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Evolutionary Perspectives

Homologies and Analogies

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Abstract

Determining homologies and analogies of brain structure and function across species is of major interest in systems neuroscience, comparative biology, and brain mapping. Prefrontal cortex (PFC) is a continued target of such analyses because it has expanded considerably throughout evolution. It is heavily differentiated and expanded in primates compared to mouse, rat, tree shrew, and marmoset brains, and it performs computational functions that are more complex than other association cortex.

This chapter reviews the major regions and circuits observed across species within PFC. It looks at the evolution of PFC and how this could produce higher-order cognition, including social behavior, as well as language elements in humans. It provides a synopsis of some main organizational principles of PFC as well as potential mechanisms by which major circuits in PFC exert control. It then reviews how unique contributions of optogenetics, chemogenetics, large-scale electrophysiology, and calcium imaging contribute to understanding PFC function. It also addresses the utility of animal models for understanding the structure and function of PFC.

The discussions that contributed to this chapter provide a modern foundation for the ongoing goal of generating a consensus statement regarding the ambition of determining the homologies and analogies of PFC, as well as the cognitive, developmental, and translational insights gleaned from the promise of such an eventual consensus statement.

Group photos (top left to bottom right) Bernard Balleine, Trevor Robbins, Kevin Weiner, Alicia Izquierdo, Michael Halassa, Jeroen Smaers, Peter Rudebeck, Trevor Robbins, Kevin Weiner, Trevor Robbins, Bernard Balleine, Jeroen Smaers, Alicia Izquierdo, Kevin Weiner, Nicola Palomero-Gallagher, Bernard Balleine, Alicia Izquierdo, Michael Halassa, Peter Rudebeck, Trevor Robbins, and Nicola Palomero-Gallagher

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Introduction

The definition of what comprises prefrontal cortex (PFC) has depended on several criteria, including simple location (i.e., regions of anterior cortex), cytoarchitectonic characteristics (notably granularity associated with lamina 4 innervation), and connectivity (e.g., mediodorsal thalamic input). None of these criteria is decisive, especially when comparing across species, specifically when considering human, nonhuman primate (NHP), and rodent. Although PFC has been classically defined as the granular cortex in the frontal lobe, how can we say that granularity is of particular importance, if we do not fully understand its biological significance?

What is understood is that PFC is a nexus for higher cognitive function and dysfunction in humans and may be the cause of numerous psychiatric disorders. Consequently, understanding PFC function is a critical aim for basic research. While some would opine that PFC can only be studied in primates or tree shrews (Preuss and Wise 2022), there are limits to the research that can be ethically and/or practically accomplished if we take this position. Thus, to make faster headway, it is reasonable to ask how best to compare and model human PFC subregions across species beyond primates. This involves issues of homology (i.e., shared ancestry between a pair of structures or genes in different taxa). One of the main aims in our discussions was to prioritize the various criteria for homology, based on micro-architectonics (including cytoarchitecture and the architecture of neurotransmitter receptors), connectivity with other brain regions, and development. Another criterion, which cannot be considered as homology in the formal sense, is based on analogy. In this chapter, we consider analogy as resemblances in function across species between organs (e.g., different regions of PFC) that may have different evolutionary origins. These may reveal essential building blocks in rodents of more complex executive processes in primates. Work in each species is in itself a significant scientific problem of great utility, with impact in areas such as artificial intelligence and human health. Specifically, insights from nonhuman animal species may ultimately inform the understanding of clinical conditions. Here, we attempted to take all these considerations into account when discussing the evolution of the PFC and its possible drivers, for example, increasing complexity of information processing required for foraging and social behavior as well as ultimately the capacity for language and moral reasoning.

We consider whether there is anything "special" about the PFC and its organization, including regional localization of function, whether there is hierarchical organization across species and dorsal-ventral or medial-lateral gradients. Allied to this analysis, we also consider whether there are unique aspects of neuronal activity of the PFC that confer its higher-order functioning (e.g., neuronal synchrony and oscillation), its plasticity and possible capacity for fast learning, as well as its top-down controllability of neurochemical modulation by the ascending monoamine and cholinergic systems. We also address

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whether the network organization of prefrontal-related circuits, as defined in human studies, is represented in other animals and how this relates to concepts of goal-directed control.

Finally, we discuss the unique opportunities for delineating functional neural circuitry involving PFC in nonhuman animals using modern neurobiological techniques, such as optogenetics and chemogenetics. These methodologies can be used to establish causal relationships at nodes within circuits, including PFC, as well as the interactions and sequencing of recruitment among prefrontal regions themselves to guide behavior. Furthermore, they can potentially be used to simulate states and mechanisms of treatments associated with clinical disorders, with implications for animal models of human clinical disorders. Of course, these are bold goals to achieve in one chapter, and while we appreciate that we will fall short from achieving these goals, we are hopeful that this discussion will motivate future experiments, models, and quantifications that come closer to understanding the evolution of neural circuits underlying the complexity (Rigotti et al. 2013) of prefrontal cortical structure and function linked to higher-level aspects of cognition that have critical insights for better understanding the neural underpinnings of neuropsychiatric disorders.

What Are the Major Regions and Circuits Observed across Species within PFC?

To answer this question, we found it necessary to define the relevant species and areas of focus. We chose to focus on widely used animal models for humans across subdisciplines in the broad fields of neuroscience and medicine: rodents and NHPs. Ultimately, one way to organize the quest for homology would be to take human PFC as the starting point and work "backward" through the evolutionary tree. Taking these issues into consideration, we consider a parcellation of PFC based on connectivity patterns and roles in cognitive and emotional processes focusing on a tripartite division involving orbitofrontal cortex (OFC), dorsolateral PFC (dlPFC), and ventrolateral PFC (vlPFC). Within these anatomical locations, the main cytoarchitectonic areas that we focus on (using Brodmann's/Walker's nomenclature) in this chapter are 10, 11, 13, and 14 (Brodmann 1909; Walker 1940). While the cingulate cortex is classically not considered to be part of PFC, it is closely interconnected (structurally) and interacts (functionally) with prefrontal areas. Thus, during our discussions, we adopted/tolerated the view that anterior cingulate cortex (ACC, areas 25, 32 and 24) are part of the PFC, and are specifically located within the medial PFC. In addition to these decisions, we also considered classic questions such as: Where, if anywhere, is PFC in rodents? To what extent are the organizational principles of the NHP PFC, specifically in macaque monkeys, comparable to those of the human PFC?

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As reviewed by Izquierdo (this volume) and elsewhere (Le Merre et al. 2021; Uylings et al. 2003; Vogt and Paxinos 2014), there are criteria for defining PFC in the rodent brain. The presence of the internal granular cell layer, layer IV (LIV), has been considered the primary definition of primate PFC. LIV is a microcircuit feature of isocortical areas considered to be especially critical in cortical regions that have expanded the most throughout evolution in association cortex such as PFC. As granularity of dorsal frontal cortex in rodents is a matter of debate and their OFC areas are agranular, and thus lack this LIV, classic research widely purported that rodents lacked any homologues to areas in primate PFC (Laubach et al. 2018; Preuss 1995). More recent criteria have been proposed beyond cytoarchitectonic features, such as functional properties (similarities in behavior) and electrophysiological neural signatures, neurochemical distribution and receptor expression, and/or architecture, embryological development (which we briefly discuss in this section), and connectivity (both the patterns as well as the density of connections) (Seamans et al. 2008; Uylings et al. 2003; Rich and Averbeck, this volume). Again, it is worth noting that the term homology refers to shared ancestry. Thus, it may be better to characterize these additional proposals of PFC features as indicators of an area being analogous to human PFC.

Adding to this complexity of the PFC homology/analogy debate is what the pioneering neuroscientist Charlie Gross once referred to as the "alphabet soup" of cortical areas (Gross 1994). That is, the inconsistency of anatomical nomenclature and the use of multiple terms/acronyms for the same subregion of the brain not only across species but also within species. This is not a new issue. It stems all the way back to the late 1800s, when Burt Green Wilder (1881, 1896) and Wilhelm His (1895) led different teams to address it, and still persists today, not only for cross-species comparisons but also within species (Weiner 2019; Weiner and Zilles 2016). For brevity, we refer the reader to Izquierdo (this volume) for a review of this issue between rodent and primate; for discussion of the different criteria recently proposed, see Barreiros et al. (2021a, b), Heilbronner et al. (2016), Izquierdo et al. (2017), Rudebeck and Rich (2018), Wallis (2011), and Wise (2008).

In addition to the tripartite parcellation of PFC noted above, we also included the inferior frontal cortex and frontopolar areas in our discussions as they are likely not homologous between rodent, marmoset, macaque, and human: areas 44 and 45 (inferior frontal cortex or "Broca's region"), the vlPFC encompassing area 12/47, and areas FP1 and FP2 in the frontal pole within Brodmann's area 10 (Bludau et al. 2014). This aspect of our discussion led logically to the next question: What are the most important criteria for similarity between species? This is especially critical considering the massive differences in brain size and the complexity of cortical convolutions across species. For example, the mouse brain is about 4,000 times smaller than the human brain and contains about 71 million neurons, whereas the macaque brain is about 15 times smaller than the human brain and contains about

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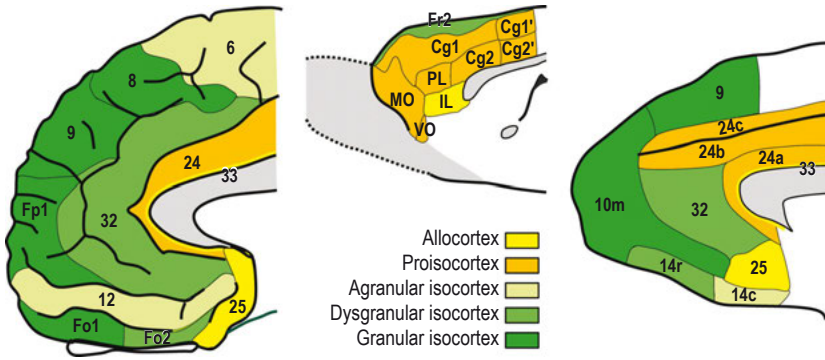

Figure 4.1 Comparative neuroanatomy of regions covered in this chapter. Medial views of the human (left; modified after Brodmann 1909), rat (middle; modified after Haghir et al. 2023), and macaque monkey (right; modified after Morecraft et al. 2012) frontal cortex. The cytoarchitecture of each area is indicated by different color shading: granular (dark green), dysgranular (light green), agranular (yellow/green), proisocortex (orange), and allocortex (yellow). Please refer to the main text for our discussion about disagreements regarding the exact parcellation of each area in this cortical expanse in each species, as well as the variously proposed combination of numbers and letters used to refer to each area since the 1800s. Note, in the schematic representation of the macaque brain we highlight the position of cortical borders in relation to the *fundus* of the cingulate sulcus (i.e., area 24c is located on the dorsal bank of the cingulate sulcus), whereas in the human brain we do not show cortex buried in the sulci.

6,376 million neurons (Azevedo et al. 2009; Herculano-Houzel 2009). For an overview of the comparative neuroanatomy of regions that are a focus of this chapter, see Figure 4.1.

What Are Important Criteria of Homology?

In terms of semantics, in neuroimaging and cognitive neuroscience, the term homology has a different definition than in comparative and evolutionary biology—a difference that can be traced back to Owen's definitions in 1843 (Gross 1993). As such, it is important for us to define homology in the context of this chapter. Here, homology refers to a shared structure among species. Through extensive discussion, it was concluded that for the purpose of determining potential homologies (or not) among these main PFC regions between rodent and primate, cytoarchitecture and connectivity were the two most critical criteria. Our analysis of the PFC is necessarily constrained by the evidence of homology in a number of areas in the medial and orbitofrontal cortex in rodents with similar structures in primates. These regions include:

- The rodent ACC areas Cg1 and Cg2, mainly considered to be homologous with primate area 24
- Prelimbic area, discussed as homologous to area 32 or more controversially, the dlPFC in primates

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- Infralimbic area, mainly thought of as homologous to primate area 25
- Lateral and medial OFC—agranular regions that may correspond to posterior lateral and medial OFC (area 14) in primates, respectively

Rodent frontal areas Fr1 and Fr2 are thought to contain areas that are functional analogues of primate premotor and supplementary motor areas as well as of the frontal eye field (Donoghue and Wise 1982; Neafsey et al. 1986). Below, we integrate and highlight prominent features of each to consider homology (or not) among species.

