clusters correspond to different regions of the cingulate sulcus and paracingulate sulcus.

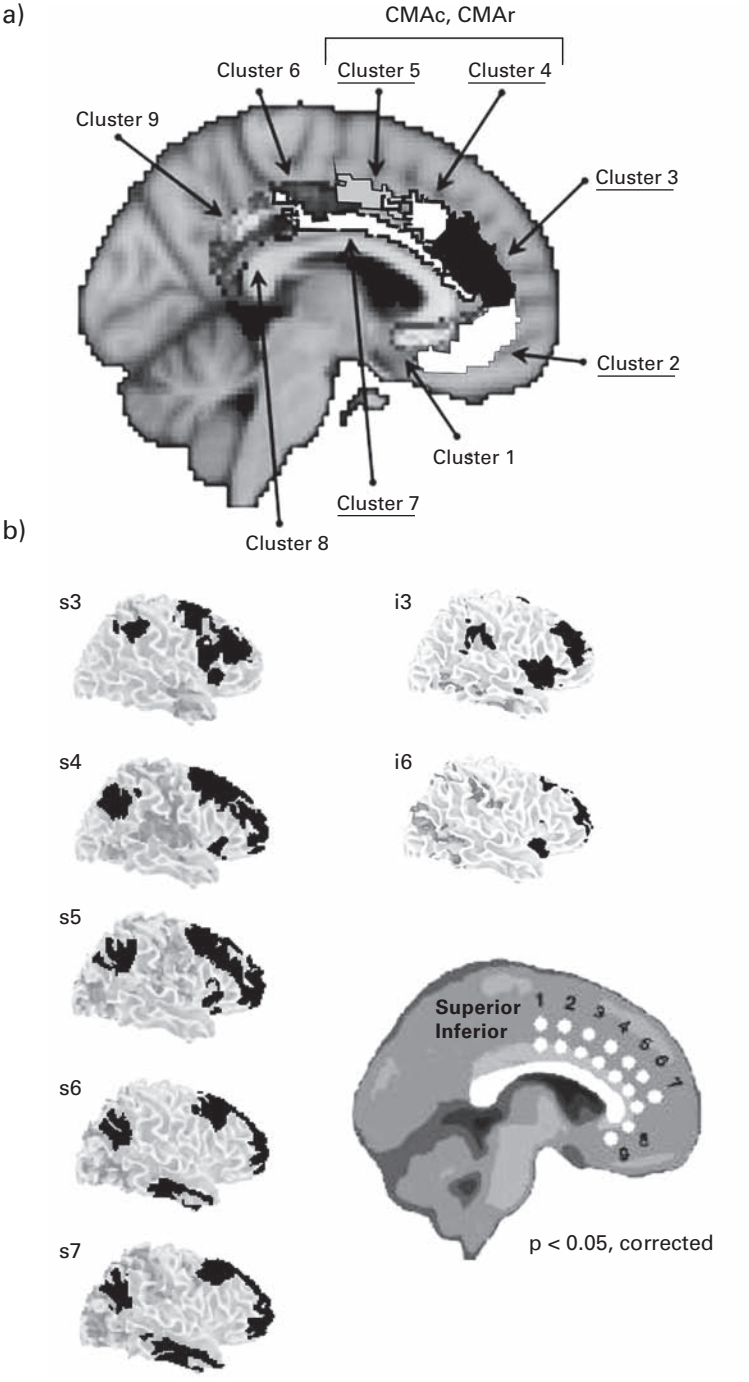
The caudal clusters have been suggested to be the cingulate motor areas (clusters 4 and 5).

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.[34,52] The most striking result of a recent study by Margulies et al.[52] is the difference between ventral and dorsal cingulate regions (figure 1.3b). Unfortunately, it is difficult to infer 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 whereas the more anterior ACC did. Two patterns of functional 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 also showed 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.[34]

Not only at rest, but also during the performance of a variety of tasks are the ACC and DLPFC coactivated. 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.[47] 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 was the case for the more rostral cingulate region (y > 10) did.

For modeling purposes, one is probably more interested in effective connectivity than in structural connectivity. Not only coactivation 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.[24] According to Kouneiher et al.,[48] 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 adjustements.[40,44,45]

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


a)
CMAc, CMAr
Cluster 6
Cluster 5
Cluster 4
Cluster 9
Cluster 3
Cluster 2
Cluster 1
Cluster 7
Cluster 8
b)
s3
i3
s4
i6
s5
s6
s7
Superior
Inferior
1
2
3
4
5
6
7
8
9
p < 0.05, corrected

Beyond the ACC or the DLPFC

This chapter principally focused 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, noradrenergic (NA) and dopaminergic (DA) systems both play a critical role in cognitive control[2,15,38] (see chapter 3, this volume).

The locus coeruleus and its two modes of response (tonic and 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).[35,41,90,91]

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.[15,38] Nevertheless, both of them implied the involvement of the direct mesocortical pathway. Though both ACC and DLPFC receive direct DA afferents, there is a regional difference in the origin of the inputs.[91] Similarly, ACC and DLPFC send sparse projections to the midbrain DA nuclei with a similar spatial organization.[31] 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 a recent study, Brischoux et al. found some functional differences between dorsal and ventral VTA in rats[13] and along a dorsoventral axis in monkeys DA midbrain nuclei.[55] Some DA cells discharge preferentially for positive outcome related events,[13,27,55,80] but some DA cells discharge also, or preferentially for negative events.[13,55] Earlier studies also reported functional heterogeneity in VTA/SN

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.[10]). 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.[52]). 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.

cells. Not only were cells that discharged to visual or outcome-related events found, but also cells that discharged to arm or mouth movement.[23,62] Finally, although often described as relatively independent systems, non-DA and DA VTA cells have been shown to project to the LC,[18] and LC cells also project to the VTA.[26] Furthermore, stimulation of VTA cells induces discharge of LC cells.[18]

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.[38]

Conclusion

Our intention was to propose some comments on computational models of control based on 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. The identities of the principal subdivisions of the macaque brain, the most frequently used model for understanding the architecture of the human brain, are still being discussed, and quantitative analysis of prefrontal cortex connectivity remains largely to be done. Nevertheless, we suggest, on the basis of anatomical connectivity studies in monkeys and functional and effective connectivity studies in humans that models of cognitive control might more precisely incorporate descriptions of regions than just "ACC" and "DLPFC."

Outstanding Questions

- What is the detailed topography of mediolateral prefrontal connections, at both 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

Vogt BA, ed. 2009. Cingulate Neurobiology and Disease. Oxford: Oxford University Press. A comprehensive volume for more detailed reviews of cingulate structures and functions.

Schmahmann JD, Pandya DN. 2006. Fiber Pathways of the Brain. Oxford: Oxford University Press. This book gives a nice overview of the major fiber pathways in the primate brain.

Johansen-Berg H, Behrens TEJ, eds. 2009. Diffusion MRI: From Quantitative Measurement to In-Vivo Neuroanatomy. Amsterdam: Academic Press. The first comprehensive overview of diffusion MRI techniques and their applications.

References

1. Arikuni T, Sako H, Murata A. 1994. Ipsilateral connections of the anterior cingulate cortex with the frontal and medial temporal cortices in the macaque monkey. *Neurosci Res* 21: 19–39.

2. Aston-Jones G, Cohen JD. 2005. Adaptive gain and the role of the locus coeruleus-norepinephrine system in optimal performance. *J Comp Neurol* 493: 99–110.

3. Averbeck BB, Seo M. 2008. The statistical neuroanatomy of frontal networks in the macaque. *PLOS Comput Biol* 4: e1000050.

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

5. Barbas H. 1986. Pattern in the laminar origin of corticocortical connections. *J Comp Neurol* 252: 415–422.

6. Barbas H, Ghashghaei H, Dombrowski SM, Rempel-Clower NL. 1999. Medial prefrontal cortices are unified by common connections with superior temporal cortices and distinguished by input from memory-related areas in the rhesus monkey. *J Comp Neurol* 410: 343–367.

