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The Two Prefrontal Streams

Evidence for Homology Across Species

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Abstract

The prefrontal cortex (PFC) plays a critical role in human cognition, but the precise mechanisms by which its circuitry accomplishes its proposed functions are unclear. Nonhuman animals are indispensable in revealing such mechanisms, as the ability to monitor and manipulate their circuitry provides necessary insights. A major impediment to linking the growing progress in animal research to insights for human cognition and applications to human health is the lack of consensus on how the PFC is homologous across species. In this perspective, we follow the classification of human PFC into medial and lateral streams, with the medial being primarily evaluative and the lateral being executive. Based on anatomy, physiology and function, we advance the proposal that the rodent medial prefrontal cortex contains elements of both streams, with functional parallels between primate ventromedial and dorsolateral PFC with rodent infralimbic and prelimbic areas, respectively. To support this argument, we highlight the granular nature of the prelimbic cortex in *Tupaia belangeri*, a basal primate whose PFC macrostructure is rodent-like. Our perspective may help provide additional input to the debate on PFC homology and lead to new testable hypotheses.

Introduction

The prefrontal cortex (PFC) is a complex and highly interconnected region that engages in a wide variety of cognitive functions, including attention, working memory, decision making, and social behavior (Miller and Cohen 2001; Soltani and Koechlin 2022). In the human brain, the PFC has shown great expansion compared to even the closest primate relatives (Preuss and Wise 2022), a process thought to be key to the unparalleled cognitive expansion seen in our species. However, both the principles by which PFC circuits contribute to cognition as well as their origin/emergence are poorly understood.

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Nonhuman animal research is poised to help fill this knowledge gap because, in addition to its basic scientific value, it offers important insights into human health given the involvement of PFC dysfunction in several neurological and psychiatric illnesses (Liston et al. 2011; Smucny et al. 2022). Given the mechanistic accessibility afforded by newer monitoring (Tian and Looger 2008; Wu et al. 2022; Xu et al. 2017) and causal tools (Kim et al. 2017; Rabut et al. 2020; Roth 2016), there has been an explosion in PFC animal research over the last decade focused on rodent PFC. Yet despite this progress, it is considerably challenging to relate these advances into insights applicable to understanding the human (and nonhuman primate) PFC given the considerable differences in macro- and microarchitecture. Specifically, while the human PFC has a large number of well-differentiated areas (Haber and Robbins 2022)—von Economo and Koskinas (1925), for example, identified 39 cytoarchitectonically distinct areas on the cortex covering the lateral, medial, and orbital portions of the frontal lobe—the rodent PFC is far less differentiated, thus making homology assignments very challenging.

Here, we follow the general two-stream human PFC classification (Domenech and Koechlin 2015) as a starting point. Specifically, this functional classification suggests that the lateral stream, which is largely composed of the lateral PFC (lPFC) is involved in executive control and rule-based behavior (Friedman and Robbins 2022). In contrast, the medial stream, which is composed of the ventromedial PFC (vmPFC) and dorsomedial PFC (dmPFC), is involved in adjusting behavioral strategies based on reinforcement and self-monitoring (Domenech and Koechlin 2015). According to the definition of Domenech and Koechlin (2015), the lPFC encompasses Brodmann's (1909) areas 44 and 45, as well as the lateral portion of areas 8, 9, and 10 (although those authors do not mention areas 46 or 47 which are commonly included in the lateral stream). Their vmPFC covers Brodmann's areas 11, 12, 14, 25, the medial part of 10, rostral part of 24, and ventral portion of 32, whereas the dmPFC encompasses the caudal and dorsal parts of 24 and 32, respectively, as well as the medial portion of areas 6, 8, and 9.

We present evidence that the rodent medial prefrontal cortex (mPFC) exhibits homology to both streams. Specifically, our thesis indicates that the rodent infralimbic cortex (i.e., area IL) is most closely related to the primate vmPFC based on both connectivity and function. On the other hand, the rodent prelimbic cortex (i.e., area PL) exhibits gradients of connectivity that makes it a likely precursor of several regions found in the primate PFC. Specifically, the evidence reviewed here supports that PL is a precursor of areas belonging to the primate medial and lateral stream regions such as dmPFC area 32, and dorsolateral PFC (dlPFC) areas 10, 9, and 8. The notion of a single rodent-like precursor of several primate cortical areas is not new and has been utilized to explain evolutionary expansion and differentiation in the sensorimotor system (Kaas 2004). Here, we extend the notion of an evolutionary precursor to prefrontal circuitry, providing a clearer context for

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relating rodent functional data to primate cognition. Consistent with our proposal, we point to *T. belangeri*, an evolutionary intermediate whose prelimbic cortex contains an area that is granular, a microcircuit feature that establishes its correspondence to primate dlPFC.