Cytoarchitectonic mapping is based on the fact that the cerebral cortex presents a laminar organization that consists of six horizontal layers that run parallel to the cortical surface and vertical columns. The most important criteria followed in classic cytoarchitectonic studies include:

- Absolute cortical thickness
- Thickness of a given layer relative to that of the remaining layers and of the cortical ribbon (a roughly 3 mm strip of gray matter on the outer surface of the cerebral cortex[1])
- Size and packing density of neuronal cell bodies
- Presence of vertical columns and/or of sharp borders between layers
- The distribution pattern of cell bodies throughout the layers (homogeneous or clustered)
- The presence of special cell types such as the giant cells of Betz

With the advent of immunohistochemistry and receptor autoradiography, modern neuroanatomists have been able to make use of the heterogeneous distribution of cytoskeletal elements or enzymes, as well as of neurotransmitters and their receptors (Palomero-Gallagher and Zilles 2018) to quantify differences directly in micro-architecture between adjacent pieces of cortical tissue. The presence of LIV, together with its thickness, has been the cytoarchitectonic definition used to segregate PFC from the rest of cortex (Table 4.1). Thus, PFC encompasses areas that are granular or lightly granular. Within this region, some areas have a broader, and others a narrower, LIV. In some cases, LIV is particularly thin and invaded by layer III and layer V pyramids so that it appears as a discontinuous layer within the cortical ribbon. Areas with such an inconspicuous LIV are classified as being dysgranular in nature. As stated above, during our discussion, we found it necessary to consider a tripartite parcellation of PFC, which also considered agranular areas in OFC and portions of ACC (which could be considered controversial) but resulted in fruitful conversations regarding homologous and analogous areas across species.

Brain connectivity also provides another means by which to assess the structural similarities and differences of PFC between species. In both rodents and NHPs, the PFC is reciprocally connected with the mediodorsal thalamus

[1] For a perspective of scale, 3mm is about how much your fingernail grows in one month.

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Table 4.1 Most prominent cytoarchitectonic features of Walker's (1940) areas (modified from Rapan et al. 2023).

Area	Cytoarchitecture
8A	Pale layer III Granular; broad and densely packed layer IV
8B	Densely packed layer II Small-sized pyramids in layer III, particularly its upper portion Dysgranular
9	Gradient in cell size within layer III Granular Layer V divided into sublayers Va and Vb
10	Prominent layer II Small-sized layer III pyramids Granular; broad and densely packed layer IV Small-sized layer IV pyramids
11	Granular Layer V divided into sublayers Va and Vb
12	Most rostral and caudal portions are dysgranular Centrolateral portion is granular Sublamination of layer V in the centrolateral but not the rostral and caudal portions
13	Caudal portion is dysgranular. Rostromedial portion is granular Layer V divided into sublayers Va and Vb
14	Pale but clearly identifiable layer II Caudal portion is agranular Rostral portion is dysgranular Columnar pattern in layers V and VI
46	Prominent layer II Scattered middle-sized pyramids in lower layer III Granular Layer V divided into sublayers Va and Vb
45	Middle-sized layer III pyramids Granular. Thin, relatively inconspicuous layer IV
44	Dysgranular Single larger pyramids scattered throughout layer V

(Ray and Price 1992, 1993). Ventral and medial PFC in both species also receive extensive connections from the amygdala, hippocampus, and sensory areas in the temporal lobe, indicating that rodents and NHPs broadly share similar connectivity (Öngür and Price 2000). While these broad similarities exist, there are key differences in the patterns of connections, which we will highlight in subsequent sections as we cover each part of the PFC.

The emergence of novel high throughput connectomic approaches may enable future studies to better reveal just how different or similar these patterns

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of connections are between rodents and NHPs (Kebschull et al. 2016; Zeisler et al. 2023). In addition to differences in the patterns of connections from one brain area to different parts of the PFC, there are major differences in the routes that projections take to their targets in the PFC. For instance, white matter pathways that carry connections to and from the PFC are organized into large bundles, such as the cingulum bundle. The presence and physical organization of these bundles in macaques are highly similar to those in humans (Lehman et al. 2011), but the correspondence between rodents and humans is much less clear. This relationship has been essential for modeling the impact of deep brain stimulation delivered to white matter to treat psychiatric disorders (e.g., Mayberg et al. 2005).

Cytoarchitecture and Connectivity

Infralimbic in Rodent and Area 25 in Primate

The term infralimbic (IL) is used in rodent but is much less common in primate research. It is widely accepted that area IL is generally homologous to primate area 25 (e.g., Preuss 1995; Room et al. 1985; Saper and Stornetta 2015; Vogt and Paxinos 2014). IL is agranular and part of the allocortex. Primate area 25 is also allocortical, and there are clear similarities in the connections of the primate area 25 and rodent IL, especially those to striatum (Heilbronner et al. 2016).

Prelimbic in Rodent and Area 32 (or dlPFC) in Primate

The term prelimbic (PL) is used in rodent but much less so in primate research, and the issue of which area in the primate brain is homologous to PL remains the subject of intense debate. Some consider PL to be homologous to cingulate area 32 (e.g., Preuss 1995; Room et al. 1985; Saper and Stornetta 2015; Vogt and Paxinos 2014), whereas others consider it to be equivalent to primate dlPFC (e.g., Kesner and Ragozzino 2003), with still others to cingulate area 24 (Milad and Quirk 2012). Rodent area PL is agranular and part of the proisocortex (transition from allocortex to isocortex), as is primate area 24. However, primate area 32 and areas of the dlPFC are all isocortical. LIV is inconspicuous in area 32 (dysgranular cortex) but clearly visible in the dlPFC (granular cortex). Because area 32 has a thin LIV, while areas in dlPFC have a prominent LIV, and PL is proisocortical, this is stronger evidence for the theory that PL in rodent is homologous to area 32 in primate. On this basis, rodent PL cannot be homologous to dlPFC in primates as they do not share a common ancestry. However, evidence from connectivity is not as clear, and results from more recent functional studies in rodents indicate that PL could be considered analogous or similar to primate dlPFC (see Vertes et al., this volume). A possible explanation for this apparent discrepancy could be that PL is a precursor of both primate area 32 and dlPFC (Vertes et al., this volume). Thus, depending

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on the aspects analyzed, researchers have uncovered the characteristics of PL that are more similar to those of 32 or of dlPFC.

Expanding beyond the potential similarities of these cortical areas across species, there is also evidence of two prefrontal "streams" across species (Vertes et al., this volume), although we note that some members in our group preferred tripartite organization for the frontal cortex. Vertes et al. (this volume) also incorporate findings from a close relative of primates, tree shrews. When considering homologies discussed in their chapter, an interesting piece of the evolutionary puzzle is that tree shrews contain a well-developed LIV in an area located within a topographical position comparable to that occupied by PL (Wong and Kaas 2009b). This further suggests that rodent PL could be a precursor to the granular dlPFC of primates.

We also highlight that PL is not likely one area, as indicated by connectivity data, and may have rostral/caudal and dorsal/ventral components. As further discussed by Vertes et al. (this volume), in an experiment that demonstrated the differences in retrograde labeling following tracer injections into the ventral versus dorsal-ventral striatum (VS), labeled cells following injections in the ventral VS were found in both the IL and PL. However, labeled cells following injections in the more dorsal VS were found primarily in PL. Closer inspection of the PL-labeled cell distributions showed a possible rostrocaudal and dorsoventral distinction. There appeared to be fewer labeled cells in the caudal PL. Moreover, the density of labeled cells from the ventral VS were found in the ventral part of the PL compared to the density of cells following injections in the dorsal VS.

The dorsoventral distinction may be critical for linking homologous PL regions with the monkey cingulate cortex. Comparing the projections from areas PL (in rodents) and 32 (in primates) to the striatum demonstrated that the PL terminates along the medial border of the striatum, similar to the projection zone of area 32 in the monkey. However, importantly, PL extends more laterally into the striatum, compared to the monkey, into the regions occupied by pregenual, area 24 in the monkey (Heilbronner et al. 2016). This may indicate that part of PL may be homologous to rostral area 24 in the monkey, as proposed by Milad and Quirk (2012) based on functional similarities with respect to threat expression. In contrast, CG (expanded on further below) projections in the rodent terminated dorsal and lateral to the PL-striatal projections. The striatal space in primates is not the main recipient of cingulate projections but is the main recipient from dlPFC and premotor projections (Heilbronner et al. 2016).

Anterior Cingulate Areas: ACAd, ACAv in Rodent and Parts of Area 24 in Primate

Cortex dorsal and caudal to PL contains proisocortical areas dorsally (ACAd) and ventrally (ACAv), which are characterized by the absence of a LIV and

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by a broad layer V with relatively large neurons (Swanson 2018). Area ACAd encompasses areas Cg1 rostrally and Cg1′ caudally, and ACAv areas Cg2 and Cg2′ (Haghir et al. 2023; Vogt and Paxinos 2014). Hereby Cg1′/Cg2′ constitute the midcingulate cortex, which is not considered relevant to this survey. Areas Cg1 and Cg2 are thought to be homologous to primate areas 24b and 24a, respectively (Vogt and Paxinos 2014). Thus, primate area 24c, located within the cingulate sulcus, would not have a homologue in the rodent brain.

Nonhuman Primate Areas 11, 13, and 14

The initial parcellation of macaque ventral frontal cortex was completed by Walker (1940). Macaque OFC area 11 is granular and can be divided into medial and lateral components based on differences in layer V (Carmichael and Price 1994; Rapan et al. 2023). Areas 13 and 14 can each be subdivided based on rostrocaudal differences in the appearance of their LIV, which in both areas becomes less prominent when moving caudally (Rapan et al. 2023). Thus, area 14r is dysgranular whereas caudal to it, area 14c is agranular. Rostral area 13b is granular, whereas caudal area 13a is dysgranular. The reason for this apparent discrepancy is that, topologically, area 13a of Rapan et al. (2023) corresponds to area 13b of Carmichael and Price (1994). Further, other research groups have subdivided area 13 into medial and lateral segments based primarily on differences in SMI-32 and parvalbumin staining (Carmichael and Price 1994). Area 12 is also granular and can be subdivided into four subregions—12r, 12l, 12m, 12o—based on differences in myelin, AChE, calbindin, and parvalbumin stains. A similar parcellation of marmoset ventral frontal cortex has also been produced (Burman and Rosa 2009). These areas also differ in their receptor architecture (for a summary of receptor densities, see Table 4.2).

In their analysis of human ventral frontal cortex, Öngür and Price revealed homologous areas to those identified in the macaque (Öngür et al. 2003; see also Wise 2008). Humans have a clear anterior to posterior gradient: posterior areas 13b, 13l, and 13m are dysgranular and more anterior areas including areas 11m and 11l are granular. All parts of area 12, like those in macaques, are also granular and split into a number of different subdivisions. The most posterior areas on the ventral surface of the frontal lobe, like those in macaques, are agranular (Öngür et al. 2003). Thus, there are clear homologues of human ventral frontal areas in macaques.

In rodents, OFC is agranular. Thus, there are no clear homologues of primate granular or dysgranular areas 11, 13, or 14 in rodent OFC (Preuss 1995; Preuss and Wise 2022; Wise 2008). Based on position and cytoarchitecture, it is reasonable to consider the rodent OFC to be similar to the agranular parts of the human and macaque ventral frontal cortex (Wise 2008). If we take the approach advocated by Wise, then rodents likely share areas 13a and 14c as well as the agranular insula areas with primates. There are other reasons to think that the OFC in rodents is similar to the OFC in primates. Like macaque

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Table 4.2 Mean (±s.d.) densities in fmol/mg protein of receptors for the classical neurotransmitters glutamate (AMPA, kainate, and NMDA receptors), GABA ($GABA_A$ and $GABA_B$ receptors, $GABA_A$ associated benzodiazepine binding sites ($GABA_A$/BZ), acetylcholine (muscarinic M_1, M_2, and M_3 receptors), noradrenaline (adrenergic α_1 and α_2 receptors), serotonin ($5\text{-}HT_{1A}$ and $5\text{-}HT_2$ receptors) and dopamine (D_1 receptors) in cytoarchitectonically identified subdivisions of macaque areas 11, 12, 13 and 14 (from Rapan et al. 2023).