7. Barbas H, Pandya DN. 1989. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *J Comp Neurol* 286: 353–375.

8. Barbas H, Zikopoulos B. 2007. The prefrontal cortex and flexible behavior. *Neuroscientist* 13: 532–545.

9. Barone P, Batardiere A, Knoblauch K, Kennedy H. 2000. Laminar distribution of neurons in extrastriate areas projecting to visual areas V1 and V4 correlates with the hierarchical rank and indicates the operation of a distance rule. *J Neurosci* 20: 3263–3281.

10. Beckmann M, Johansen-Berg H, Rushworth MF. 2009. Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *J Neurosci* 29: 1175–1190.

11. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. 2001. Conflict monitoring and cognitive control. *Psychol Rev* 108: 624–652.

12. Bozkurt A, Zilles K, Schleicher A, Kamper L, Arigita ES, Uylings HB, Kotter R. 2005. Distributions of transmitter receptors in the macaque cingulate cortex. *Neuroimage* 25: 219–229.

13. Brischoux F, Chakraborty S, Brierley DI, Ungless MA. 2009. Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proc Natl Acad Sci USA* 106: 4894–4899.

14. Brown JW, Braver TS. 2005. Learned predictions of error likelihood in the anterior cingulate cortex. *Science* 307: 1118–1121.

15. Cohen JD, Aston-Jones G, Gilzenrat MS. (2004) A systems-level perspective on attention and cognitive control. In: Cognitive Neuroscience of Attention (Posner MI, ed), pp 71–90. New York: Guilford.

16. Crick F, Koch C. 1998. Constraints on cortical and thalamic projections: the no-strong-loops hypothesis. *Nature* 391: 245–250.

17. Croxson PL, Johansen-Berg H, Behrens TE, Robson MD, Pinsk MA, Gross CG, Richter W, Richter MC, Kastner S, Rushworth MF. 2005. Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. *J Neurosci* 25: 8854–8866.

18. Deutch AY, Goldstein M, Roth RH. 1986. Activation of the locus coeruleus induced by selective stimulation of the ventral tegmental area. *Brain Res* 363: 307–314.

19. Dombrowski SM, Hilgetag CC, Barbas H. 2001. Quantitative architecture distinguishes prefrontal cortical systems in the rhesus monkey. *Cereb Cortex* 11: 975–988.

20. Dum RP, Strick PL. 1991. The origin of corticospinal projections from the premotor areas in the frontal lobe. *J Neurosci* 11: 667–689.

21. Elston GN, Benavides-Piccione R, Defelipe J. 2005. A study of pyramidal cell structure in the cingulate cortex of the macaque monkey with comparative notes on inferotemporal and primary visual cortex. *Cereb Cortex* 15: 64–73.

22. Elston GN, Benavides-Piccione R, Elston A, Zietsch B, Defelipe J, Manger P, Casagrande V, Kaas JH. 2006. Specializations of the granular prefrontal cortex of primates: implications for cognitive processing. *Anat Rec A Discov Mol Cell Evol Biol* 288: 26–35.

23. Fabre M, Rolls ET, Ashton JP, Williams G. 1983. Activity of neurons in the ventral tegmental region of the behaving monkey. *Behav Brain Res* 9: 213–235.

24. Fan J, Hof PR, Guise KG, Fossella JA, Posner MI. 2008. The functional integration of the anterior cingulate cortex during conflict processing. *Cereb Cortex* 18: 796–805.

25. Felleman DJ, Van Essen DC. 1991. Distributed hierarchical processing in the primate cerebral cortex. *Cereb Cortex* 1: 1–47.

26. Fields HL, Hjelmstad GO, Margolis EB, Nicola SM. 2007. Ventral tegmental area neurons in learned appetitive behavior and positive reinforcement. *Annu Rev Neurosci* 30: 289–316.

27. Fiorillo CD, Tobler PN, Schultz W. 2003. Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* 299: 1898–1902.

28. Fonteijn HM, Norris DG, Verstraten FA. 2008. Exploring the anatomical basis of effective connectivity models with DTI-based fiber tractography. *Int J Biomed Imaging* 2008: 423192.

29. Fornito A, Whittle S, Wood SJ, Velakoulis D, Pantelis C, Yucel M. 2006. The influence of sulcal variability on morphometry of the human anterior cingulate and paracingulate cortex. *Neuroimage* 33: 843–854.

30. Fornito A, Yucel M, Wood S, Stuart GW, Buchanan JA, Proffitt T, Anderson V, Velakoulis D, Pantelis C. 2004. Individual differences in anterior cingulate/paracingulate morphology are related to executive functions in healthy males. *Cereb Cortex* 14: 424–431.

31. Frankle WG, Laruelle M, Haber SN. 2006. Prefrontal cortical projections to the midbrain in primates: evidence for a sparse connection. *Neuropsychopharmacology* 31: 1627–1636.

32. Gabbott PL, Bacon SJ. 1996. Local circuit neurons in the medial prefrontal cortex (areas 24a,b,c, 25 and 32) in the monkey: I. Cell morphology and morphometrics. *J Comp Neurol* 364: 567–608.

33. Gabbott PL, Bacon SJ. 1996. Local circuit neurons in the medial prefrontal cortex (areas 24a,b,c, 25 and 32) in the monkey: II. Quantitative areal and laminar distributions. *J Comp Neurol* 364: 609–636.

34. Habas C. 2010. Functional connectivity of the human rostral and caudal cingulate motor areas in the brain resting state at 3T. *Neuroradiology* 52: 47–59.

35. Haber SN, Fudge JL, McFarland NR. 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 20: 2369–2382.

36. Hatanaka N, Tokuno H, Hamada I, Inase M, Ito Y, Imanishi M, Hasegawa N, Akazawa T, Nambu A, Takada M. 2003. Thalamocortical and intracortical connections of monkey cingulate motor areas. *J Comp Neurol* 462: 121–138.

37. Holroyd C, Nieuwenhuis S, Mars RB, Coles MGH. 2004. Anterior cingulate cortex, selection for action, and error processing. In: Cognitive Neuroscience of Attention (Posner MI, ed), pp 219–231. New York: Guilford Press.

38. Holroyd CB, Coles MG. 2002. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol Rev* 109: 679–709.

39. Huerta MF, Krubitzer LA, Kaas JH. 1987. Frontal eye field as defined by intracortical microstimulation in squirrel monkeys, owl monkeys, and macaque monkeys. II. Cortical connections. *J Comp Neurol* 265: 332–361.

40. Hyafil A, Summerfield C, Koechlin E. 2009. Two mechanisms for task switching in the prefrontal cortex. *J Neurosci* 29: 5135–5142.

41. Ilinsky IA, Jouandet ML, Goldman-Rakic PS. 1985. Organization of the nigrothalamocortical system in the rhesus monkey. *J Comp Neurol* 236: 315–330.

42. Jacobson S, Trojanowski JQ. 1977. Prefrontal granular cortex of the rhesus monkey. I. Intrahemispheric cortical afferents. *Brain Res* 132: 209–233.

43. Johansen-Berg H, Rushworth MF. 2009. Using diffusion imaging to study human connectional anatomy. *Annu Rev Neurosci* 32: 75–94.

44. Kerns JG. 2006. Anterior cingulate and prefrontal cortex activity in an FMRI study of trial-to-trial adjustments on the Simon task. *Neuroimage* 33: 399–405.

45. Kerns JG, Cohen JD, MacDonald AW, 3rd, Cho RY, Stenger VA, Carter CS. 2004. Anterior cingulate conflict monitoring and adjustments in control. *Science* 303: 1023–1026.

46. Koechlin E, Ody C, Kouneiher F. 2003. The architecture of cognitive control in the human prefrontal cortex. *Science* 302: 1181–1185.

47. Koski L, Paus T. 2000. Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Exp Brain Res* 133: 55–65.

48. Kouneiher F, Charron S, Koechlin E. 2009. Motivation and cognitive control in the human prefrontal cortex. *Nat Neurosci* 12: 939–945.

49. Lewis DA, Melchitzky DS, Burgos GG. 2002. Specificity in the functional architecture of primate prefrontal cortex. *J Neurocytol* 31: 265–276.

50. Lu MT, Preston JB, Strick PL. 1994. Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. *J Comp Neurol* 341: 375–392.