The Prelimbic Cortex As a Precursor of Dorsomedial and Dorsolateral Prefrontal Cortex

The cerebral cortex has undergone significant changes and differentiations throughout evolution, providing space for the development of distinct cortical areas with specialized functions. The evolution of somatomotor control, for example, from simple reflexive movements to highly coordinated and precise voluntary actions, is associated with a significant cortical expansion and segregation as well as neuronal specialization. Indeed, the *Bauplan* of the brain of opossums resembles that of small-brained placental mammals in all but one aspect: it contains a "somatosensory-motor amalgam," with a complete overlap of somatosensory representation and motor control maps (Dooley et al. 2014; Karlen and Krubitzer 2007; Wong and Kaas 2009a). Since marsupials diverged from placental mammals around 130 million years ago, Kaas (2004) proposed that this somatosensory-motor amalgam could be considered a "precursor area" of the architectonically distinct sensory and motor areas found in the brains of the latter infraclass. Small placental mammals, including tenrecs (Krubitzer et al. 1997), hedgehogs (Catania et al. 2000), or rats (Haghir et al. 2023), present a distinct primary motor cortex (M1), and in most cases their somatosensory region encompasses four areas: a primary (S1) and a secondary (S2) somatosensory area as well as rostral and caudal somatosensory belt areas. A secondary motor area has also been described in the rat brain, and some of these species present a further somatosensory area located ventrocaudally to S2 (for a comprehensive review, see Kaas 2004). In addition to these two motor and five somatosensory areas, the brain of tree shrews (the closest relatives of primates) presents a rudimentary somatosensory posterior parietal area (Wong and Kaas 2009a). A further differentiation occurs in the brains of small primates such as galagos (Wu and Kaas 2003) and slow lorises (Carlson and Fitzpatrick 1982), which display additional somatosensory areas located in the lateral fissure. In macaque monkeys, but not in marmosets, the caudal somatosensory belt area developed further into areas 1 and 2 (Kaas 2004), and three subfields can be identified within M1 (Rapan et al. 2023). This cortical segregation reaches its apex in humans, where both the motor and somatosensory cortex have expanded significantly in terms of size and complexity to enable finer control of movements, including intricate finger and hand movements, as well as the production of speech, and enhance the individual's capacity for motor planning and decision making. The gradual changes in cytoarchitecture associated with the phylogenetically related emergence of multiple areas from

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the marsupial somatosensory-motor amalgam are in line with the "gradation theory" postulated by Sanides (1962) to explain cortical differentiation in the human PFC. Specifically, his systematic analysis revealed that segregation in the human PFC is associated with discontinuous step-wise changes of cyto-architectonic features which not only follow phylogenetically related cortical expansion (i.e., when moving medio-laterally from allocortical through meso-cortical to neocortical areas), but also when moving in a poleward direction throughout the prefrontal neocortex (Sanides 1962). Below, we present both structural and functional evidence in support of the framework that rodent area PL could be considered a precursor of primate dmPFC area 32 *and* of areas belonging to the primate dlPFC.

Structural Studies

The prelimbic cortex occupies a very large area of the prefrontal cortex in rodents. In rats, the PL extends rostro-caudally for about 3 mm, from the anterior pole of the PFC, sitting above the medial orbital cortex, to caudally situated dorsal to IL (Swanson 2004). While PL has generally been regarded as a single entity, recent evidence leads us to propose that PL may anatomically and functionally consist of two major divisions: rostrodorsal and caudoventral divisions. Specifically, there are notable anatomical differences between these two parts of PL with respect to both their inputs and outputs. For instance, in an early examination of PFC projections to the striatum, Berendse et al. (1992) reported that the dorsal part of PL projected to mid-regions of the dorsal striatum, whereas ventrally PL selectively distributed to the nucleus accumbens (ACB), and we could confirm this distinction (Vertes, pers. comm.; see also Figure 3.1).