	11m	11l	12r	12m	12l	12o	13b	13m	13l	14r
AMPA	604	623	659	598	630	670	489	753	713	470
	(100)	(111)	(122)	(136)	(112)	(165)	(44)	(67)	(95)	(81)
Kainate	771	807	854	799	840	817	820	856	756	818
	(65)	(123)	(120)	(55)	(73)	(97)	(103)	(111)	(60)	(107)
NMDA	1585	1562	1406	1533	1400	1527	1548	1499	1498	1442
	(139)	(113)	(121)	(175)	(126)	(158)	(223)	(122)	(187)	(255)
$GABA_A$	1762	1876	1843	1792	1494	1579	1615	1622	1683	1427
	(142)	(235)	(283)	(246)	(221)	(267)	(120)	(126)	(180)	(162)
$GABA_B$	2476	2644	2412	2222	2010	2142	2311	1908	2057	2482
	(466)	(478)	(312)	(353)	(483)	(414)	(452)	(429)	(240)	(424)
$GABA_A$/BZ	1975	2066	1991	1873	1789	2102	1901	1864	2052	1715
	(218	(247)	(307)	(421)	(417)	(436)	(431)	(269)	(303)	(542)
M_1	1094	1050	1026	1152	824	888	1039	1059	1054	921
	(200	(228)	(301)	(262)	(347)	(174)	(263)	(121)	(148)	(385)
M_2	159	159	180	202	182	209	166	206	223	134
	(64)	(54)	(72)	(74)	(75)	(64)	(57)	(94)	(78)	(35)
M_3	965	944	922	918	780	832	897	918	826	833
	(132)	(101)	(96)	(108)	(132)	(149)	(104)	(130)	(108)	(118)
α_1	473	462	439	481	491	484	480	485	461	497
	(50)	(46)	(38)	(48)	(82)	(32)	(73)	(21)	(15)	(109)
α_2	342	351	306	379	320	401	350	417	404	297
	(40)	(45)	(52)	(71)	(43)	(66)	(75)	(21)	(26)	(95)
$5\text{-}HT_{1A}$	549	529	540	504	531	541	562	527	460	583
	(167)	(116)	(88)	(103)	(163)	(87)	(206)	(138)	(107)	(119)
$5\text{-}HT_2$	357	357	350	354	351	384	355	357	351	323
	(60)	(51)	(51)	(45)	(48)	(61)	(57)	(50)	(43)	(44)
D_1	92	96	86	86	71	89	93	78	70	86
	(27)	(29)	(9)	(22)	(6)	(20)	(22)	(11)	(4)	(15)

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OFC, parts of the rodent OFC receive inputs from all of the sensory modalities as well as mediodorsal thalamus, amygdala, and hippocampus (Öngür and Price 2000; Rudebeck and Izquierdo 2022). Indeed, similar to macaques, there are similar medial to lateral gradients in the patterns of amygdala and hippocampal connections, where connections from the basolateral amygdala (BLA) complex primarily target more lateral parts of OFC, whereas hippocampal connections are relatively stronger in the more medial areas. Further, Barreiros et al. (2021b) have identified anterior to posterior gradients of connections in rat OFC, which indicate that, like macaques and humans, there may also be anterior-posterior distinctions. Taken together, these patterns of connections and cytoarchitecture indicate that rodent OFC bears many of the features of primate OFC.

It is also important to note that while macaque and human ventral frontal cortex is highly similar, there are also differences. For instance, on the basis of connectional fingerprinting, Neubert et al. (2015) found that no area in the macaque frontal cortex has a similar connectivity profile to anterior lateral OFC in humans. The area that they identified likely corresponds to area 11l in humans; this highlights that there are human anatomical specializations in ventral frontal cortex.

Subdivisions of Primate vlPFC, Area 47/12

The cortex on the ventral and lateral convexity of the PFC in humans was identified by Brodmann as area 47 (Brodmann 1909), and this cortical area contains both granular and dysgranular cortical areas (Rapan et al. 2023). A similar vlPFC area in macaques was also identified by Walker (1940) as the cytoarchitecture of the area made it distinct from the medially adjacent OFC and the more dorsally situated dlPFC. In their comparative analysis of macaques and humans, Petrides and Pandya (2002) designated this part of the PFC as area 47/12. Careful cytoarchitectonic analysis of this area by different investigators (Carmichael and Price 1994; Rapan et al. 2023) further subdivided the vlPFC into four main subdivisions: 12l, 12r, 12o, and 12m. Areas 12l and 12m are granular, whereas 12o and 12r are dysgranular. Analysis of the marmoset vlPFC found the same subdivisions of area 12 with the exception of 12r, which did not appear to be present.

Subdivisions of Primate Area 10

The frontopolar cortex is occupied by Brodmann's area 10, characterized by a broad and densely packed LIV (Brodmann 1909). In humans, quantitative cytoarchitectonic analysis revealed the existence of lateral and medial parts of BA10—areas Fp1 and Fp2, respectively (Bludau et al. 2014): Fp1 has a broader LIV as well as more densely packed layer II and IIIc than does Fp2. Differences in the densities of multiple receptor types confirm this mediolateral

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segregation (Palomero-Gallagher and Zilles 2018). In the macaque monkey, four cyto- and receptor-architectonically distinct subdivisions of area 10 have been identified (Rapan et al. 2023):

- 10d (on the dorsolateral surface of the frontal pole)
- 10o (on the most ventral aspect of the frontal pole)
- 10mv (medial surface, ventrally)
- 10md (medial surface, dorsally)

As in humans, all subdivisions of area 10 have a prominent LIV, though it is slightly broader in 10d and 10o than in 10md or 10mv. The marmoset, too, has a clearly defined area 10, although unlike macaque and humans, it is not really subdivided (Burman and Rosa 2009). The rat (and mouse) does not have an architectonic correlate of area 10, although we discuss functional homologues of area 10 in rodents below.

Broca's Region

In humans, Broca's region is considered to be the cytoarchitectonic correlate of Brodmann's areas 44 and 45 (Brodmann 1909; Amunts et al. 1999). However, receptor architectonic analyses have demonstrated a more complex picture, with dorsal and ventral subdivisions of 44 (44d and 44v) as well as anterior and posterior parts of 45 (45a and 45p) (Amunts et al. 2010). Areas 44d and 44v are both dysgranular: 44d has a higher acetylcholine M2, but lower glutamate AMPA receptor density, than 44v (Amunts et al. 2010). Areas 45a and 45p are granular: 45a has a higher acetylcholine M1, but lower glutamate kainate receptor density, than does 45p. Given the dominance of the left hemisphere in language production, it is not surprising that Broca's region has been subject of numerous studies aiming to link this functional asymmetry with an anatomical one (Sprung-Much et al. 2022). In this framework, extraordinary competence in language performance was found to be associated with cytoarchitectonic alterations in areas 44 and 45 and differences in interhemispheric asymmetries (Amunts et al. 2004).

The lateral PFC of macaques contains areas 44, 45a, and 45b, which are thought to be the homologues of Broca's region in humans (Petrides and Pandya 2002). Area 44 is located mainly on the ventral wall of the inferior arcuate sulcus, close to the fundus, and encroaches onto its dorsal wall, where it is followed by area 45b (Petrides and Pandya 2002; Rapan et al. 2023). Area 45a occupies the prearcuate convexity and its border with 45B was consistently found at the tip of the inferior arcuate sulcus (Rapan et al. 2023). As in humans, macaque area 44 is dysgranular and 45 is granular (Petrides and Pandya 2002; Rapan et al. 2023). In 45b, LIV is narrower than in 45a, and LIII pyramids tend to build clusters. As in humans, macaque areas 45a and 45b differed in their M1 and kainate receptor densities. Interestingly, area 44 presents one of the

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highest, and 45a the second lowest, 5-HT1A receptor densities within macaque PFC (Rapan et al. 2023). In contrast, the marmoset has a single area 45 with no A and B subdivision and no identified area 44 (Paxinos et al. 2012).

Finally, functional connectivity analysis of macaque areas 44, 45a, and 45b revealed a strong intercorrelation of 45a and 45b as well as their association with the auditory core region within the temporal cortex. Whereas 45a is correlated with areas of the OFC, 45b presents a widespread connectivity throughout the medial and inferior parietal cortex. The connectivity pattern of area 44 resembles that of 45b, although it does not include the primary auditory cortex: it does, however, show a strong correlation with the somatosensory cortex and area 4p of the primary motor cortex (Rapan et al. 2023). In accordance with these findings, electrical intracortical microstimulation of area 44 was found to elicit somatomotor responses in the orofacial musculature of macaque monkeys (Petrides et al. 2005).

Are There Functional Similarities of the PFC Across Species?

Whether putative homologous regions across species exhibit comparable functionality would appear to be an important consideration for understanding the evolution of PFC, but it does raise several potential problems. For example, suppose a region is defined to be homologous between rodent and primate, but then appears to have different functions. This problem arises when considering the IL and PL cortex in rodents, hypothesized to be homologous to area 25 and 32 in primates, respectively, based on their cytoarchitecture and connectivity patterns (Vogt and Paxinos 2014). However, comparison of their functional contributions to threat regulation in the rat and marmoset is inconsistent with this. Using a similar Pavlovian-conditioned threat paradigm to that used in rats, inactivation of marmoset area 25 increased the rate of extinction of a behavioral and cardiovascular conditioned threat response, whereas inactivation of area 32 produced the opposite effect, at least with respect to the behavioral response, thus decreasing the rate of conditioned threat extinction (Wallis et al. 2017). Consistent with this, area 25 overactivation induced generalization of the conditioned threat response and heightened anxiety-like behavior to uncertain threat (Alexander et al. 2020). This is diametrically opposite to that demonstrated in rats in which inactivation of IL decreases extinction of the conditioned freezing response while inactivation of PL accelerates extinction (Sierra-Mercado et al. 2011). Thus, at the level of the regulation of conditioned threat responses, these regions across primates and rats do not appear functionally analogous. In contrast, when considering the regulation of appetitive responses, there is greater correspondence between rat IL and marmoset area 25. Both regions, when activated, reduce aspects of reward processing (Alexander et al. 2019; John et al. 2012) via their effects on the nucleus accumbens (Wood et al. 2023). Thus, there is no simple functional correspondence between these regions across marmosets and rats.

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At the level of cognitive function, distinct from emotional function, three of the main domains of human executive function have been defined as working memory, inhibition, and cognitive flexibility (Miyake et al. 2000). Simulations of each of these have been tested in rodents and NHPs, allowing possible behavioral similarities in PFC function to be explored across species. In such comparisons, there is always the issue of whether superficially similar performance of humans and other animals is determined by similar psychological processes. If it can be shown that homologous areas contribute to such performance across species, this provides evidence that they are likely to be employing at least the building blocks of more complex human executive functions.

Cognitive Flexibility

An early study by Dias et al. (1996a) showed that excitotoxic lesions of the OFC and vlPFC selectively impaired reversal learning and extra-dimensional set shifting in the marmoset, a double dissociation of function that has also been shown in the rat (Birrell and Brown 2000) and mouse (Bissonette et al. 2008), using an odor/tactile set-shifting task. The role of the medial PFC in rodents in extra-dimensional shifting is also consistent with work on so-called strategy shifting in rats, for example from visual to spatial cues or vice versa (Floresco et al. 2006). A study in humans has shown that resting-state functional connectivity between PFC regions including, lateral (12/47) PFC and caudate nucleus, correlated with deficits in extra-dimensional set shifting in patients with obsessive-compulsive disorder (Vaghi et al. 2017). Hence, there appears to be a degree of cross-species similarity in this capacity.

Reversal Learning

OFC has been heavily implicated in cognitive flexibility due to the effects that lesions have on this part of the frontal lobe in reversal learning paradigms. Reversal learning impairments have been consistently reported in rodents, new world primates, old world primates, and humans. There are, however, species differences in the nature of the tasks that may affect recruitment of OFC. For example, reversal learning tasks in rats and mice use spatial/action in their response (Barlow et al. 2015; Boulougouris et al. 2007; Dalton et al. 2016; Groman et al. 2019) more than stimulus/cue (Clarke et al. 2004; Izquierdo et al. 2013; Schoenbaum et al. 2003), whereas macaques and marmosets are most often tested using instrumental visual tasks.