51. Luppino G, Matelli M, Camarda RM, Gallese V, Rizzolatti G. 1991. Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: an intracortical microstimulation study in the macaque monkey. *J Comp Neurol* 311: 463–482.

52. Margulies DS, Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. 2007. Mapping the functional connectivity of anterior cingulate cortex. *Neuroimage* 37: 579–588.

53. Matelli M, Luppino G, Rizzolatti G. 1985. Patterns of cytochrome oxidase activity in the frontal agranular cortex of the macaque monkey. *Behav Brain Res* 18: 125–136.

54. Matelli M, Luppino G, Rizzolatti G. 1991. Architecture of superior and mesial area 6 and the adjacent cingulate cortex in the macaque monkey. *J Comp Neurol* 311: 445–462.

55. Matsumoto M, Hikosaka O. 2009. Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature* 459: 837–841.

56. Medalla M, Barbas H. 2009. Synapses with inhibitory neurons differentiate anterior cingulate from dorsolateral prefrontal pathways associated with cognitive control. *Neuron* 61: 609–620.

57. Medalla M, Barbas H. 2010. Anterior cingulate synapses in prefrontal areas 10 and 46 suggest differential influence in cognitive control. *J Neurosci* 30: 16068–16081.

58. Miller EK, Cohen JD. 2001. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 24: 167–202.

59. Morecraft RJ, Tanji J. 2009. Cingulofrontal interactions and the cingulate motor areas. In: Cingulate Neurobiology and Disease (Vogt B, ed), pp 113–144. Oxford: Oxford University Press.

60. Morris R, Pandya DN, Petrides M. 1999. Fiber system linking the mid-dorsolateral frontal cortex with the retrosplenial/presubicular region in the rhesus monkey. *J Comp Neurol* 407: 183–192.

61. Nimchinsky EA, Hof PR, Young WG, Morrison JH. 1996. Neurochemical, morphologic, and laminar characterization of cortical projection neurons in the cingulate motor areas of the macaque monkey. *J Comp Neurol* 374: 136–160.

62. Nishino H, Ono T, Muramoto K, Fukuda M, Sasaki K. 1987. Neuronal activity in the ventral tegmental area (VTA) during motivated bar press feeding in the monkey. *Brain Res* 413: 302–313.

63. Palomero-Gallagher N, Vogt BA, Schleicher A, Mayberg HS, Zilles K. 2009. Receptor architecture of human cingulate cortex: evaluation of the four-region neurobiological model. *Hum Brain Mapp* 30: 2336–2355.

64. Pandya DN, Yeterian EH. 1998. Comparison of prefrontal architecture and connections. In: The Prefrontal Cortex. Executive and Cognitive Functions (Roberts AC, Robbins TW, Weiskrantz L, eds), pp 51–66. New York: Oxford University Press.

65. Passingham RE, Stephan KE, Kotter R. 2002. The anatomical basis of functional localization in the cortex. *Nat Rev Neurosci* 3: 606–616.

66. Petrides M. 2002. The mid-ventrolateral prefrontal cortex and active mnemonic retrieval. *Neurobiol Learn Mem* 78: 528–538.

67. Petrides M. 2005. Lateral prefrontal cortex: architectonic and functional organization. *Philos Trans R Soc Lond B Biol Sci* 360: 781–795.

68. Petrides M, Pandya DN. 1994. Comparative architectonic analysis of the human and the macaque frontal cortex. In: Handbook of Neuropsychology (Boller F, Grafman J, eds), pp 17–58: Amsterdam: Elsevier Science.

69. Petrides M, Pandya DN. 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur J Neurosci* 11: 1011–1036.

70. Petrides M, Pandya DN. 2004. The frontal cortex. In: The Human Nervous System, 2nd ed. (Paxinos G, Mai JK, eds), pp 950–972: Amsterdam: Elsevier.

71. Petrides M, Pandya DN. 2006. Efferent association pathways originating in the caudal prefrontal cortex in the macaque monkey. *J Comp Neurol* 498: 227–251.

72. Petrides M, Pandya DN. 2007. Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. *J Neurosci* 27: 11573–11586.

73. Picard N, Strick PL. 1996. Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* 6: 342–353.

74. Pucak ML, Levitt JB, Lund JS, Lewis DA. 1996. Patterns of intrinsic and associational circuitry in monkey prefrontal cortex. *J Comp Neurol* 376: 614–630.

75. Quilodran R, Rothe M, Procyk E. 2008. Behavioral shifts and action valuation in the anterior cingulate cortex. *Neuron* 57: 314–325.

76. Rushworth MF, Behrens TE. 2008. Choice, uncertainty and value in prefrontal and cingulate cortex. *Nat Neurosci* 11: 389–397.

77. Schmahmann JD, Pandya DN. 2006. Fiber Pathways of the Brain. Oxford: Oxford University Press.

78. Schmahmann JD, Pandya DN, Wang R, Dai G, D'Arceuil HE, de Crespigny AJ, Wedeen VJ. 2007. Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. *Brain* 130: 630–653.

79. Sporns O. 2009. The human connectome: linking structure and function in the human brain. In: Diffusion MRI (Johansen-Berg H, Behrens T, eds). London: Academic Press.

80. Takada M, Nambu A, Hatanaka N, Tachibana Y, Miyachi S, Taira M, Inase M. 2004. Organization of prefrontal outflow toward frontal motor-related areas in macaque monkeys. *Eur J Neurosci* 19: 3328–3342.

81. Tobler PN, Fiorillo CD, Schultz W. 2005. Adaptive coding of reward value by dopamine neurons. *Science* 307: 1642–1645.

82. Vezoli J, Falchier A, Jouve B, Knoblauch K, Young M, Kennedy H. 2004. Quantitative analysis of connectivity in the visual cortex: extracting function from structure. *Neuroscientist* 10: 476–482.

83. Vogt BA, ed. 2009. Cingulate Neurobiology and Disease. Oxford: Oxford University Press.

84. Vogt BA, Nimchinsky EA, Hof PR. 1995. Human cingulate cortex: surface features, flat maps, and cytoarchitecture. *J Comp Neurol* 359: 490–506.

85. Vogt BA, Pandya DN. 1987. Cingulate cortex of the rhesus monkey: II. Cortical afferents. *J Comp Neurol* 262: 271–289.

86. Vogt BA, Vogt L. 2003. Cytology of human dorsal midcingulate and supplementary motor cortices. *J Chem Neuroanat* 26: 301–309.

87. Vogt BA, Vogt L, Farber NB, Bush G. 2005. Architecture and neurocytology of monkey cingulate gyrus. *J Comp Neurol* 485: 218–239.

88. Volz HP, Rzanny R, May S, Hegewald H, Preussler B, Hajek M, Kaiser WA, Sauer H. 1997. 31P magnetic resonance spectroscopy in the dorsolateral prefrontal cortex of schizophrenics with a volume selective technique—preliminary findings. *Biol Psychiatry* 41: 644–648.

89. Wang Y, Shima K, Isoda M, Sawamura H, Tanji J. 2002. Spatial distribution and density of prefrontal cortical cells projecting to three sectors of the premotor cortex. *Neuroreport* 13: 1341–1344.

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

91. Williams SM, Goldman-Rakic PS. 1998. Widespread origin of the primate mesofrontal dopamine system. *Cereb Cortex* 8: 321–345.