As is well established, the mediodorsal nucleus (MD) of the thalamus is strongly connected reciprocally with the mPFC. However, the caudoventral PL distributes specifically to the medial segment of MD, whereas the rostro-dorsal PL projects selectively to the lateral segment of MD (Groenewegen 1988; Vertes 2004). Taken together, this pattern indicates that the rostrodorsal PL communicates primarily with action/premotor-associated structures and may therefore serve a role in executive control, similar to areas of the primate dlPFC. On the other hand, caudoventral PL is strongly interconnected with limbic structures and may accordingly be involved primarily in affective behaviors, comparable to those of area 32 of primates.

With respect to limbic connections, the caudoventral PL receives pronounced projections from the hippocampus, mainly originating from CA1 and the subiculum of the ventral hippocampus. Thalamic afferents to this division of PL arise predominantly from medial/central regions of the thalamus including MD (as mentioned above), rostral intralaminar nuclei, and the midline nuclei: the paraventricular, paratenial, rhomboid, and reuniens (RE) nuclei (Hoover and Vertes 2007; Vertes 2004, 2006). Finally, the caudoventral PL

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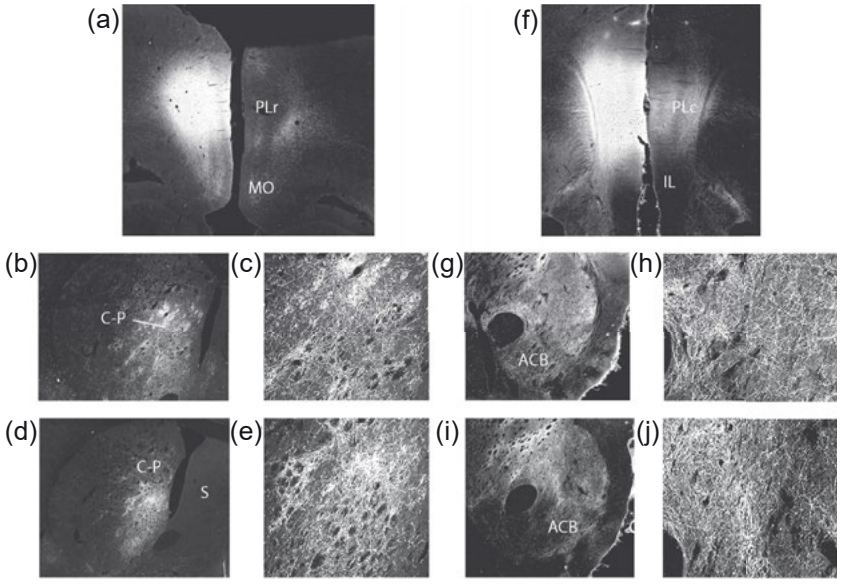

Figure 3.1 Pattern of distribution of labeled fibers at rostral (b, c) and caudal (d, e) levels of the dorsal striatum (C-P) at low (b, d) and high (c, e) magnification produced by a PHA-L injection in the rostral part of the prelimbic cortex (a). Pattern of distribution of labeled fibers at rostral (g, h) and caudal (i, j) levels of the nucleus accumbens (ACB) at low (g, i) and high (h, j) magnification produced by a PHA-L injection in the caudal part of the prelimbic cortex (f). Note that projections from the rostral prelimbic area (PLr) distribute selectively to medial aspects of C-P, whereas those from the caudal prelimbic area (PLc) project selectively to the ACB. IL: infralimbic cortex; MO: medial orbital cortex; S: septum.

receives significant projections from the basal nuclei of the amygdala as well as from monoaminergic nuclei (e.g., dopaminergic, noradrenergic and serotonergic) of the brainstem. It is well recognized that the monoaminergic nuclei exert pronounced modulatory effects on PL in affective and cognitive functions (Friedman and Robbins 2022).

With some exceptions, the output of caudoventral PL parallels its input (Hoover and Vertes 2007; Vertes 2004). Cortically, this caudoventral PL strongly targets other prefrontal cortical regions, including the medial orbital cortex, the dorsal and ventral agranular insular cortex, the anterior piriform cortex, and the entorhinal cortex. Subcortically, caudoventral PL distributes heavily to (a) the ACB, olfactory tubercle, and claustrum of the basal forebrain; (b) the central and basal nuclei of the amygdala; (c) the MD, intermediodorsal, paraventricular, paratenial, reuniens, and centromedial thalamic nuclei; and (d) the substantia nigra, pars compacta, ventral tegmental area, and dorsal and median raphe nuclei of the midbrain. In summary, the inputs and outputs of the caudoventral PL largely mirror those of area 32 of primates.