As reviewed by Izquierdo et al. (2017), several subprocesses captured in most reversal learning tasks include rule implementation and reinforcement learning. For the sake of brevity, we highlight cross-species concordance of findings on reinforcement learning and the related function of "credit assignment." Credit assignment (i.e., the ability to assign an outcome to its contingent stimulus, cue, or action so that the most reliable prediction of future

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reward) relies on OFC in rodents and primates (Akaishi et al. 2016; Hervig et al. 2019; Izquierdo et al. 2013; Noonan et al. 2010; Schoenbaum et al. 1999; Walton et al. 2010). In addition, OFC and distinct circuits involving OFC across species (Aguirre et al. 2023; Dalton et al. 2016; Groman et al. 2019; Hervig et al. 2019; Lee and D'Esposito 2012; Wallis 2007) support multiple facets of reinforcement learning, including the maintenance of value across delay and/or trials, which is often probed in reversal learning tasks. Reversal learning tasks with probabilistic outcomes, in particular, permit estimation of choice behavior based on trial history using reinforcement learning algorithms (Sutton and Barto 2018), which provide estimates for how different features (e.g., learning rate, exploration) drive behavior. Importantly, reversal learning tasks differ in their engagement of reinforcement learning processes, which is likely a feature that determines OFC involvement and should be systematically compared across species in the future.

In recent years, there has been a point of controversy about the role of OFC in reversal learning in NHPs. In macaques, an old world NHP, aspiration lesions of the OFC were consistently found to produce a profound effect on reversal learning performance (Butter 1969; Iversen and Mishkin 1970; Izquierdo et al. 2004). This mirrors the effects seen in humans after damage to the OFC (Fellows and Farah 2003; Rahman et al. 1999) as well as marmoset with excitotoxic lesions of OFC (centered on BA 11) (Clarke et al. 2008; Dias et al. 1996b). In the marmoset and rat, there is also evidence that selective serotonin depletion from the OFC impairs reversal learning (Alsiö et al. 2020; Barlow et al. 2015; Clarke et al. 2004). Moreover, similar excitotoxic OFC lesions in the marmoset impaired the reversal of a Pavlovian-conditioned appetitive task in terms of both autonomic and behavioral responding (Reekie et al. 2008).

Recent work, however, found that excitotoxic lesions of the OFC in macaques (including Walker's areas 11, 13, and 14) do not cause deficits on instrumental deterministic reversal learning tasks (Rudebeck et al. 2013b). Follow-up studies using more complex three-choice probabilistic reversal learning tasks also failed to find any effect of excitotoxic OFC lesions on performance of the reversal or credit assignment (Rudebeck et al. 2017b). Instead, the deficits caused by aspiration lesions to OFC in macaques appear in part to be caused by damage to white matter pathways (Rudebeck et al. 2013b). Further, data from multiple modalities, including excitotoxic lesions (Rudebeck et al. 2017b), focused ultrasound (Folloni et al. 2021), and fMRI in macaques (Chau et al. 2015), indicated that the vlPFC (Walker's area 12)—and not OFC—is essential for credit assignment during reversal learning paradigms regardless of whether they include reversals or not.

One way to think about this apparent discrepancy between macaques and rodents, as well as macaques and marmosets, is to appreciate the point that we made earlier—namely, that reversal learning tasks probe two related, but distinct, functions: reinforcement learning and rule implementation. Viewed as a task that probes reinforcement learning, it appears that this function in

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macaques has become the purview of the vlPFC. Data from positron emission tomography (PET) studies of humans performing stimulus-reward learning tasks also appear to support this role for vlPFC. As people learn new stimulus-reward mappings, there is greater activity in Brodmann's area 47/12 in vlPFC (Rogers et al. 2000; Zald et al. 2005) instead of in OFC areas 11 and 13. In the latter study, participants showed more robust activation when humans were learning the rule versus after they learned the rule; this provided human evidence that supported the findings from macaques on the role of area 47/12 in reinforcement learning. Increased dlPFC activity emerged during delayed spatial alternation but not delayed object alternation, whereas orbitofrontal activations emerged in both alternation tasks. Moreover, the use of PET to image human OFC avoided the susceptibility artifacts when imaging OFC with fMRI. Thus, in macaques and humans, it appears that functions that were solely the purview of OFC in rodents (and potentially marmosets) are now subserved by area 47/12.

This leaves open the role of central OFC in macaques (Walker's areas 11 and 13) and humans (Brodmann areas 11 and 13) and how this compares to rodents. Here, there may be a clear functional similarity; namely, the updating of specific stimulus-reward associations. This function is classically assessed using reinforcer devaluation tasks (Holland and Straub 1979; Málková et al. 1997). Across a range of approaches and species, OFC appears to be essential for learning and updating specific stimulus-reward associations (Gottfried et al. 2003; Izquierdo et al. 2004; Malvaez et al. 2019; Ostlund and Balleine 2007). Thus, this computation appears to be a possible core function of OFC across species. It might be useful to determine whether the change in value is accompanied by a reduction of autonomic response to the appetitive conditioned or unconditioned stimuli in macaques, or to an uncoupling of such visceral responses with the behavioral response, as occurs in the marmoset following excitotoxic lesions of the OFC (Reekie et al. 2008). In rodents and marmoset, however, it is clear that OFC plays an important role in several forms of reversal learning; perhaps this is related to more caudal agranular regions in the primate ventral frontal cortex.

Inhibition

Behavioral inhibition can be measured in several different ways, which may indicate that this construct can be fractionated into precise behavioral processes and neural substrates (see Dalley and Robbins 2017). One prominent test paradigm is the stop signal reaction time (SSRT) procedure, which measures the ability to stop an initiated response. This can be effected in humans (Logan et al. 2014), monkeys (Schall et al. 2017), and in rodents (Eagle et al. 2008b) using either oculomotor or limb responses, respectively, in the SSRT task. There is evidence that SSRT performance in humans is dependent on a network that includes the right inferior PFC (areas 44, 45) (Aron et al. 2014;

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Cai et al. 2014), probably in conjunction with the adjacent insular cortex. The latter may mediate the salience component of the SSRT task, whereas the "motor braking" inhibitory element is thought to depend on a network that includes not only ACC and PFC regions such as 44/45, but also the hyper-direct pathway to the subthalamic nucleus (Aron et al. 2014).

The involvement of the right inferior frontal gyrus has been substantiated by fMRI studies that also include a pharmacological intervention; atomoxetine (a noradrenergic reuptake inhibitor) enhanced SSRT performance in healthy volunteers and was associated with a larger BOLD activation in the right inferior frontal gyrus (Chamberlain et al. 2009). Of relevance to the issue of comparable behavioral findings, Eagle et al. (2008b) showed that large excitotoxic lesions of the lateral OFC in rats severely impaired performance by selectively prolonging SSRT whereas medial PFC lesions, perhaps surprisingly, had no effect. Bari et al. (2011) extended these results by demonstrating that temporarily inactivating the rat ACC/dorsal PL region lengthened the SSRT. However, atomoxetine infused into the rat lateral OFC improved performance, as it had done so following systematic administration in humans, whereas intra-dorsal PL infusion had a smaller effect. The functional significance lies in considering whether areas 44 and 45 would exhibit homology in the rat brain. From many considerations, it would appear that such lateral PFC structures are not, in fact, represented in rats (Preuss and Wise 2022). However, this apparently common behavioral inhibitory function does appear to be mediated by structures in the medial PFC of the rat (i.e., ACC/dorsal prelimbic) as well as by the rodent lateral OFC (and perhaps the adjacent insula), possibly simulating the inferolateral frontal cortex involvement in humans. What is clear is that further anatomical and behavioral studies are required to understand whether and how rodent OFC can be used as a model for the role of human vlPFC in behavioral inhibition.

Closely related to response inhibition is the ability to wait or tolerate delays. There is significant evidence that subregions of PFC across species, including OFC, contribute to explicit timing (Bakhurin et al. 2017), in making decisions in delay discounting tasks (Hosokawa et al. 2013; Roesch et al. 2006; Sellitto et al. 2010; Winstanley et al. 2004), and in temporal wagering tasks as models of decision confidence (Lak et al. 2014; Sosa et al. 2021; Stolyarova et al. 2019).

Working Memory and Attentional Control

When considering the analogy between certain functional properties of rodent PL cortex and primate dlPFC, it is important to point to the engagement of both networks in working memory and attentional control. With respect to working memory, there is correspondence between delayed alternation tasks across primates and rodents with respect to the selective engagement of dlPFC and PL, respectively. In macaques, lesions of the dlPFC impair several types of delayed alternation tasks (Goldman and Rosvold 1970; Stamm and Weber-Levine

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1971), and neural recordings in this region show delay period activity patterns reflective of the working memory correlates (Kubota and Niki 1971). This is mirrored in delayed saccade tasks (Funahashi et al. 1989), which have inspired several neural models of working memory (Compte et al. 2003). Spatial alternation tasks have been extensively implemented in rodents, consistently implicating the engagement of PL. For example, work by Brito et al. (1982) showed the impact of PL neurotoxic lesions on delayed alternation in the rat, and more recent optogenetic inactivation of area PL in the mouse shows similar effects (Bolkan et al. 2017). Interestingly, both rodents and NHPs show delay period activity in these cortical areas as well as in their connected mediodorsal thalamic regions (Bolkan et al. 2017; Funahashi et al. 1989).

Working memory is closely linked to the endogenous control of attention. Classical work by several investigators has implicated the dlPFC in attentional control (e.g., Lebedev et al. 2004), which provides a complementary interpretation to its role in short-term memory maintenance (Fuster and Alexander 1971). Building on the primate task design of a cross-modal attentional task by McAlonan et al. (2006), Wimmer et al. (2015) developed an attentional control task in rats and mice. Here, a freely behaving animal chooses between two target stimuli (either a visual or an auditory target) on single trials in a cued manner; at the beginning of each trial, it receives one of two learned cues that varies on a trial-by-trial basis. Multiple performance metrics and manipulations have corroborated that mice use a rule-based strategy across most trials (Rikhye et al. 2018; Schmitt et al. 2017; Wimmer et al. 2015). This sets the stage for interpreting temporally precise optogenetic manipulations: out of several cortical areas inactivated in the PFC, including OFC, ACC, and premotor cortex, only area PL showed a delay period-specific effect (Wimmer et al. 2015). Recordings from PL showed a persistent network activity pattern over the delay in which single neurons exhibited temporally precise increase in firing rate during the delay period (sequential activity pattern). These network patterns were "rule specific" (Rikhye et al. 2018; Wimmer et al. 2015), consistent with the finding from primate dlPFC that shows the highest proportion of neurons encoding abstract rules in working memory tasks (Wallis 2011). In addition, Bolkan et al. (2017) found evidence for a sequential PL activity pattern in the context of a spatial working memory task. Interestingly, this activity pattern was not spatially specific, potentially also reflective of PL's function in the generation of abstract rules.

Beyond our main regions of interest here, a common area targeted to study working memory in the macaque is the frontal eye field (FEF). Some neurons in dlPFC tend to maintain an elevated rate of spiking, relative to pretrial baseline firing rates, during working memory retention intervals (Fuster and Alexander 1971; Kubota and Niki 1971). Funahashi et al. (1989) demonstrated that activity persists in the principal sulcus of the PFC during memory-guided saccade delays, and experimental lesions that presumably abolish this persistent activity impact memory for the spatial location of targets in the contralesioned

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hemifield (Funahashi et al. 1993a). Given the potential impact of these findings on theories of working memory, researchers launched attempts to translate these findings to humans. However, and contrary to expectations, the first neuroimaging (PET) study of spatial working memory (Jonides et al. 1993) found delayed activity in superior precentral sulcus, not dlPFC. Then, the failure of several studies to find spatial working memory-related delay period activity in a homologous part of human dlPFC became the norm rather than an exception (Courtney et al. 1998; Rowe et al. 2000; Smith et al. 1996; Zarahn et al. 1999). On the other hand, fMRI measurements during memory-guided saccade delays consistently provided evidence of persistent activity in the human superior precentral sulcus (Curtis and D'Esposito 2006; Curtis et al. 2004; Duffau 2011; Hallenbeck et al. 2021; Jerde et al. 2012; Rahmati et al. 2020; Saber et al. 2015; Schluppeck et al. 2006; Sprague et al. 2014; Srimal and Curtis 2008; Tark and Curtis 2009). Moreover, dlPFC lesions that spare the precentral sulcus in humans do not impact working memory, whereas lesions that do encroach on the precentral sulcus cause memory-guided saccade errors (Mackey et al. 2016). In a follow-up study, Mackey and Curtis (2017) found that transcranial magnetic stimulation to the precentral, but not a more anterior, part of the putative homologue of monkey principal sulcus perturbs the accuracy of memory-guided saccades (Mackey and Curtis 2017). There are different ways to think about these findings with respect to interspecies PFC homologies. Anatomically, they represent a clear difference: in the monkey, but not human, dlPFC neural activity persists and is necessary for working memory. Functionally however, the findings align, albeit in a slightly different part of the dlPFC. In addition, the human superior precentral sulcus is thought to be the human homologue of the monkey FEF (Paus 1996). Lesions to the monkey FEF impairs working memory performance (Dias and Segraves 1999; Sommer and Tehovnik 1997), and neurons in monkey FEF show persistent activity during working memory delays (Bruce and Goldberg 1985; Sommer and Wurtz 2001).