2 Neural Circuits of Reward and Decision Making: Integrative Networks across Corticobasal Ganglia Loops

Suzanne N. Haber

Anatomical connectivity studies provide a key element for understanding the neural networks involved in evaluating environmental stimuli that transform this information into actions, thus leading to expected outcomes. The reward circuit is a central component of the network that drives incentive-based learning, appropriate responses to stimuli, and good decision making. The idea that there is an anatomically identifiable reward circuit initially came from experiments that demonstrated rats would work for electrical stimulation in specific brain sites[51] and was later supported by pharmacological manipulation of those sites through intracranial injections of drugs of abuse.[8] Although this circuit included several brain regions, the orbital (OFC) and anterior cingulate cortices (ACC), the n. accumbens (NAcc), and the ventral tegmental area (VTA) dopamine neurons are central.[29,60,62,71] Recent studies extend the striatal and midbrain reward-related areas to include the entire ventral striatum (VS) and the dopamine neurons of the substantia nigra, pars compacta (SNc).* The VS receives its main cortical input from the OFC and ACC, and a massive dopaminergic input from the midbrain. The VS projects to the ventral pallidum (VP) and to the VTA-SN, which in turn project back to the prefrontal cortex (PFC), via the medial dorsal nucleus (MD) of the thalamus. These structures are part of the corticobasal ganglia system and are at the center of the reward circuit (figure 2.1).[25]

While the reward circuit is now considered part of the corticobasal ganglia network, historically, the basal ganglia was considered solely part of the sensory–motor control system.[47] The conceptual change from a purely sensory–motor function to a more complex set of functions can be traced to the demonstration that an additional (and separate) functional loop, the limbic loop, exists within the basal ganglia.[30] The idea of separate cortical loops in the basal ganglia was subsequently

* In addition, other structures, including the other prefrontal cortical areas, amygdala, hippocampus, hypothalamus, lateral habenular nucleus, and specific brainstem structures, such as the pedunculopontine nucleus, and the raphe nuclei, are also key components that regulate the reward circuit.

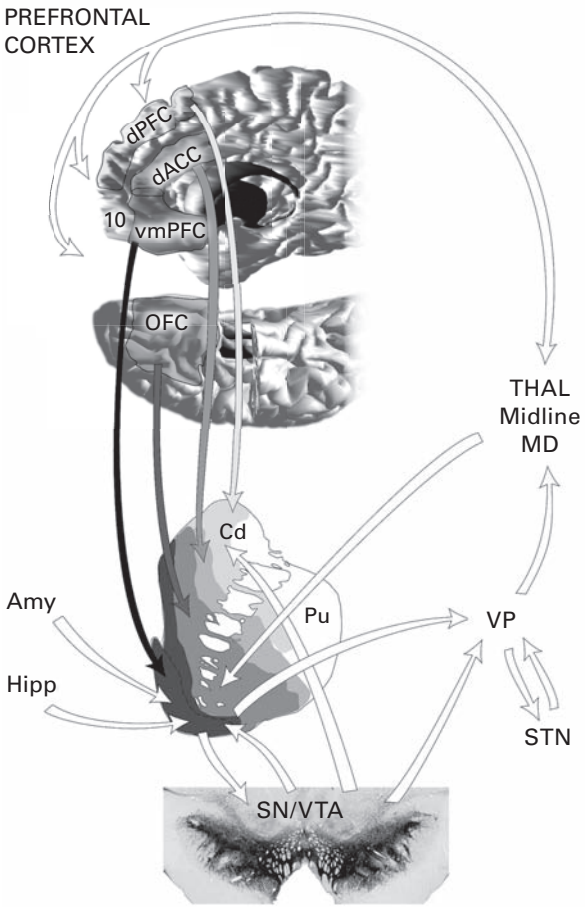


Figure 2.1
Schematic illustrating key structures and pathways of the reward circuit. Black arrow = input from the vmPFC; dark gray arrow = input from the OFC; light medium gray arrow = input from the dACC; light gray arrow = input from the dPFC; white arrows = other main connections of the reward circuit. Amy, amygdala; dACC, dorsal anterior cingulate cortex; dPFC, dorsal prefrontal cortex; Cd, caudate nucleus; Hipp, hippocampus; MD, medial dorsal nucleus of the thalamus; OFC, orbital frontal cortex; Pu, putamen; S, shell; SN, substantia nigra; STN, subthalamic n.; Thal, thalamus; VP, ventral pallidum; VTA, ventral tegmental area; vmPFC, ventral medial prefrontal cortex.

expanded to include several parallel and segregated functional loops (limbic, associative, and sensorimotor).[1] Although this concept has dominated the field for the past 20 years, several studies demonstrate integration across these circuits. Network crosstalk between limbic associative functions is consistent with the idea that adaptive behaviors require a combination of reward evaluation and associative learning to develop appropriate action plans and inhibit inappropriate choices. Not surprisingly, the idea of motivation-to-movement interface through basal ganglia circuits was developed soon after the discovery of the limbic component to the basal ganglia.[43,46] Thus, the ventral corticobasal ganglia network, while at the heart of reward processing, does not work in isolation.[3,5,12,23,24] In fact, within each station of the circuit there are interfaces between pathways that allow communication between different parts of the reward circuit and between the reward circuit and the associative circuit. In this chapter, we describe first the organization of the reward (and associative) circuit(s) and second, specific places in the network where crosstalk between circuits can occur.

Organization of the Reward Circuit

Prefrontal Cortex and Its Projections to the Striatum

The PFC comprises multifunctional regions involved in reinforcement-based learning and decision making. Different prefrontal cortical areas and corresponding striatal regions are involved in these various aspects of motivation and learning, and pathophysiology in the circuit is associated with sadness and depression, pathological risk taking, addictive behaviors, and obsessive-compulsive disorder.[15,38,41,50,69] The PFC is a complex and heterogenous region, but can broadly be divided into (1) the orbitofrontal cortex, or OFC (lateral OFC and part of insular cortex); (2) a ventral, medial prefrontal cortex, or vmPFC (medial OFC, subgenual ACC, and area 10); (3) the dorsal anterior cingulate cortex, or dACC (area 24); and (4) the dorsal prefrontal cortex, or dPFC (areas 9 and 46).[10,25,52] The vmPFC and OFC, collectively referred to as the ventral prefrontal cortex (vPFC), and the dACC, along with its basal ganglia components, mediate different aspects of reward-based behaviors, error prediction, and conflict detection.[6,15,49,61] In addition, the vmPFC has also been shown to be important for extinction and extinction recall.[42] In contrast, the dPFC is associated with cognitive processing and working memory, and provides cognitive control over motivational and emotional behaviors.[12,33] Overall, PFC regions work together in a complementary fashion to compare valued options and choose among them. The main subcortical outputs from the vPFC are to the VS and thalamus.

The VS includes the NAcc and the broad ventral continuity between the caudate nucleus and the putamen rostral to the anterior commissure.[24,31] This entire region

has been a focus for the study of reinforcement, and the transition between drug use for a reward and as a habit.[16,56] However, neither cytoarchitectonic nor histochemistry distinctions mark a clear boundary between the VS and the dorsal striatum. The best way to define the VS, therefore, is to use its cortical afferent projections from areas that mediate different aspects of reward and emotional processing, that is, inputs from the vPFC, dACC, and the medial temporal lobe, including the amygdala. Using these projections as a guide, the VS occupies over 20% of the striatum in nonhuman primates.[24]

Corticostriatal projections form dense, focal patches that are organized in a functional topographic manner.[24,64] Inputs from the vmPFC, OFC, and dACC terminate within subregions of the VS (figure 2.1).[26] The focal projection field from the vmPFC is the most limited. It is concentrated within the most ventral and medial parts of the VS, including the shell. The vmPFC also projects to the medial wall of the caudate n., adjacent to the ventricle. The densest input from agranular insular cortex also terminates in the NAcc and at the medial wall of the caudate.[9] Fewer data are available concerning the projections of area 10 to the VS, particularly medial area 10. However, one might assume that the medial and ventral area 10 would also terminate in the ventral, medial VS, given the overall topography of other projections from the vPFC. Thus, this VS region receives convergent input from the olfactory and visceral-associated insula, from the vmPFC, and most likely from area 10.

The dorsal and lateral parts of the VS receive inputs from the OFC. These terminals also extend dorsally, along the medial caudate n., but lateral to those derived from the vmPFC. The medial to lateral and rostral to caudal topographic organization of the OFC terminal fields is consistent with the positions of OFC regions in the PFC. That is, inputs from lateral parts of the OFC (i.e., area 12) terminate lateral to those derived from more medial areas (area 13). Projections from the dACC terminate lateral to those from the OFC. Taken together, the vmPFC, OFC, and dACC project primarily to the rostral striatum, with the vmPFC projecting most medially, and the dACC most laterally, with the OFC terminal fields positioned in between.[24] In contrast, the dPFC projects throughout the rostrocaudal extent of the striatum, terminating primarily in the head of the caudate and in part of the rostral putamen, but continuing into the caudal caudate nucleus. Like vPFC projections, axons from areas 9 and 46 also occupy somewhat different territories that, at rostral levels, span across the internal capsule.[7] At more caudal levels, these inputs are primarily confined to the dorsal caudate n. The two other main afferent projections to the striatum are derived from the midbrain and thalamus. Additional inputs from the amygdala and hippocampus make the VS a unique striatal region, in that these two structures do not innervate the dorsal striatum.