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Functional Studies

While the debate on the rodent homologue of the dlPFC of primates may never be resolved to everyone's satisfaction, primates (especially humans) possess abilities that undeniably exceed those of rodents, and this undoubtedly is tied to cortical evolution including that of the dlPFC. Still, it must be acknowledged that rodents exhibit executive functions that are classically attributed to primate dlPFC. In addition to the anatomical evidence discussed above, behavioral evidence suggests that rostrodorsal PL is a "functional homologue" of primate dlPFC.

Granon and Poucet (2000) were among the first to make this proposal. Specifically, they reviewed evidence showing that alterations of PL in rodents (but not other mPFC regions) produced severe impairments on various spatial and nonspatial delay tasks. This indicated a profound working memory deficit—a hallmark of damage to the dlPFC. The working memory deficits were part of a constellation of cognitive impairments produced by alterations of PL that included attentional deficits. In addition, Granon and Poucet pointed out that rostrodorsal PL is reciprocally connected to the lateral subdivision of the MD, paralleling primate dlPFC projections to the lateral MD (Granon and Poucet 2000). Several other studies described similar reciprocal connections between PL and lateral MD in rodents (Bolkan et al. 2017; Mukherjee et al. 2020; Schmitt et al. 2017; Wolff et al. 2008). Granon and Poucet (2000:235) concluded that "in both species [rodents and primates], the prefrontal cortex, seems to share some common function in those aspects of cognitive processing that, in humans, are usually referred to as executive functions. Within the rat prefrontal cortex, the prelimbic area appears to play a central role in such processes."

Several subsequent reports have confirmed the role of PL of rodents in working memory and in several additional cognitive functions including attentional processes, set shifting behavior, reversal learning, and decision making (for reviews, see Chudasama 2011; Friedman and Robbins 2022). Specifically, these are all functions that in primates are associated with activation of the dlPFC.

Physiological evidence also supports the idea that the rostrodorsal PL and dlPFC are homologous. Classical work by Fuster, Goldman-Rakic, and others (Funahashi et al. 1993b; Fuster and Alexander 1971) have shown that neurons in the dlPFC exhibit persistent increase in spike rates in the context of working memory, which has been considered to be a cellular correlate for this cognitive process (Fuster and Alexander 1971). Newer studies have corroborated these observations, albeit they emphasize a persistent network activity pattern (rather than individual neurons) and perhaps temporally sparser patterns of working memory correlates at the level of single neurons (Lundqvist et al. 2016). Consistent with these latter observations, and with the PL homology, multiple studies have found evidence for persistent network activity patterns in

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the context of working memory tasks. For example, 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 reflective of the PL's function in the generation of abstract rules, which are a known attribute of dlPFC. This was corroborated by data from Schmitt et al. (2017), who trained mice on a cross-modal attentional control task where mice selected between visual and auditory target stimuli based on a cue that varied on a trial-by-trial basis. Out of several cortical areas inactivated in the PFC, including orbitofrontal cortex, anterior cingulate cortex, and premotor cortex, only the PL showed a delay period specific effect (Wimmer et al. 2015). Recordings from the PL showed a persistent network activity pattern over the delay, where single neurons exhibited a temporally precise increase in firing rate tiling the delay period (sequential activity pattern). These network patterns where "rule specific" (Rikhye et al. 2018; Schmitt et al. 2017), consistent with the finding from primate dlPFC which showed the highest proportion of neurons encoding abstract rules in working memory tasks (Wallis et al. 2001). Perhaps the most compelling link to the specificity of these observations to the rostrodorsal PL is the work by Nakajima et al. (2019), which showed that neurons in this particular region project to the dorsal striatum (Figure 3.2a) and exhibit activity patterns consistent with attentional modulation (Figure 3.2b, c).

Lastly, in studying the architectonic subdivisions of the neocortex of the tree shrew, *T. belangeri*, a close relative of primates, Wong and Kaas (2009a) found that the PL of that species (and which they designated as area MF) contained a well-developed layer 4, which was densely populated with granule cells. This suggests that area PL of rodents, which occupies the same relative position as area MF of tree shrews, dorsally on the medial wall of the PFC, could be the antecedent of the granule cell layer of primates. Consistent with this notion, we show comparative sections of this region across rats, Tupaia, and macaques (Figure 3.3).