Goal-Directed Action

The PFC has long been implicated in executive control generally and in goal-directed action in particular (Stuss and Benson 1984). Consistent with this, early experiments investigating PL in rats found that lesions that occur before training abolished the acquisition of a goal-directed action, such as lever pressing for a food reward, the performance of which depends on (a) encoding the relationship between specific actions and their consequences—that is, action-outcome (AO) associations—and (b) the value of those consequences (Balleine and O'Doherty 2009). This conclusion was based on the failure of lesioned animals to pass specific tests: a contingency degradation test, which assesses sensitivity to changes in the AO relationship, and an outcome devaluation test, which assesses sensitivity of action to changes in the value of a

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specific outcome. In animals with an intact PL, degrading the AO relationship or devaluing the outcome produced an appropriate change in action. In rats without a PL, performance was inflexible and the animals failed to adjust.

Similar effects have emerged in humans. When trained to press buttons for specific food outcomes, variations in the instrumental contingency modified performance and altered self-reported measures of the causal status of actions with respect to their consequences. When assessed using fMRI, goal-directed actions were found to activate regions of medial and ventromedial PFC (area 32) and anterior medial orbital cortex (area 14) (Liljeholm et al. 2011; Tanaka et al. 2008). Importantly, recent work suggests these areas mediate different functions: area 32 activity mediates the encoding of specific AO associations (Morris et al. 2022), whereas, in both humans (Morris et al. 2014) and rats (Bradfield et al. 2015), anterior medial orbital activity appears more essential for the performance of "action" based on the retrieval of a specific valued "outcome." With regard specifically to degradation of the instrumental contingency in humans, evidence suggests that, with contingency reduction, activity in vmPFC (particularly areas 32 and anterior 14) is modulated by dlPFC (BA9): the latter tracks concomitant changes in the value of the action (Morris et al. 2014), whereas changes in the value of the background as the action value declines is tracked by ACC (area 24). The covariance between action and background activity is tracked by caudate nucleus in humans (Morris et al. 2022), which is similar to findings in rodents in which activity in mPFC ultimately results in changes in posterior dorsomedial striatum associated with the long-term encoding of specific AO associations (for a review, see Balleine 2019).

Importantly, possibly similar effects have been reported in the marmoset in which lesions of both OFC and perigenual ACC (including areas 24 and 32) abolished sensitivity to contingency degradation in acquisition (Jackson et al. 2016). Subsequently, in a more extensive comparison of established instrumental performance using both pharmacological inactivation and overactivation, this effect was restricted to area 24 (Duan et al. 2021); this suggests that rodent area 32 (particularly its most dorsal aspects stretching into the ACC) may have some compatible functions with area 24 in the primate in controlling goal-directed action and its balance with habitual behavior (Figure 4.3a, p. 72). It is thus possible that area 24 does not directly control AO learning but other processes important to degradation of the instrumental contingency. This could fit with work in macaques and highlight a role of area 24 in sustaining responding after changes in contingency (Kennerley et al. 2006). An important aspect of the latter is the role of detecting changes in the background rate of reward. From an associative perspective, during instrumental acquisition, the action (A) is the best predictor of its specific outcome (O). However, in contingency degradation, during which O is presented unpaired with A, the background or context (C) becomes a better predictor. This is because, during initial conditioning, AC → O whereas C predicts no outcome (C → Ø)

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whereas, during degradation, C now predicts O: that is, AC → O plus C → O, causing A to lose predictive power to C. The question, with regard to Duan et al. (2021), is whether there is any evidence that area 24 in the marmoset mediates sensitivity to these changes in context conditioning? If so, then perhaps area 24 is not directly involved in A → O learning/performance but in the competing C → O learning. Unfortunately, at present, the evidence is not straightforward. Although marmosets can clearly show evidence of context conditioning (Duarte et al. 2014, 2015), no studies to date have evaluated the role of BA24 in this effect. There is some evidence, however, for BA32 and adjacent BA24 involvement in contextual conditioning (Lang et al. 2009) and, as mentioned above, for context associations during contingency degradation in humans (Morris et al. 2022) as well as for context conditioning in NHPs (Chien et al. 2023; Mansouri and Buckley 2018), although not in directly comparable situations. As such, this interpretation of Duan et al. (2021) awaits a more definitive test.

Motivational Control of Goal-Directed Action

Another source of functional PFC similarity across species emerges from consideration of the motivational control of goal-directed action. As mentioned, there is evidence that medial PFC circuits mediate sensitivity to changes in outcome value. Interestingly, these circuits do not mediate sensitivity to the control of action by specific predictions based on environmental stimuli. Our ability to extract predictive information from the environment to inform future actions is a critical component of decision making. This psychological process encapsulates the essential function of the cognitive control of action as being (a) fundamentally integrative, requiring the ability to integrate predictive information with action-related learning processes, but nevertheless (b) its function is not simply to acquire information but to do so in the service of future actions; that is, in a manner which allows the animal to use this information to choose between distinct (and sometimes competing) courses of action to achieve specific future goals.

To study this interaction in the laboratory, researchers have refined over a number of years a paradigm called *Pavlovian-instrumental transfer*. Here, subjects, whether rodents or humans, are first given the opportunity to learn various predictive relationships between stimuli (S) and specific outcomes (O) (e.g., S1O1, S2O2) as well as various goal-directed actions (e.g., A1O1, A2O2). These relationships are acquired across separate experimental phases before the effect of the stimulus predictions on action selection is assessed, usually in the absence of any outcomes, to ensure any changes in choice performance are determined by prior learning. Typically, the stimulus events (S1 and S2) strongly bias choice between the two actions (A1 and A2) toward the action that previously earned the predicted outcome. For example, given S1O1, S2O2 and A1O1, A2O2, S1 biases choice toward A1 (S1: A1 > A2) and

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S2 toward A2 (S2: A1 < A2). This effect is referred to as *specific transfer* (for a review, see Cartoni et al. 2016).

We have learned quite a lot about the neural circuit that mediates this transfer effect, which implicates subcortical structures interacting with the PFC in a well-defined neural circuitry. In rodents, studies have found that during Pavlovian conditioning, the BLA is key to encoding specific SO associations and for coordinating conditioned responses based on these associations (Ostlund and Balleine 2007). However, to influence future actions, the BLA encodes these specific relations in the nucleus accumbens shell (NAc-S) via activity in a direct amygdalo-striatal pathway (Morse et al. 2020). This encoding is complex and is reviewed in detail elsewhere (e.g., Laurent and Balleine 2021). Briefly, during encoding, BLA inputs to NAc-S cause cellular changes in both the NAc-S and in its inputs from the IL cortex, which differ based on each specific SO. During retrieval in the transfer test, stimulus presentation produces activity in the IL NAc-S pathway, resulting in increased activation of specific targets of the NAc-S in ventral pallidum. The ventral pallidum output targets both the ventral tegmental area and mediodorsal thalamus, and it is this latter projection that has been found to be critical for the transfer effect (Leung and Balleine 2015). The ventral pallidum sends an inhibitory projection to the mediodorsal thalamus, which ultimately causes the activation of ventrolateral OFC, from which its targets in the dorsal striatum directly modulate action selection. As a consequence, this research establishes evidence for a PFC–striatal–pallidal–thalamic–PFC feedback network whose function is critical for the cognitive control of action.

A similar circuit has been implicated in human transfer effects. The initial studies using fMRI found evidence for activation in a ventral putamen/pallidal area (Bray et al. 2008) and in the BLA (Prévost et al. 2012), produced during the increased performance of an action when it was associated with the outcome predicted by the stimulus. More recently, dynamic causal modeling identified evidence of a circuit involving VS modulation of mediodorsal thalamus in this same effect (Balleine et al. 2015) and, in another study, for activation of lateral OFC in this effect and specifically when the action was associated with the same versus a different outcome to that predicted by the stimulus (Perkes et al. 2023). Interestingly, in this latter study, causal evidence for OFC activity was established with reference to transfer effects in adolescents with obsessive-compulsive disorder. This group was found not to express the specific transfer effect; instead, predictive stimuli were found to have no effect on action selection and, when assessed using fMRI, the lateral OFC was found to be hypoactive in these adolescents. These data provide clear evidence for functional similarity across this same circuit. This identification of neural circuitry in the motivational control of goal-directed behavior is highly relevant to the discussion of network organization of PFC circuitry below.

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How Did the PFC Evolve and How Has This Evolution Led to Produce Higher-Order Cognition, Including Social Behavior and Language Elements in Humans?

One possible avenue to analyze the evolution of PFC is to use a phylogenetic comparative framework. Such studies do not focus on particular model species but rather on many species within the context of their phylogenetic relatives (Passingham 1975). Such analyses have huge potential but also clear limitations. The potential lies primarily in being able to capture patterns of cross-species differences that provide a detailed view on how brain regions have changed in response to evolutionary pressures. The informative nature of this type of variation is derived from the fact that present-day variation across species is the result of a series of natural experiments that have taken place over millions of years of evolution, across all continents, and in all species. The scope of these experiments is such that they can never be replicated in the lab. The results of these experiments provide an unmatched and largely untapped wealth of information on how genotypic changes can shape phenotypic changes in response to environmental changes. One of the primary limitations of the phylogenetic comparative approach is that there is a clear tradeoff between a higher comparative resolution (in terms of number of species) and the resolution of neuroanatomical specificity. Significant advances have, however, been made such that recent studies incorporate a variety of different measures (e.g., size, modularity, neuronal density, synapse density) across an increasingly wider variety of different brain regions and different species. The expectation is that the field of phylogenetic comparative analyses of the brain will continue to increase its neuroanatomical specificity and, as such, become increasingly relevant for understanding neurocircuitry, neurodevelopment, and neurogenetics.

The phylogenetic comparative approach can also be used to investigate the evolution of PFC. Because brain region sizes all scale with brain size, comparisons between the size of PFC with the size of brain regions with which PFC shares a type of neurobiological association are most informative (Passingham and Smaers 2014). For example, comparing PFC size with V1 uses first-order visual input as a baseline to assess volumetric investment in PFC's higher-order processing. Such comparisons reveal stepwise grade changes in great apes and humans, indicating a selective expansion of PFC size relative to V1 in these species (Smaers et al. 2017). In other words, great apes and humans have significantly more PFC size relative to V1 than expected for their brain sizes. The same pattern of evolution is observed when comparing PFC volume against the volume of frontal motor cortex, and when using either the Brodmann or Smaers datasets (Figure 4.2).

Because size is a good indicator of growth, the occurrence of such evolutionary grade shifts suggests that great apes and humans both indicate concordant

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shifts in the developmental body plan of prefrontal growth (Smaers et al. 2019). This evolutionary expectation aligns with evidence for a developmental heterochronic shift in human prefrontal growth (Somel et al. 2009; Somel et al. 2011). The recapitulation of evolutionary grade shifts in ontogenetic growth patterns provides a largely untapped source of information that may help elucidate the molecular pathways that underpin prefrontal growth.

Additionally, phylogenetic comparative analyses can also contribute to insights on which brain circuits have expanded the most throughout evolution. In primates, volumetric variation in brain regions involved in the cortico-cerebellar system have been found to explain almost all of variation in brain size across species (Smaers et al. 2019). This suggests that aspects of the same neural system may be selected across primates. In turn, this may suggest that primate brain evolution may emphasize domain general abilities. One concept that provides a powerful explanatory framework is that of relational learning (Genovesio et al. 2014). Part of the broadly defined prefrontal-parietal network, relational learning can be materialized across modalities and results in complex behavior across the social, motor, and affective domains. When considering putative behavioral evolutionary drivers of brain evolution, emphasizing cognitive processes that have interpretable roots in neural circuitry may be preferred over emphasizing particular behavioral outputs of such processes (e.g., sociality) (Passingham et al. 2017). In the case of human evolution, it is clear that any behavioral specializations were ultimately the result of early humans having to adapt to a changing environment when the formation of the Great Rift valley separated early Australopithecus from early Pan, confronting the species that ultimately lead to *Homo* with a changing climate and an environment that was more unpredictable than the jungle environment (King and Bailey 2006). Relational learning was hereby the likely key to the success of early Homo to adapt to this new, unpredictable, and seasonal environment.