Midbrain Dopamine Projections to the VS

The central role of the dopamine neurons in the reward circuit is well established, along with the fact that this role in not limited to the VTA, but includes cells of the SNc.[63,71] The midbrain dopamine striatal projection follows a general mediolateral and inverse dorsoventral topography.[34] Thus, the VTA and the dorsal tier of SNc neurons project to the VS, and the ventral SNc neurons project to the dorsolateral striatum. The shell receives the most limited midbrain input, primarily derived from the medial VTA. The rest of the VS receives input from the VTA and from the medial and dorsal part of the SNc. In contrast to the VS, the striatal area innervated by the dPFC receives input from a wider region of centrally located dopamine cells. The dorsolateral (motor-related) striatum receives the largest midbrain projection from cells throughout the ventral SNc. Thus, in addition to an inverse topography, there is also a differential ratio of dopamine projections to the different striatal areas,[23] with the VS receiving the most limited dopamine input and the dorsolateral striatum receiving the largest input. It's important to note, however, that despite the overall topographic organization, individual dopamine axons arborize extensively within the striatum and are therefore likely to cross regional striatal boundaries.[37]

Thalamic Projections to the VS

The midline, medial intralaminar and medial MD thalamic nuclei project to medial prefrontal areas, the VS, amygdala, and hippocampus, and are referred to as the limbic-related thalamic groups.[20,21,32,72] The shell receives the most limited input, derived almost exclusively from the midline nuclei. The medial wall of the caudate n. receives projections, not only from the midline and the medial intralaminar nuclei, but also from the central superior lateral nucleus. In contrast, the lateral part of the VS receives a limited projection from the midline thalamic nuclei. Its input is derived from the intralaminar nuclei (the parafascicular nucleus and the central superior lateral nucleus). In addition to the midline and intralaminar thalamostriatal projections, there is a large input from the "specific" thalamic basal ganglia relay nuclei: the MD, ventral anterior, and ventral lateral nuclei.[39] The VS receives this input from the MD and a limited projection from the magnocellular subdivision of the ventral anterior nucleus. Thalamic input to the striatum is glutamatergic and can be distinguished from cortical synapses. Recent studies show that the thalamic and cortical synapses associated with dopaminergic terminals are similar.[44]

The amygdala is a prominent limbic structure that plays a key role in emotional coding of environmental stimuli.[45,58] Overall, the basal nucleus and the magnocellular division of the accessory basal nucleus are the main sources of inputs to the VS.[19] The amygdala has few inputs to the dorsal striatum in primates. The shell is

set apart from the rest of the VS by a specific set of connections derived from the medial part of the central nucleus (CeM), periamygdaloid cortex, and the medial nucleus of the amygdala. In contrast to the amygdala, the hippocampal formation projection is essentially confined to the shell.[18] Taken together, the existence of convergent fibers from cortex within the VS, along with hippocampal and amygdalostriatal projections along with broad dopamine modulation, places the VS as a key entry port for processing emotional and motivational information.

Efferent Projections of the VS

The VS, like the dorsal striatum, primarily projects to the pallidum and midbrain.[28] The VP is an important component of the reward circuit in that cells in this forebrain region respond specifically during the learning and performance of reward-incentive behaviors and play a central role in addictive behaviors.[65,68] The VP is best described as the pallidal region that receives its input from the VS. VS fibers terminate topographically in the subcommissural VP, the rostral pole of the external segment, and the rostromedial portion of the internal segment. For example, the shell projects to the border areas between the VP and the bed nucleus of the stria terminalis, and more lateral VS areas project to the lateral VP.[28] The topography created by vPFC and dACC projections to the VS, is reflected in the VS output to the VP.[26] Like the dorsal pallidum, components of the VP project topographically to the subthalamic nucleus (STN), SN, and thalamus.

Striatal projections to the midbrain terminate in both the pars reticulata and the pars compacta. In fact, the striatonigral projection provides a massive projection to the midbrain dopamine cells, terminating in both the VTA and SNc. These projection fields are not as topographically organized as those projecting to the pallidum. As seen with the nigrostriatal projection, these projections have a medial-lateral and an inverse ventral-dorsal topography. In other words, the VS projects to the dorsal midbrain and the dorsal striatum terminates in the ventral midbrain.[23,35,67] The largest terminal fields are derived from the VS and the associative striatum. In contrast, the dorsolateral striatal projection to the SN is confined to a relatively small ventrolateral position. The output from the medial SNr and VP are primarily to the MD nucleus, which, in turn, projects to the frontal cortex, and is the final link in the reward circuit.[27,59]

Crosstalk between Functional Circuits

Integration between Corticostriatal Projections

Although the topographic organization of corticostriatal projections is well documented, there is increasing evidence of regions of interface between terminals from

different cortical areas, suggesting functional integration. For example, early studies showed that corticostriatal terminals from sensory and motor cortex converge within the striatum.[17] Here, axons from each area synapse onto single fast-spiking GABAergic interneurons. Interestingly, these interneurons are more responsive to cortical input than the medium spiny cells, suggesting a potentially critical role for interneurons to integrate information from different cortical areas before passing that information on to the medium spiny projection cells.[36,57]

Projections from the OFC, vmPFC, and dACC also converge in specific regions within the VS. Thus, focal terminal fields from the vmPFC, OFC, and dACC show a complex interweaving and convergence[24] (figure 2.2a). For example, axons from the dACC and OFC regions do not occupy completely separate territories in any part

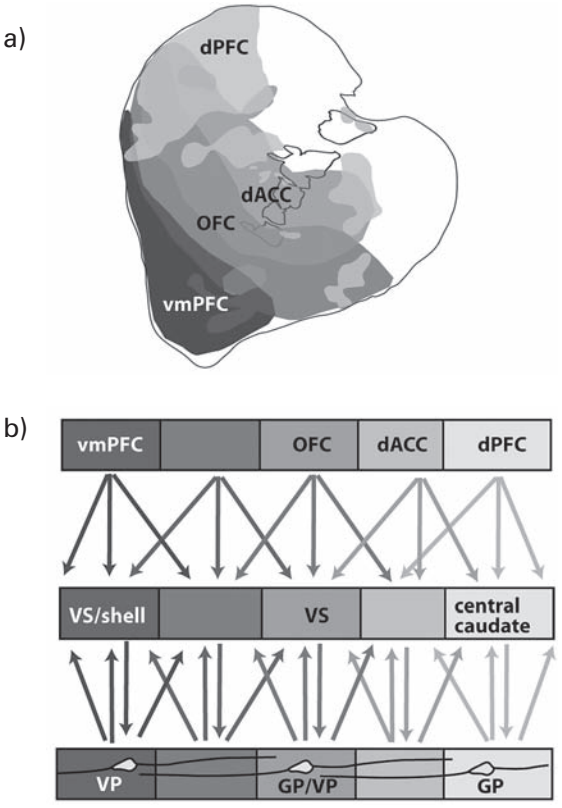


Figure 2.2
Schematics illustrating integrative connections through convergence of terminals from different functional regions. (a) A mediofrontal view of a three-dimensional reconstruction illustrating convergence of inputs from PFC inputs. (b) Schematic illustrating convergence at the PFC-striatal and the striatopallidostriatal levels.

of the striatum. They converge most extensively at rostral levels, providing an anatomical substrate for modulation between these circuits. In addition, projections from dACC and OFC also converge with inputs from the dPFC, particularly at the most rostral striatal levels. A similar pattern of both topographic and integrative connectivity of corticostriatal projections has recently been demonstrated in the human brain using diffusion tensor imaging (DTI). These data show a similar overall organization of the different cortical regions and the striatum, and provide a strong correlation between monkey anatomical tracing studies and human DTI studies.[14] Taken together, a coordinated activation of dPFC, dACC, and/or OFC terminals in these subregions could produce a unique combinatorial activation at the specific sites for channeling reward-based incentive drive in selecting among different valued options. The existence of these areas may help explain complex activation patterns following different reward-related paradigms or the interface between reward and cognitive feedback.[12]