Homology between Infralimbic Cortex and vmPFC

Whereas the rodent homologue to the dlPFC of primates remains controversial, there appears to be a general consensus that ventral parts of the mPFC of rodents are anatomically and functionally equivalent to the agranular ventral medial PFC (vmPFC) of primates. More specifically, area IL of rodents appears anatomically homologous to area 25 (A25) of primates.

For instance, the IL of rodents and A25 of primates serve well-recognized roles in autonomic, visceral, and affective functions. IL has been described as a visceromotor cortex. The projections of IL reflect its involvement in visceral/affective functions. Specifically, Vertes (2004) examined IL projections in rats and showed that IL distributes to several sites of the forebrain and brainstem

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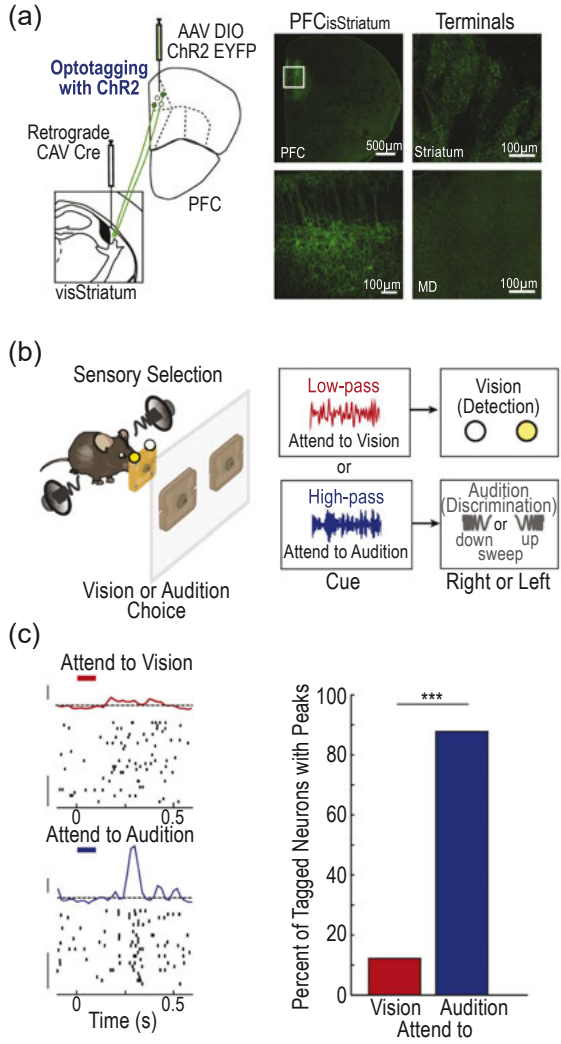

Figure 3.2 Rostrodorsal prelimbic neurons project to the dorsal striatum and show attentional modulation. (a) Schematic of the strategy of intersectional canine associated virus 2 (CAV2)-Cre based retrograde labeling of PFC neurons projecting to visual striatum. Expression of channel rhodopsin 2 (ChR2) in these neurons allows for optogenetic tagging. (b) Cartoon of the 2AFC cross-modal attention task (Wimmer et al. 2015). (c) Left: Example raster and peri-stimulus time histograms (PSTHs) of the response of an optogenetically tagged PFC neuron projecting to the visual striatum recorded in the cross-modal two alternative forced choice (2AFC) task. Zero time indicates cue presentation (100 msec duration, LP–Red bar, HP–Blue bar, PSTH y-axis scale bar: 1 Zscore, Raster y-axis scale bar: 10 trials). Right: The majority of tagged neurons showed peaks only in attend to audition (blue) but not during attend to vision trials (red) ($N = 2$ mice per condition, $n = 112$ neurons; *** $p < 0.001$ pairwise binomial test). Figure adapted from Nakajima et al. (2019).

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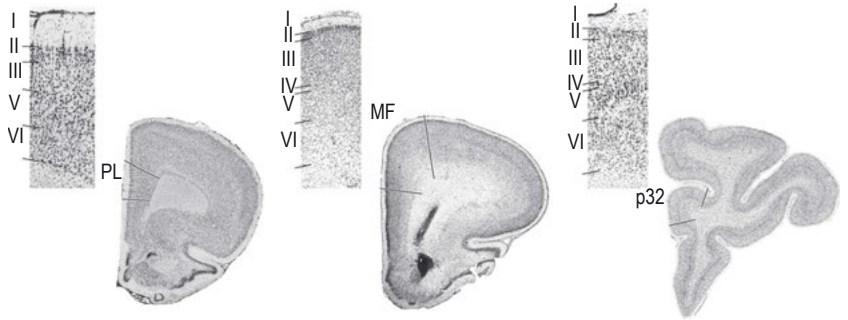