As mentioned above, one of the key drivers of relational learning was likely sociality (Humphrey 1976) but living in an uncertain environment, where understanding the behavior of prey or availability of food, most likely contributed as well. Indeed, one way to improve foraging success in sparse and unpredictable environments is to forage or hunt with a group of conspecifics. The chances of finding food is increased if each member of a group alerts the others when sustenance is found, widening the search area. Such foraging, therefore, has a major social component to it. As further noted above, the ACC in humans and other primates has been identified as a brain area that plays a key role in both foraging and social aspects of behavior. For instance, humans choosing to change foraging locations show increased activity within the dorsal ACC (Kolling et al. 2012), neurons in macaque dorsal ACC ramp in anticipation of changing foraging locations (Hayden et al. 2011), and lesions (Kennerley et al. 2006), inactivations (Shima and Tanji 1998), or electrical stimulation (Sarafyazd and Jazayeri 2019) of dorsal ACC lead to a decrease in the rate of reward procurement during foraging. A similar pattern of effects

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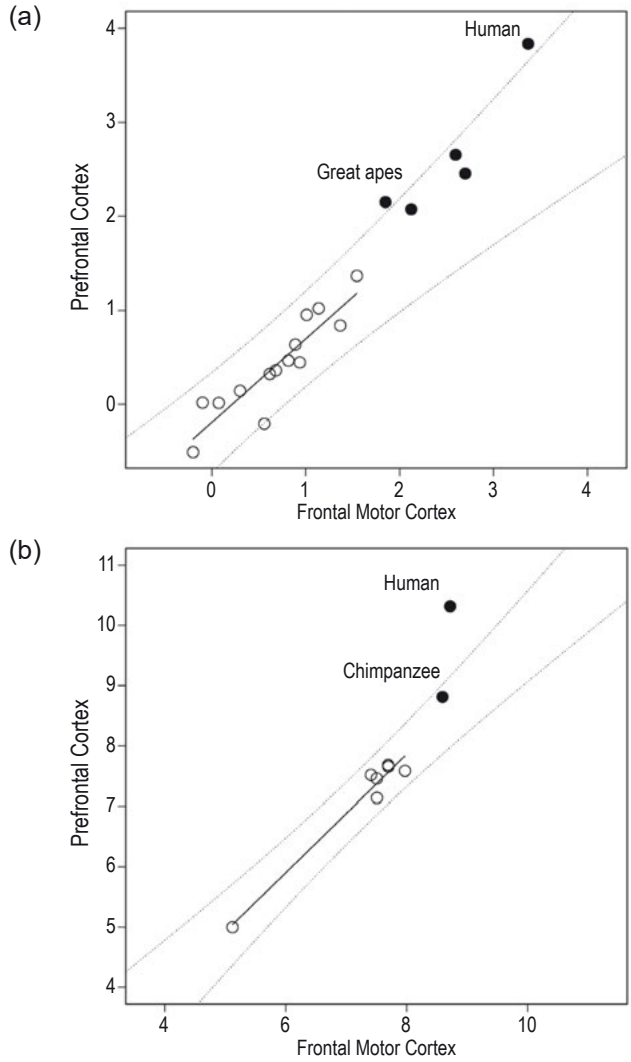

Figure 4.2 Phylogenetic regression of PFC volume against the volume of frontal motor cortex for the (a) Smaers and (b) Brodmann data. Prefrontal volume and volume of frontal motor cortex for all species in the sample, rank-ordered according to the size of PFC for (c) Smaers and (d) Brodmann data. Modified from Figures 2–4 in Smaers et al. (2017).

is also evident in the equivalent of primate dorsal ACC in rodents, CG1/CG1 subfields of medial frontal cortex (Lapish et al. 2008; Seamans et al. 2008). At the same time, medial frontal cortex, including dorsal ACC, has been shown to be essential for appropriately guiding social behaviors in humans, macaques, rats, and mice (Basile et al. 2020; Rudebeck et al. 2006; Rudebeck et al. 2007;

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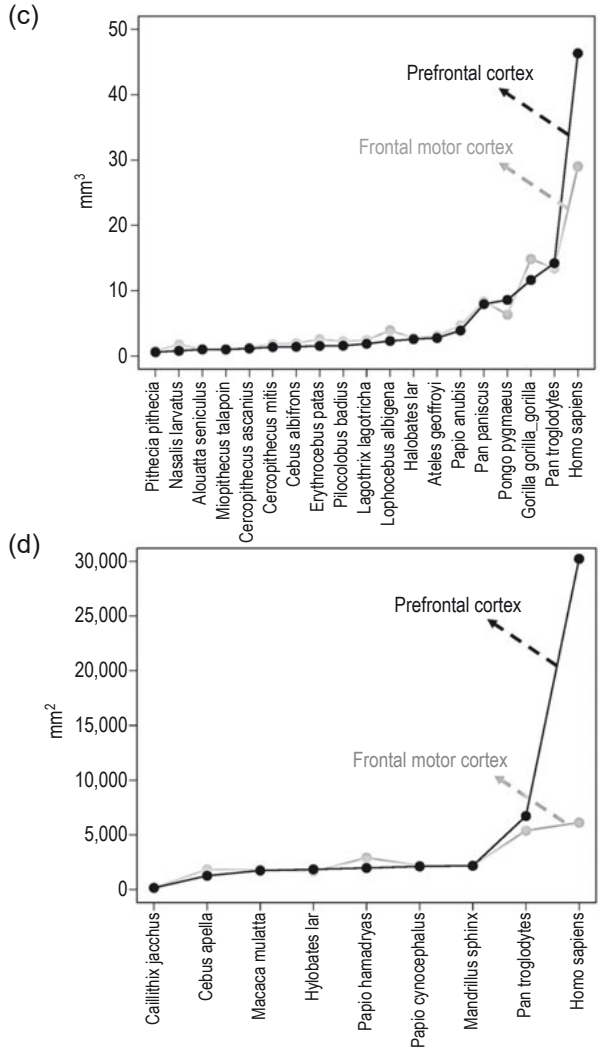

Figure 4.2 *(continued)*

Yizhar et al. 2011). This correspondence between species is notable. It indicates that the role of the dorsal ACC in both social behavior and foraging has a common origin (Apps et al. 2016), possibly in cognitive processes that are not specific to social behaviors (Humphrey 1976). The expansion of ACC in primates has likely led to these areas taking on additional functions to accommodate higher-level cognitive operations such as relational learning.

Altogether, we are far from understanding how and why new anatomical PFC areas arose throughout evolution. In addition to the ideas summarized

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in this section, several investigators have put forth ideas regarding the expansion of the PFC. For instance, consistent with the previously discussed ideas, it has been suggested that the selective pressures leading to the large brains of primates reflect the emergence of complex social systems (Dunbar and Shultz 2007). Others have suggested that because early primates were nocturnal, PFC expansion was likely related to foraging behaviors and diet (DeCasien et al. 2017). On this view, the earliest new PFC areas (e.g., granular OFC and FEF) provided adaptive advantages in the ability to identify, attend to, and plan grasping movements aimed at valuable nutrients in the fine branch niche in which they lived (Murray et al. 2017). Additional PFC areas that emerged in simian primates (e.g., vlPFC, dlPFC) have been proposed to improve foraging efficiency by reducing the frequency of poor foraging choices and reducing predation risks. Additional ideas are that expansion of visual cortex and frontal cortex in primates is tied to adaptive advantages related to predation and maternal investment, among others. It seems likely that no single driving force is responsible for the multiple stages of PFC expansion and that PFC expansion and the evolution of new areas within the PFC occurred in response to several selective factors: at different times and in different ancestral species.

What Are the Main Organizational Principles of PFC?

Definitively answering this question, of course, requires a textbook in and of itself and is above and beyond the week of discussion that we had together. Given this time constraint, we considered three features: (a) cortical folding, (b) network organization of the frontal lobe and its relationship to goal-directed action, and (c) hierarchies and gradients in PFC.

Cortical Folding

Our discussion considered how the structure and function of different aspects of PFC contributed to different aspects of behavior and cognition across many species that had either smooth, lissencephalic, or convoluted gyrencephalic brains (Miller et al. 2021b; Van Essen et al. 2013). For example, the cerebral cortices of mice and rats lack indentations, or sulci, whereas the cerebral cortices of macaques, chimpanzees, and humans have an extensive amount of sulci—in which human association cortices have sulci that are even absent in nonhuman hominoid hemispheres. Here, we focus on cortical folding features that are specific to the human cerebral cortex and address how those features relate to individual differences in functional organization with cognitive and clinical implications. Separately we consider lateral PFC, medial PFC, and OFC. As tertiary sulci are small in surface area and shallow in depth, we refer to newly identified small and shallow sulci as putative tertiary sulci. Future studies examining these sulci in lateral PFC,

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medial PFC, and OFC will determine if they are truly tertiary sulci based on their emergence in gestation, which is the classic definition (Armstrong et al. 1995; Chi et al. 1977; Welker 1990).

In human lateral PFC, there are several putative tertiary sulci that are (a) identifiable in every hemisphere (Petrides 2019) and (b) functionally (Miller et al. 2021a, b) and cognitively relevant (Voorhies et al. 2021; Willbrand et al. 2023d; Yao et al. 2022). In addition, some putative tertiary sulci in lateral PFC are not identifiable in every hemisphere, but their presence or absence is functionally and/or cognitively relevant. For instance, the presence of one such sulcus is related to a 20–34% improvement in reasoning ability in children, adolescents, and adults (Willbrand et al. 2023b). Further, this sulcus is absent in macaques and seldomly present in chimpanzees (Hathaway et al. 2023) and interestingly, the presence or absence of this sulcus is related to the functional architecture of lateral PFC (Willbrand et al. 2023a). Thus, future work should test the relationship between the presence/absence of these sulci relative to the functional and structural organization of lateral PFC in different clinical populations and species (Hathaway et al. 2023). While these studies focus on local structural-functional links, we emphasize that previous findings serve as a foundation for uncovering the infrastructure of a complex neural network linking aspects of brain structure and function to cognition in lateral PFC.

In medial PFC, perhaps the most widely studied and variable tertiary sulcus is the paracingulate sulcus across age groups, species, and in different clinical populations. The morphology of the paracingulate sulcus is related to individual differences in functional representations, cognitive performance, and the severity of clinical symptoms (Amiez et al. 2013, 2018; Amiez and Petrides 2014; Borst et al. 2014; Cachia et al. 2016; Crosson et al. 1999; Fornito et al. 2004, 2006; Garrison et al. 2015; Lopez-Persem et al. 2019; Rollins et al. 2020). The presence/absence of the paracingulate sulcus is also related to the boundaries of cytoarchitectonic areas in medial PFC (Amiez et al. 2021; Palomero-Gallagher et al. 2009a; Vogt et al. 1995). Recent research has shown that the paracingulate sulcus is present in nonhuman hominids but not NHPs such as baboons and macaques (Amiez et al. 2019, 2021; Miller et al. 2021a). Additional putative tertiary sulci have also been identified and related to different aspects of the functional organization of medial PFC (Amiez et al. 2013; Amiez and Petrides 2014; Lopez-Persem et al. 2019). Future research is needed to pinpoint whether individual differences in the morphology of these putative tertiary sulci in medial PFC are also related to individual differences in cognition.

In human OFC, sulcal morphology is related to the complexity of representations of value (Li et al. 2015). Different OFC sulcal patterns (or "types") are also related to the complexity of different clinical disorders (Cardenas et al. 2011; Drevets 2007; Eckart et al. 2011; Nakamura et al. 2020; Patti and Troiani 2017; Rogers and De Brito 2016). Recent findings also show that the local gyrification of specific parts of OFC are related to emotion-related impulsivity,

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which is a transdiagnostic feature of several different clinical disorders (Elliott 2022). Future research is needed to bridge the gap with the results in lateral and medial OFC by testing if the morphology of sulci, including putative tertiary sulci, in OFC is related to cognition and the severity of clinical symptoms.