Ventral Pallidal Connections

Pallidal dendrites are long, stretching across multiple functional regions, and are oriented perpendicular to incoming striatal fibers. Thus, each pallidal dendrite is in a position to intercept efferents originating from more than one functional striatal district[54] (figure 2.2b). In addition, descending projections from the VP converge with those from the dorsal pallidum on single dopaminergic neurons.[5] Therefore, individual SN cells receive both limbic and nonlimbic input. This convergence has important implications for the role of the dopamine cells in processing diverse information, which in turn is sent back to the striatum. Moreover, VP and dorsal pallidal projections also converge at the interface between the projection fields in the STN.[4] An additional unique projection of the VP is to both the internal and external segments of the dorsal pallidum. The dorsal pallidum does not seem to project ventrally.[27] Finally, part of the VP (as with the external segment of the pallidum) also projects to the striatum.[66] This pallidostriatal pathway is extensive and more widespread than reciprocal striatopallidal projection, providing a broad feedback signal (figure 2.2b).

The Striatonigrostriatal Network

VS (limbic) influence on the dorsal striatum (motor) through the midbrain dopamine cells was originally shown in rats.[48] The concept of transferring information through different striatal regions via the midbrain was expanded on, taking into account the functionally more complex and diverse primate striatum.[23] The VTA and medial SN are associated with limbic regions, and the central and ventral SN are associated with the associative and motor striatal regions, respectively. However, as described previously, each functional region differs in its proportional projections. The VS receives a limited midbrain input, but projects to a large region. In contrast,

the dorsolateral striatum receives a wide input, but projects to a limited region. In other words, the VS influences a wide range of dopamine neurons, but is itself influenced by a relatively limited group of dopamine cells. On the other hand, the dorsolateral striatum influences a limited midbrain region, but is affected by a relatively large midbrain region.

Thus, while the main efferent projection from the VS to the midbrain is to the dorsal tier of dopamine cells, this projection field extends beyond the tight VS–dorsal tier–VS circuit. Indeed, the VS also terminates more ventrally, in a position to influence more dorsal striatal regions, particularly those that receive input from associative cortical regions (e.g., dPFC). This part of the ventral tier is reciprocally connected to the central (or associative) striatum. The central striatum also projects to a more ventral region than it receives input from. This region, in turn, projects to the dorsolateral (or motor) striatum. Taken together, the interface between different striatal regions via the midbrain DA cells is organized in an ascending spiral that interconnects different functional regions of the striatum and creates a feedforward organization, from reward-related regions of the striatum to cognitive and motor areas (figure 2.3a).

Although the short latency burst-firing activity of dopamine that signals immediate reinforcement is likely to be triggered from brainstem nuclei,[13] the corticostriato-midbrain pathway is in the position to influence dopamine cells to distinguish rewards and modify responses to incoming salient stimuli over time, placing the striatonigrostriatal pathway in a pivotal position for transferring information from the VS to the dorsal striatum during learning and habit formation. Indeed, cells in the dorsal striatum are progressively recruited during different types of learning and habit formation.[3,53,55,70]

Additional VS Connections

The VS also terminates in non–basal ganglia regions.[28] The shell sends fibers caudally and medially into the lateral hypothalamus and, to some extent, into the periaqueductal gray. Axons from the medial VS also terminate in the bed nucleus of the stria terminalis, indicating a direct striatal influence on the extended amygdala. Finally, fibers from ventral regions of the VS terminate in the nucleus basalis.[2,22,73] The n. basalis is the main source of cholinergic fibers to the cerebral cortex and the amygdala. Thus, the VS can influence cortex directly through a connection that does not pass through the pallidal thalamic circuit, providing a route through which the reward circuit has wide access to multiple regions of frontal cortex.

Thalamocorticothalamic Connection

Thalamocortical connections are bidirectional. However, the corticothalamic projections are more extensive than the thalamocortical projections.[11,40] Moreover,

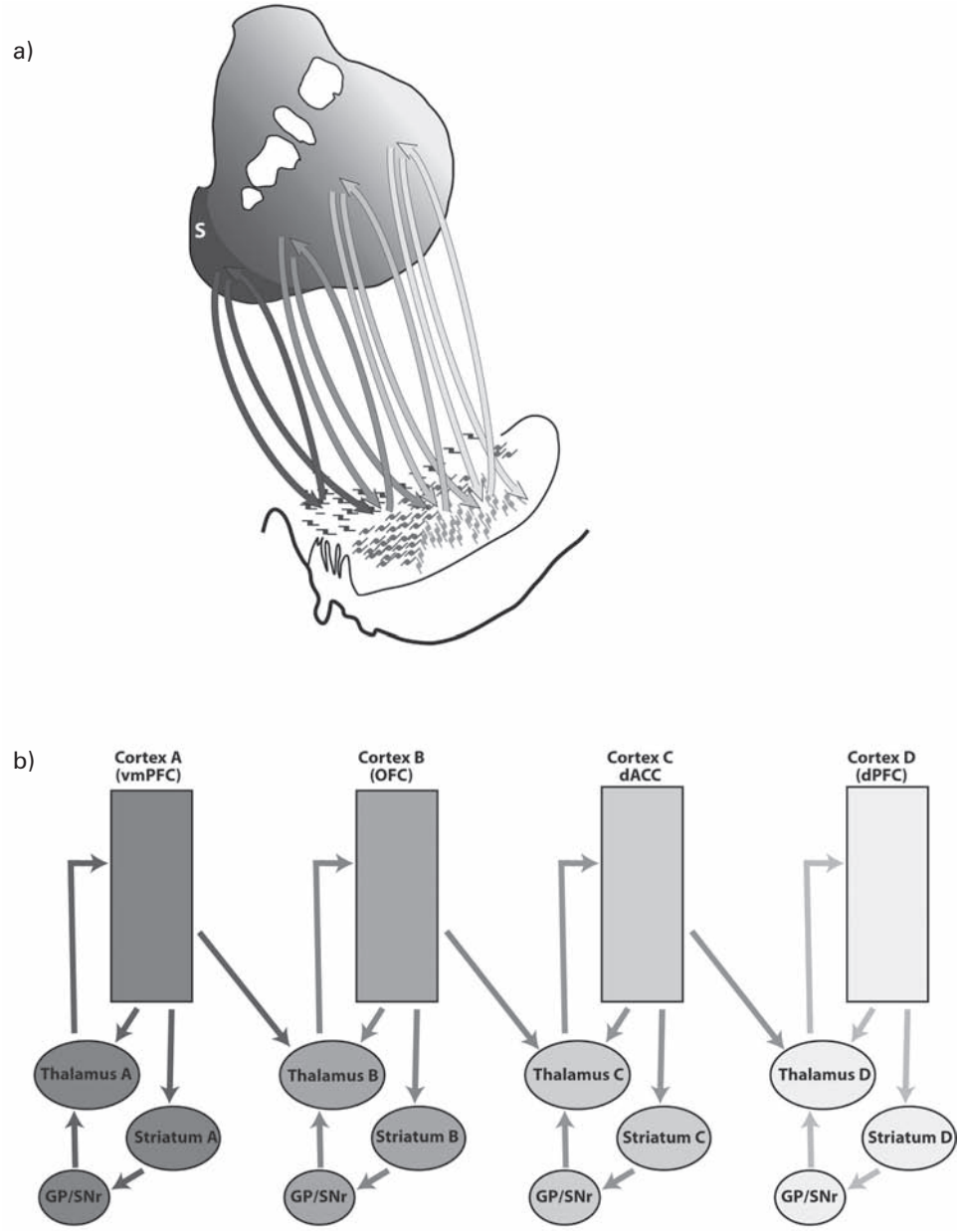


Figure 2.3
Schematics illustrating integrative connections through reciprocal and nonreciprocal connections. (a) Connections between the striatum and substantia nigra. The arrows indicated illustrate how the ventral striatum can influence the dorsal striatum through the midbrain dopamine cells. Shades of gray indicate functional regions of the striatum, based on cortical inputs (figure 2.1). Midbrain projections from the shell target both the VTA and ventromedial SNc. Projections from the VTA to the shell form a "closed," reciprocal loop, but also project more laterally to impact on dopamine cells projecting the rest of the ventral striatum forming the first part of a feed forward loop (or spiral). The spiral continues through the striatonigrostriatal projections through which the ventral striatum impacts on cognitive and motor striatal areas (not illustrated) via the midbrain dopamine cells. (b) Connections between the cortex and thalamus. Arrows illustrate how the nonreciprocal component of the corticothalamic projection can influence another cortico–basal ganglia function loop through the thalamus. Black arrows = inputs from the vmPFC; dark gray arrows = inputs form the OFC and dACC; light arrows = inputs from the dPFC.