Altogether, as in other cortical expanses—such as ventral temporal (Ammons et al. 2021; Chen et al. 2023; Parker et al. 2023; Weiner 2019; Weiner and Willbrand 2023), lateral parietal (Willbrand et al. 2023d), and medial parietal cortices (Aponik-Gremillion et al. 2022; Willbrand et al. 2023c; Willbrand et al. 2022)—putative tertiary sulci in lateral and medial PFC, as well as OFC in hominid brains seem to serve as a mesoscale infrastructure bridging between micro-architectonic and network features. This has cognitive and clinical implications, and awaits further elucidation through future research, especially as pertains to the hypothesis of fundal cognition (Weiner 2023).

Network Organization of the Frontal Lobe and its Relationship to Goal-Directed Action

Resting-state fMRI (rs-fMRI) has emerged as an important method for assessing neural networks and has enabled extensive connectivity analyses between multiple brain regions (Gratton et al. 2023; Lurie et al. 2020). Another interesting and important cross-specifies comparison should also be made between prominent network analyses of PFC, based on resting-state functional connectivity versus the circuits that have been implicated in goal-directed action by more conventional functional analyses. Although there are clear differences in brain complexity and function, reports of sensory, motor, and default networks in human, NHPs, and rodents suggest that common principles may underlie resting-state brain organization across species (Xu et al. 2020). This research has obvious implications for studying the evolution of brain function and connectivity as well as our understanding of the fundamental mechanisms underlying sensory perception, motor control, and cognitive processes. Sensory networks corresponding to visual, auditory, and somatosensory modalities, involving corresponding functional regions of the cortex, have been described and, in NHP and rodents, studies have shown similar resting-state networks associated to those described in humans, reflecting the spontaneous activity and functional connectivity of brain regions involved in sensory perception. Similarly, common resting-state motor networks have also been identified associated with motor planning, control, coordination, and execution during rest, suggesting a common role in the preparation and execution of motor tasks. Similarities in a default mode-like network have also been reported across species (summarized in Buckner and DiNicola 2019) and although those described in NHP and rodents may not be as complex as in humans, their presence also suggests a level of conservation, as well as differences, in brain organization related to cognitive functions (Garin et al. 2022).

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Nevertheless, despite these impressive similarities, the relationship of these networks to those underlying goal-directed action is not at all clear. As described above, this form of action is strongly linked, across species, to the integration of cognitive and emotion processes, controlling both the learning process through which the relationship between specific actions and their consequences is encoded (Figure 4.3a) and integrated with goal values. As such, one might expect close similarities to the sensory, motor, and cognitive networks described using rs-fMRI. This should be particularly true of the default mode network (DMN), which is concerned primarily with "higher" cognitive processes (Raichle 2015). As commonly conceived, the DMN in humans and NHPs includes regions of ventromedial PFC (BA9, 10, 11), ACC (BA24 and 32), and, more posteriorly, the retrosplenial cortex, the precuneus, posterior parietal cortex, and medial temporal lobe. Many of the prefrontal structures implicated in the DMN are also involved in goal-directed action (Figure 4.2a); however, the more posterior structures have not been implicated (although activity in the caudate nucleus and posterior parietal cortex has been reported to track outcome identity covariance during changes in AO contingency (Morris et al. 2022). With increasing attention being paid to individual differences rather than group averaging, it appears likely that networks such as DMN may become further subdivided (DiNicola et al. 2023), thus accounting for this apparent discrepancy.

Perhaps more notably is the almost complete silence of the basal ganglia in rs-fMRI, given that interactions between prefrontal regions and the striatum have been heavily implicated in goal-directed control in rodents, NHPs, and humans. The same distinction can be drawn with sensory and motor resting-state functional connectivity networks. These identify converging regions of sensory and motor cortices (including the dlPFC, posterior cingulate, and cerebellum), respectively, but again, completely avoid the basal ganglia, most notably the ventral striatal networks identified with the stimulus control (Figure 4.3b) and value-based control (Figure 4.3c) of goal-directed performance. These general networks involving sensory, motor, and default modes, including the executive network, do not appear, therefore, to have much in common with any of the networks implicated in goal-directed action using cross-species functional analyses. However, this may not be as true of another resting-state network associated with more specialized sensory processing, often referred to as "the saliency network" (Menon and Uddin 2010). This network has been argued to involve strong interconnectivity of anterior insular cortex and ACC together with midline thalamus, ventral striatum, and central amygdala and could be argued, therefore, to have much in common with some features of the stimulus- and value-based control networks described by Balleine and O'Doherty (2010) and illustrated in Figure 4.3. However, the results of a meta review of this literature showed that the ACC and insular cortex respond to saliency independently of changes in value (Bartra et al. 2013), whether predicted or experienced, and appears more closely linked to autonomic feedback

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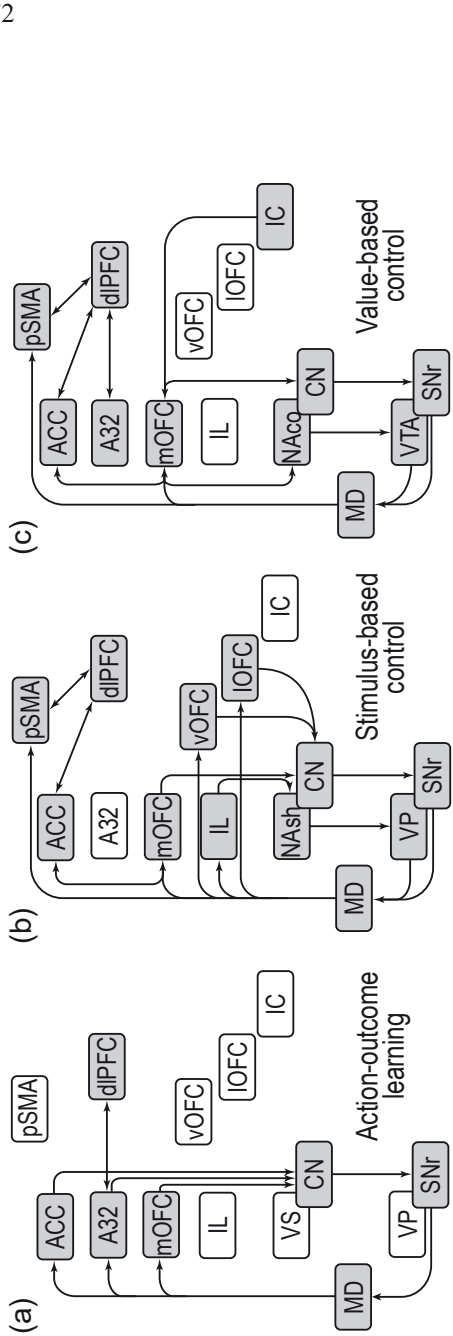

Figure 4.3 Circuit models of the neural structures involved in various aspects of goal-directed learning. (a) Action-outcome learning: Prefrontal regions involving dorsal and anterior regions of medial PFC (BA32, extending to BA10) and ACC (BA24) have been directly implicated in encoding the action-outcome contingency during goal-directed learning, with dlPFC (BA9) implicated in action value comparisons. These structures play a key role in striatal learning processes, particularly the caudate nucleus (CN), for long-term memory and together with basal ganglia feed back to medial OFC (BA14) to control action-outcome retrieval for subsequent performance. (b) Stimulus-based control: Predictive learning, particularly specific stimulus-outcome associations, have been found to exert control over goal-directed actions via a circuit involving mOFC and infralimbic (IL) cortical control of the nucleus accumbens. For specific outcome predictions, this circuit involves IL to accumbens shell (NAsh), ventral pallidum (VP) and feedback to lateral OFC (lOFC) via substantia nigra pars reticulata (SNr) mediodorsal thalamus (MD), and consequent activation of a cortical-basal ganglia feedback circuit to cingulate and presupplementary motor areas (pSMA) that elicit changes in performance. (c) Value-based control: The control of actions after changes in the reward value of their consequences is critical to maintaining value-based decision making. Such control is mediated by a limbic-cortical "incentive memory" involving amygdala and insular cortical (IC) connections with mOFC and its inputs to other medial wall structures including A32, and its output to accumbens core (NAco) and the parallel in retrieval of specific action-outcome associations via CN and basal ganglia feedback to motor regions.

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or homeostatic demands (Seeley 2019). As such, it seems reasonable to remain agnostic on the relationship between activity in this network and functional networks mediating the motivational and emotional control of goal-directed action. It should also be noted that there may be technical reasons for the relative lack of evidence for basal ganglia network involvement, particularly the use of ultrafast (multiband) imaging protocols which tend to favor cortical structures (Srirangarajan et al. 2021).

Hierarchies and Gradients in PFC

A ubiquitous organizational principle in the portions of human PFC (and somewhat in the species discussed here) is different types of hierarchy. For example, in different portions of PFC, Burt et al. (2018) showed a tight coupling between transcriptomic expression and structural imaging correlated with myelin that contributes to an area's position in a cortical hierarchy, including PFC, in both human and macaque. These authors also considered position in the cortical hierarchy in macaque as determined based on the ratio of efferent to afferent projections (see Murray and Constantinidis, this volume), which further provides details of the microcircuitry contributing to the anterior-posterior PFC hierarchy.

In the medial PFC, there is also a gradient in both humans and macaques running along an anterior-posterior axis in which primary/sensory motor regions are situated more posteriorly and transmodal regions associated with the DMN are situated more anteriorly (Margulies et al. 2016). Consistent with this anterior-posterior hierarchy in medial PFC, there is also evidence of a hierarchy of concepts, again with simpler concepts represented more posteriorly and vice versa (Theves et al. 2021). Earlier in this chapter, we provided other examples of apparent hierarchical PFC organization, including neurochemical gradients (see Table 4.2 and Rapan et al. 2023).

Furthermore, Murray et al. (2014) showed a hierarchy of intrinsic timescales across primate cortex; for example, the intrinsic timescale was slowest in ACC compared to OFC and lateral PFC (Knudsen and Wallis 2022; Padoa-Schioppa 2009). These findings, which are based on measures such as spiking autocorrelations, fit nicely with task findings in macaques (Lin et al. 2020). Nevertheless, in recent years, several studies have explored timescale hierarchies in humans (Baldassano et al. 2017; Huntenburg et al. 2018) that are also consistent with this hierarchy.

Further consistent with this dorsal-ventral hierarchy, Hunt et al. (2018) recorded in macaque OFC, ACC, and dlPFC and found that (a) OFC performs a value comparison, (b) ACC integrates several features of individual values to a decision bound, and (c) dlPFC routes attention to salient features of the task, relevant for decision making. Single unit and population activity were largely consistent with this pattern, indicating an increasing level of complexity from ventral-to-dorsal (or dorsal-ventral control) of PFC function in macaque. A

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similar pattern holds true in rat OFC and ACC for value comparison and final actions, respectively. Rat OFC is involved in value computations of specific outcomes (Schoenbaum et al. 2011), whereas ACC is involved in *relative* value comparisons in the action or effort space (Akam et al. 2021; Hart et al. 2020; Mashhoori et al. 2018). Thus, ACC likely contains an integrated, multiplexed signal with information from OFC and more.

Though not discussed extensively during the Forum, hierarchies in lateral PFC should also be mentioned. Whereas previously it was thought that the most anterior regions of the frontal pole in humans were located at highest stages of the processing hierarchy (Badre, this volume, Badre 2008; Badre and D'Esposito 2009), recent findings support two separate hierarchical gradients: one related to temporal abstraction and the other to feature abstraction. They both converge in the mid-PFC (Nee and D'Esposito 2016, 2017), which would be considered at the "apex" (Badre, this volume) of the hierarchy. The findings of this modification of the anterior-posterior gradient in lateral PFC was also supported by rs-fMRI data (Margulies et al. 2016). Interestingly, this is consistent with connectivity data in macaque. As connectivity is commonly used to assess hierarchical positions in the brain—specifically a ratio of efferent to afferent connections—Goulas et al. (2014) explored this ratio in lateral PFC in which an anterior-posterior hierarchy predicts the highest ratio at the frontal pole in BA10 and identified the highest asymmetry within the middle portion of dlPFC. A recent meta-analysis by Abdallah et al. (2022) also shows that there is evidence for a dorsal-ventral hierarchy in dlPFC across over 14,000 studies. In a much smaller sample size, this is consistent with a recently proposed dorsal-ventral hierarchy within lateral PFC in which the mid-dlPFC was identified as critical for working memory, whereas the mid-vlPFC was proposed to be critical for active retrieval and encoding of information (Petrides 1994, 1996, 2005; Petrides et al. 2002).

In human OFC, previous work shows evidence of a hierarchy of value representations along an anterior-posterior axis: simpler reward representations were situated more posteriorly and more complicated reward representations were situated more anteriorly (Sescousse et al. 2010, 2013). These findings were consistent with a proposed hypothesis of an anterior-posterior functional gradient, reflecting the abstractness of reinforcers in OFC (Kringelbach 2005; Kringelbach and Rolls 2004). Interestingly, functional regions related to the complexity of reward also couple with sulcal morphology at the level of individual participants in human OFC (Li et al. 2015). Linking back to our discussion earlier, more anterior sulci emerge later in gestation in OFC; this indicates that the sulcal-functional coupling in anterior OFC may develop later in life than posterior OFC. Further, the posterior region is located in dysgranular cortex, while the anterior region is located in granular cortex (Henssen et al. 2016; Mackey and Petrides 2009; Öngür et al. 2003; Öngür and Price 2000; Price 2007). Because OFC also contains representations other than value and reward (Knudsen and Wallis

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2022; Wallis and Miller 2003b), future research is needed to show if human OFC contains hierarchies for additional representations.

Mechanisms By Which Major Circuits Exert Control: Is There Anything Special about Neuronal Physiology of PFC?

Oscillations

In comparing meso- to macroscopic measurements across primates and rodents (e.g., oscillations), it is important to consider that primate dlPFC, for example, appears to have some clustering of neurons that show similar task-relevant tuning (e.g., Wallis et al. 2001). In rodents, these features are less observed (Rikhye et al. 2018; Schmitt et al. 2017). This is not dissimilar from the differences observed in visual areas of the two species: primate V1, for instance, shows clustering in the form of orientation columns (Hubel and Wiesel 1977), whereas rodent V1 shows a salt and pepper organization (Priebe and Ferster 2012).

Network-level oscillations are features of cognition and behavior, though ideas differ as to whether they are considered mechanisms or epiphenomena. Irrespective of the strong opinions, measuring oscillatory activity can capture information transfer across regions, across hemispheres, and many neuropsychiatric conditions like schizophrenia and bipolar disorder are characterized by aberrant oscillations. Certain frequency bands have been previously associated with certain functions of the PFC, including, for example, gamma oscillations (40–100 Hz) in working memory, as well as the theta frequency band (5–10 Hz) in reversal learning and value-based decision making across species (Amarante et al. 2017; Fatahi et al. 2020; Knudsen and Wallis 2020; Marquardt et al. 2017; Ye et al. 2023b). Furthermore, Sohal et al. (2009) first showed that mouse medial PFC parvalbumin+ neurons play an important role in generating synchronized rhythmic activity in the gamma frequency range. In more recent work, Cho et al. (2020, 2023) empirically showed that this synchrony was necessary for learning about rule shifts in an attentional set-shifting task and not required for learning initial associations between cues and rewards, or even in reversals of individual cue-reward associations. This type of specificity on behavior is an interesting and important extension to lesion experiments in rats, indicating medial frontal cortex is necessary for attentional set shifting (Birrell and Brown 2000). Thus, overall, there is good evidence that fronto-cortical gamma and theta oscillations could be studied as biomarkers across species, particularly as preclinical models of disorders in which one finds impaired reward learning and value-based decision making paired with aberrant oscillatory activity. Future work should combine measures of oscillations partnered with viral-mediated, cell type specific targeting.

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While we have shown that temporal hierarchical, transcriptomic, and receptor architectural features differ in the main PFC regions that are the focus of this chapter, further details can be provided that lead to mechanistic insight into aspects of cognition associated with PFC, such as working memory. For example, NMDA, but not AMPA, receptors are prominent in subregions of PFC, which is meaningful as NMDA receptors have slow decay time constants and AMPA receptors have fast decay time constants (Constantinidis and Wang 2004; Wang 2001). Thus, the former have sustained firing rates associated with a delay period during a memory task, while the latter do not (Murray and Constantinidis, this volume).

Rapid Learning

A key domain in which PFC circuits may exert control over sensorimotor transformations is rapid learning. Human and other primates can adjust behavioral strategies within seconds, even following a single error (Thoroughman and Shadmehr 2000). This behavioral capacity is thought to rely on mechanisms that are faster than what synaptic plasticity supports. The notion of computation through dynamics has thus been suggested as a mechanism for this process (Sohn et al. 2021). Within this framework, a cortical area's population activity patterns are a function of its internal connectivity and external drive (Vyas et al. 2020). That is, changing the external drive alters the initial conditions of the neural dynamical system and, in turn, would change the quality or even the nature of the implemented computations (Gurnani and Cayco Gajic 2023). One example is derived from primate dorsomedial PFC of monkeys trained to generate a timed motor response based on a sensory measurement of a corresponding interval on single trials (Remington et al. 2018). Changing the sensorimotor context, or the relationship between the sensory measurement and motor output, generated dorsomedial PFC motor production neural dynamics consistent with changing their initial conditions. Computationally, this resulted in different speeds at which the population activity evolved, allowing monkeys to produce flexibly different time intervals within exceedingly short periods of time. Although not explicitly measured in this setup, the lack of synaptic-level adjustments in such rapid learning conditions was observed in a primate motor adaptation task, in which single trial adjustments did not result in any changes to the activity covariance structure within either premotor or motor cortex (Perich et al. 2018). These population-level activity mechanisms may also be relevant for more cognitive strategy adjustments as recently observed in changes of dlPFC neural geometry in macaques performing value-based decisions (Wang et al. 2023).

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What Unique Contributions Does Work with Optogenetics, Chemogenetics, Large-Scale Electrophysiology, and Calcium Imaging Contribute to Understanding PFC Function?

There has been a steep increase in the use of high-channel, high-density probes for electrophysiological recordings in both rodents and primates, enabling the collection of an unprecedented amount of data from just a few animals (Juavinett et al. 2019; Jun et al. 2017; Luo et al. 2020). These methods are expected to offer unique insights into a functional dorsal-ventral "gradient" organization for PFC, as described by Rich and Averbeck (this volume). Viral-mediated technology also allows powerful correlate and causal approaches in both rodents and primates (see Izquierdo, this volume). The major advance associated with transgene targeting using specific promoters is the ability to identify selectively and track individual cells and cell types over time or over processes (i.e., learning). For example, targeting and manipulating pyramidal neurons in PFC is now possible with single-cell calcium imaging combined with opsin/optogenetic tagging. This level of resolution is commonplace in mice and rats (for a review, see Resendez et al. 2016) and has gained momentum over recent years in macaques (Jazayeri and Afraz 2017; Oguchi et al. 2021a; Seidemann et al. 2016). Though optogenetic techniques probing PFC circuits have demonstrated promise in NHPs, they have mostly been applied to the interrogation of sensorimotor systems, less to learning, decision making, or other functions of the PFC. An important factor to consider here is the duration of activation/inhibition, especially because PFC functions tend to unfold over longer timescales, whereas sensorimotor functions occur much more quickly. In addition, optogenetic perturbation relies on implantation of a fiber to deliver different wavelengths of light, making it less of a viable therapeutic option for human patients in the future (i.e., limiting its translational appeal), though progress is being made in delivering light to deep brain structures transcranially (Chen et al. 2021). Similarly, fiber photometry enables the measurement of bulk calcium signals (analogous to the relationship of local field potentials to single-unit activity measures in electrophysiology) and is often used to confirm causal manipulations in systems neuroscience experiments in rodents. This technology, however, has not been widely adopted in nonhuman or human primate studies.

Of particular promise for cross-species translation is the chemogenetic approach. Chemogenetic techniques work through viral introduction of mutant G-protein coupled receptors or designer receptors exclusively activated by designer drugs, DREADDs (Armbruster et al. 2007; Roth 2016). Though this technology does require invasive intracerebral surgery to introduce the mutant receptors, the timescale of this method during behavior is ideal, similar to traditional pharmacological approaches, requiring no chronic implant for activation. Similar to pathway-specific DREADD experiments conducted in

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rodents, the more refined double-virus method to introduce retrograde cre in the target region (i.e., terminals), cre-dependent DREADD at the origin (i.e., cell bodies), and similar approaches are now frequently being employed in NHPs (Oguchi et al. 2021b; Oyama et al. 2022; Vancraeyenest et al. 2020; Wood et al. 2023). Consequently, there should be a critical mass of studies in the near future to provide a thorough cross-species comparison of rodent and NHP studies on the function of PFC circuits.

Utility of Animal Models

Understanding the structure and function of PFC circuits in species other than humans is an important intellectual goal in its own right. However, this endeavor also has utility in various applications of our understanding and treatment of human mental disorders, even despite their evident complexity and heterogeneity. The optimal approach may be to model human symptoms or symptom clusters by explaining them in terms of theoretical constructs (at both functional neural and behavioral levels) derived from cross-species studies, as described earlier in this chapter. We anticipate that this would at least provide building blocks for understanding the greater complexities of human executive function. This approach may then, for example, identify a relatively finite number of neural systems or circuits, which in many cases (limited by homology) can be investigated using such methods as chemogenetics or optogenetics, combined with suitable behavioral measures having cross-species translational validity. Ideally, tests which show functional similarities (e.g., see earlier discussion on criteria for homology) across species should be employed rather than simple behavioral "readouts."

The second important component of any such model is to simulate a deficit in a particular neural circuitry that may mirror what has been discovered in studies of a human disorder. Of course, in most cases, the etiology of some human mental disorders is obscure and multifactorial, which makes single transgenic preparations and global manipulations of stress of limited use. However, given knowledge about neural systems involvement in human mental disorders, it may now be more feasible to make these simulations. For example, overactivation of subcallosal cingulate cortex in marmosets to mimic the overactivation of this region in depression has revealed both anxiety and anhedonia-like symptoms, which appear dependent upon separate pathways to the amygdala and different parts of the nucleus accumbens, respectively (Wood et al. 2023). Other excellent examples are provided by the use of optogenetics to provide excitatory or inhibitory drive, respectively, to the medial and lateral OFC in *Sapap* knockout mice to produce compulsive grooming behavior mediated by the striatum, as well as other behavioral signs, which may likely be relevant to human obsessive-compulsive disorder (Ahmari et al. 2013; Burguière et al. 2013).

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The aim would be to develop interventions such as selective microinfusions of pharmacological agents, electrical stimulation (deep brain stimulation, DBS), or even behavioral interventions. For instance, in the work on marmoset subcallosal cingulate cortex, only anhedonia, but not anxiety, was ameliorated by the rapidly acting antidepressant ketamine administered systemically 24 hours earlier (Alexander et al. 2019). Further, in the work by Ahmari et al. (2013), the behavior was remediated by treatment with SSRIs as used (with limited success in the clinical population), which also further strengthens the validity of their model. The advent of newer technologies, however, also enables much more specific-circuit interventions, which have greater cellular specificity in the form of optogenetic and, more feasibly from the clinical therapeutic perspective, chemogenetic interventions via DREADDs receptors. This approach may also help us understand how some existing treatments (e.g., DBS) actually work at a mechanistic level.

It should not, of course, be underestimated just how ambitious such an undertaking actually is. It is inconceivable, for instance, that chemogenetics could be readily applied to human mental health disorders without monumental ethical groundwork. Perhaps an early tractable approach could be to use chemogenetics to reduce the side effects of existing and successful pharmacotherapies. Viral-mediated technology is also technically challenging to employ in NHPs, although considerable progress is being made. Nevertheless, parallel work with rodents validating, for example, noninvasive methods for implant-free deep brain transcranial photoactivation of deep brain circuits (Chen et al. 2021) should help to establish proof of principle, given the constraints on translation imposed by species differences.

Conclusion

As reflected in this chapter, our discussion at this Ernst Strüngmann Forum focused on key principles that underpin the determination of homologies and analogies of PFC. Our discussion built on previous work that dates back to the 1800s as well as highlights ongoing efforts to determine how the structure and function of PFC relates to similarities and differences across species with cognitive, developmental, and translational insights. Throughout, we highlighted areas for future research to motivate future experiments, both empirical and theoretical. In addition, we hope that this discussion will spur further discussion and reviews and eventually lead to a consensus regarding the ambitious goal of determining the homologies and analogies of PFC, as well as the cognitive, developmental, and translational insights gleaned from those homologies and analogies.

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