in addition to the reciprocal thalamocorticothalamic connection, there is also a nonreciprocal corticothalamic component. Thus, while the MD completes the reward circuit back to cortex, a nonreciprocal cortical input to the MD is derived from functionally distinct frontal cortical areas. For example, the central MD has not only reciprocal projections with the OFC, but also a nonreciprocal input from vmPFC. Similarly, more lateral MD areas are reciprocally connected to the dPFC, but also have a nonreciprocal input from the OFC.[40] Therefore, similar to the striatonigrostriatal projection system, the thalamic relay nuclei from the basal ganglia also appear to integrate information flow from reward and higher cortical "association" areas of the prefrontal cortex (figure 2.3b). A recent DTI study indicates that integration between these cortical areas in the thalamus is also likely to exist in humans.[14]

Summary

Although the reward network comprises a specific set of connections, it does not work in isolation, but also interfaces with circuits that mediate cognitive function and motor planning. Integration across cortico–basal ganglia circuits occurs through convergence zones, for example, between corticostriatal projections or pallidal-nigral connections, that can link areas associated with different functions to permit dissemination of cortical information across multiple functional regions. It also occurs via reciprocal-nonreciprocal networks (through the striatonigrostriatal pathway and thalamocorticothalamic circuit). Through these interactive networks, information about reward can be channeled through cognitive and motor control circuits to mediate the development of adaptive action plans. Thus, whereas reward anticipation tends to coactivate the VS and midbrain, reward outcomes subsequently recruit the medial caudate and putamen, followed by the dorsal caudate. This recruitment likely involves the dopamine pathways, through the striatonigrostriatal spiral.[3,55] Thus, knowledge gained from anatomical connectivity studies, including areas of potential network interfaces, will increase our understanding and ability to predict how and when seemingly unconnected structures might be activated or coactivated.

Outstanding Questions

- Prefrontal cortex receives dopamine connections, but there is only a limited cortical projection to the dopamine cells (see Frankle et al. in Further Reading). How does the cortex influence the dopamine neurons?
- The striatum has been described as being composed of striosomes and matrisomes, with prefrontal cortex projecting only to the striosomes. Could this concept be

included in the description proposed in this chapter? If so, what would be the functional impact of such implementation?

- Do the different DA populations have different roles?

Further Reading

Haber SN, Knutson B. 2010. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 35: 4–26. A nice review linking data regarding anatomy in monkeys and imaging data in humans.

Frankle WG, Laruelle M, Haber SN. 2006. Prefrontal cortical projections to the midbrain in primates: evidence for a sparse connection. *Neuropsychopharmacology* 31:1627–1636. This paper describes anatomical evidence that the prefrontal cortex could influence DA midbrain activity.

Graybiel AM. 2008. Habits, rituals, and the evaluative brain. *Annu Rev Neurosci* 31:359–387. A review of how habitual behaviors emerge as a result experience-dependent plasticity in basal ganglia–based networks.

References

1. Alexander GE, Crutcher MD, DeLong MR. 1990. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res* 85: 119–146.

2. Beach TG, Tago H, McGeer EG. 1987. Light microscopic evidence for a substance P-containing innervation of the human nucleus basalis of Meynert. *Brain Res* 408: 251–257.

3. Belin D, Everitt BJ. 2008. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. *Neuron* 57: 432–441.

4. Bevan MD, Clarke NP, Bolam JP. 1997. Synaptic integration of functionally diverse pallidal information in the entopeduncular nucleus and subthalamic nucleus in the rat. *J Neurosci* 17: 308–324.

5. Bevan MD, Smith AD, Bolam JP. 1996. The substantia nigra as a site of synaptic integration of functionally diverse information arising from the ventral pallidum and the globus pallidus in the rat. *Neuroscience* 75: 5–12.

6. Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 402: 179–181.

7. Calzavara R, Mailly P, Haber SN. 2007. Relationship between the corticostriatal terminals from areas 9 and 46, and those from area 8A, dorsal and rostral premotor cortex and area 24c: an anatomical substrate for cognition to action. *Eur J Neurosci* 26: 2005–2024.

8. Carlezon WA, Wise RA. 1996. Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. *J Neurosci* 16: 3112–3122.

9. Chikama M, McFarland N, Amaral DG, Haber SN. 1997. Insular cortical projections to functional regions of the striatum correlate with cortical cytoarchitectonic organization in the primate. *J Neurosci* 17: 9686–9705.

10. Croxson PL, Johansen-Berg H, Behrens TE, Robson MD, Pinsk MA, Gross CG, Richter W, Richter MC, Kastner S, Rushworth MF. 2005. Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. *J Neurosci* 25: 8854–8866.

11. Darian-Smith C, Tan A, Edwards S. 1999. Comparing thalamocortical and corticothalamic microstructure and spatial reciprocity in the macaque ventral posterolateral nucleus (VPLc) and medial pulvinar. *J Comp Neurol* 410: 211–234.

12. Delgado MR, Gillis MM, Phelps EA. 2008. Regulating the expectation of reward via cognitive strategies. *Nat Neurosci* 11: 880–881.

13. Dommett E, Coizet V, Blaha CD, Martindale J, Lefebvre V, Walton N, Mayhew JE, Overton PG, Redgrave P. 2005. How visual stimuli activate dopaminergic neurons at short latency. *Science* 307: 1476–1479.

14. Draganski B, Kherif F, Kloppel S, Cook PA, Alexander DC, Parker GJ, Deichmann R, Ashburner J, Frackowiak RS. 2008. Evidence for segregated and integrative connectivity patterns in the human basal ganglia. *J Neurosci* 28: 7143–7152.

15. Elliott R, Newman JL, Longe OA, Deakin JF. 2003. Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. *J Neurosci* 23: 303–307.

16. Everitt BJ, Robbins TW. 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 8: 1481–1489.

17. Flaherty AW, Graybiel AM. 1993. Two input systems for body representations in the primate striatal matrix: experimental evidence in the squirrel monkey. *J Neurosci* 13: 1120–1137.

18. Friedman DP, Aggleton JP, Saunders RC. 2002. Comparison of hippocampal, amygdala, and perirhinal projections to the nucleus accumbens: combined anterograde and retrograde tracing study in the macaque brain. *J Comp Neurol* 450: 345–365.

19. Fudge JL, Kunishio K, Walsh C, Richard D, Haber SN. 2002. Amygdaloid projections to ventromedial striatal subterritories in the primate. *Neuroscience* 110: 257–275.

20. Gaffan D, Murray EA. 1990. Amygdalar interaction with the mediodorsal nucleus of the thalamus and the ventromedial prefrontal cortex in stimulus reward associative learning in the monkey. *J Neurosci* 10: 3479–3493.

21. Giménez-Amaya JM, McFarland NR, de las Heras S, Haber SN. 1995. Organization of thalamic projections to the ventral striatum in the primate. *J Comp Neurol* 354: 127–149.

22. Haber SN. 1987. Anatomical relationship between the basal ganglia and the basal nucleus of Maynert in human and monkey forebrain. *Proc Natl Acad Sci USA* 84: 1408–1412.

23. Haber SN, Fudge JL, McFarland NR. 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 20: 2369–2382.

24. Haber SN, Kim KS, Mailly P, Calzavara R. 2006. Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical inputs, providing a substrate for incentive-based learning. *J Neurosci* 26: 8368–8376.

25. Haber SN, Knutson B. 2010. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 35: 4–26.

26. Haber SN, Kunishio K, Mizobuchi M, Lynd-Balta E. 1995. The orbital and medial prefrontal circuit through the primate basal ganglia. *J Neurosci* 15: 4851–4867.

27. Haber SN, Lynd-Balta E, Mitchell SJ. 1993. The organization of the descending ventral pallidal projections in the monkey. *J Comp Neurol* 329: 111–129.

28. Haber SN, Lynd E, Klein C, Groenewegen HJ. 1990. Topographic organization of the ventral striatal efferent projections in the rhesus monkey: an anterograde tracing study. *J Comp Neurol* 293: 282–298.

29. Hayden BY, Platt ML. 2010. Neurons in anterior cingulate cortex multiplex information about reward and action. *J Neurosci* 30: 3339–3346.

30. Heimer L. 1978. The olfactory cortex and the ventral striatum. In: Limbic Mechanisms (Livingston KE, Hornykiewicz O, eds), pp 95–187. New York: Plenum Press.

31. Heimer L, De Olmos JS, Alheid GF, Person J, Sakamoto N, Shinoda K, Marksteiner J, Switzer RC. 1999. The human basal forebrain. Part II. In: Handbook of Chemical Neuroanatomy (Bloom FE, Bjorkland A, Hokfelt T, eds), pp 57–226. Amsterdam: Elsevier.

32. Hsu DT, Price JL. 2007. Midline and intralaminar thalamic connections with the orbital and medial prefrontal networks in macaque monkeys. *J Comp Neurol* 504: 89–111.

33. Levy R, Goldman-Rakic PS. 2000. Segregation of working memory functions within the dorsolateral prefrontal cortex. *Exp Brain Res* 133: 23–32.

34. Lynd-Balta E, Haber SN. 1994. The organization of midbrain projections to the striatum in the primate: sensorimotor-related striatum versus ventral striatum. *Neuroscience* 59: 625–640.

35. Lynd-Balta E, Haber SN. 1994. Primate striatonigral projections: a comparison of the sensorimotor-related striatum and the ventral striatum. *J Comp Neurol* 345: 562–578.

36. Mallet N, Le Moine C, Charpier S, Gonon F. 2005. Feedforward inhibition of projection neurons by fast-spiking GABA interneurons in the rat striatum in vivo. *J Neurosci* 25: 3857–3869.

37. Matsuda W, Furuta T, Nakamura KC, Hioki H, Fujiyama F, Arai R, Kaneko T. 2009. Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. *J Neurosci* 29: 444–453.

38. Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, Jerabek PA. 2000. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol Psychiatry* 48: 830–843.

39. McFarland NR, Haber SN. 2001. Organization of thalamostriatal terminals from the ventral motor nuclei in the macaque. *J Comp Neurol* 429: 321–336.

40. McFarland NR, Haber SN. 2002. Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. *J Neurosci* 22: 8117–8132.

41. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. 2008. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev* 32: 525–549.

42. Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. 2007. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol Psychiatry* 62: 446–454.

43. Mogenson GJ, Jones DL, Yim CY. 1980. From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol* 14: 69–97.

44. Moss J, Bolam JP. 2008. A dopaminergic axon lattice in the striatum and its relationship with cortical and thalamic terminals. *J Neurosci* 28: 11221–11230.

45. Murray EA. 2007. The amygdala, reward and emotion. *Trends Cogn Sci* 11: 489–497.

46. Nauta HJW. 1986. The relationship of the basal ganglia to the limbic system. In: Handbook of Clinical Neurology: Extrapyramidal Disorders (Vinken PJ, Bruyn GW, Klawans JJ, eds), pp 19–31. Amsterdam: Elsevier.

47. Nauta WJ, Mehler WR. 1966. Projections of the lentiform nucleus in the monkey. *Brain Res* 1: 3–42.

48. Nauta WJH, Smith GP, Faull RLM, Domesick VB. 1978. Efferent connections and nigral afferents of the nucleus accumbens septi in the rat. *Neuroscience* 3: 385–401.

49. O'Doherty J, Critchley H, Deichmann R, Dolan RJ. 2003. Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *J Neurosci* 23: 7931–7939.

50. O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ. 2004. Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304: 452–454.

51. Olds J, Milner P. 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol* 47: 419–427.

52. Passingham RE, Stephan KE, Kotter R. 2002. The anatomical basis of functional localization in the cortex. *Nat Rev Neurosci* 3: 606–616.

53. Pasupathy A, Miller EK. 2005. Different time courses of learning-related activity in the prefrontal cortex and striatum. *Nature* 433: 873–876.

54. Percheron G, Yelnik J, Francois C. 1984. The primate striato-pallido-nigral system: an integrative system for cortical information. In: The Basal Ganglia: Structure and Function (McKenzie JS, Kemm RE, Wilcock LN, eds), pp 87–105. London: Plenum Press.

55. Porrino LJ, Lyons D, Smith HR, Daunais JB, Nader MA. 2004. Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. *J Neurosci* 24: 3554–3562.

56. Porrino LJ, Smith HR, Nader MA, Beveridge TJ. 2007. The effects of cocaine: a shifting target over the course of addiction. *Prog Neuropsychopharmacol Biol Psychiatry* 31: 1593–1600.

57. Ramanathan S, Hanley JJ, Deniau JM, Bolam JP. 2002. Synaptic convergence of motor and somatosensory cortical afferents onto GABAergic interneurons in the rat striatum. *J Neurosci* 22: 8158–8169.

58. Ramirez DR, Savage LM. 2007. Differential involvement of the basolateral amygdala, orbitofrontal cortex, and nucleus accumbens core in the acquisition and use of reward expectancies. *Behav Neurosci* 121: 896–906.

59. Ray JP, Price JL. 1993. The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol* 337: 1–31.

60. Rolls ET. 2000. The orbitofrontal cortex and reward. *Cereb Cortex* 10: 284–294.

61. Rushworth MF, Behrens TE. 2008. Choice, uncertainty and value in prefrontal and cingulate cortex. *Nat Neurosci* 11: 389–397.

62. Schultz W. 2000. Multiple reward signals in the brain. *Nat Rev Neurosci* 1: 199–207.

63. Schultz W. 2002. Getting formal with dopamine and reward. *Neuron* 36: 241–263.

64. Selemon LD, Goldman-Rakic PS. 1985. Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J Neurosci* 5: 776–794.

65. Smith KS, Tindell AJ, Aldridge JW, Berridge KC. 2009. Ventral pallidum roles in reward and motivation. *Behav Brain Res* 196: 155–167.

66. Spooren WPJM, Lynd-Balta E, Mitchell S, Haber SN. 1996. Ventral pallidostriatal pathway in the monkey: evidence for modulation of basal ganglia circuits. *J Comp Neurol* 370: 295–312.

67. Szabo J. 1979. Strionigral and nigrostriatal connections. Anatomical studies. *Appl Neurophysiol* 42: 9–12.

68. Tindell AJ, Smith KS, Pecina S, Berridge KC, Aldridge JW. 2006. Ventral pallidum firing codes hedonic reward: when a bad taste turns good. *J Neurophysiol* 96: 2399–2409.

69. Volkow ND, Wang GJ, Ma Y, Fowler JS, Wong C, Ding YS, Hitzemann R, Swanson JM, Kalivas P. 2005. Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. *J Neurosci* 25: 3932–3939.

70. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. 2006. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci* 26:6583–6588.

71. Wise RA. 2002. Brain reward circuitry: insights from unsensed incentives. *Neuron* 36: 229–240.

72. Yakovlev PI, Locke S, Koskoff DY, Patton RA. 1960. Limbic nuclei of thalamus and connections of limbic cortex. I. Organization of the projections of the anterior group of nuclei and of the midline nuclei of the thalamus to the anterior cingulate gyrus and hippocampal rudiment in the monkey. *Arch Neurol* 3: 620–641.

73. Zaborszky L, Cullinan WE. 1992. Projections from the nucleus accumbens to cholinergic neurons of the ventral pallidum: a correlated light and electron microscopic double-immunolabeling study in rat. *Brain Res* 570: 92–101.