Figure 3.3 Coronal sections through the rat (left), Tupaia (middle) and a macaque (right) prelimbic region and processed for the visualization of cell bodies. Insets provide a detailed view of the cytoarchitecture of prelimbic area in each species. Note the lack of an inner granular layer (layer IV) in the rat prelimbic area (PL) and the presence of a few scattered granule cells indicative of an incipient layer IV in prelimbic area MF of Tupaia. Prelimbic area p32 of the macaque brain presents a dysgranular layer IV. Roman numerals indicate cortical layers.

linked to autonomic and affective behavior. These included orbitofrontal cortices, shell of nucleus accumbens (sACB), lateral septum, bed nucleus of stria terminalis (BST), medial and lateral preoptic nuclei, central nucleus of the amygdala, lateral and posterior nuclei of the hypothalamus, and the periaqueductal gray, parabrachial nucleus and solitary nucleus of the brainstem. Each of the structures has been shown to modulate autonomic/visceral activity, and thus emotional behavior, and importantly as a group, these nuclei receive input almost exclusively from IL and little from PL.

Although fewer reports have examined vmPFC (or A25) projections in primates, A25 projections in the monkey appear to directly parallel those of IL in rodents. Specifically, an early report by Chiba et al. (2001) compared the efferent projections of A25 (IL) and A32 (PL) in the Japanese monkey and showed that the output of A25, like that of IL in rodents, strongly targeted sites involved in autonomic/visceral control, primarily including the sACB, the preoptic area, BST, central nucleus of the amygdala (CeM) and the periaqueductal gray and parabrachial nucleus of the brainstem. They thus concluded that their findings "support the hypothesis that IL is a major cortical autonomic motor area." Several subsequent examinations of A25 projections in monkeys and have similarly demonstrated that A25 prominently distributes to several "visceral-related" subcortical structures of the basal forebrain, amygdala, hypothalamus and brainstem (Barbas et al. 2003; Ghashghaei et al. 2007; Heilbronner et al. 2016; Joyce and Barbas 2018; Rios-Florez et al. 2021; Roberts et al. 2007). Major targets included the ACB, BST, central nucleus of the amygdala, posterior and lateral nuclei of the hypothalamus, periaqueductal gray and parabrachial nucleus.

Barbas et al. (2003) described projections from mPFC in primates, including A25, to discrete nuclei of the amygdala and hypothalamus that directly

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distribute to (autonomic) brainstem and spinal cord nuclei which innervate peripheral autonomic sites. This system of connections linked mPFC/A25 with autonomic effector sites in the modulation of visceral functions and emotional behavior. However, in subsequent studies Barbas and colleagues have suggested that the connections of posterior OFC with the intercalated cell masses of the amygdala more resemble rodent IL, than primate A25 (Zikopoulos et al. 2017).

In contrast, Heilbronner et al. (2016) compared the projections to the striatum from A25 in macaques and IL in rats. Specifically, they first identified a region of the sACB (termed the "striatal emotion processing network" or EPN) and conserved across these species. The EPN is a convergence zone of projections from the amygdala and hippocampus to the sACB. Importantly, they showed that both IL and A25 distributed heavily to the striatal EPN, whereas other prefrontal cortical areas (of both species) projected at best weakly to EPN. They concluded that "consistent with prior literature, the infralimbic cortex and area 25 are likely homologous" (Heilbronner et al. 2016:509). Future studies should perform whole brain connectivity fingerprints across species for a more comprehensive comparison. However, it should be noted that even if rodent IL and primate A25 show overall similar connectivity patterns, the evolutionary expansion of the PFC may endow primate A25 with unique interregional connectivity patterns and divergent functions.

Recently, Roberts and colleagues (Alexander et al. 2023) comprehensively reviewed the structural and functional properties of the vmPFC across species (rat, monkey, human) and cited evidence showing that (a) the IL of rats and A25 of primates show some functional homology/analogy in the regulation of behavior in the reward domain but not in the punishment domain. Specifically, they showed that A25 overactivation in marmosets blunted Pavlovian approach and motivated responding, comparable to that reported following similar manipulations in rodents. In marked contrast, the same manipulation heightened behavioral and cardiovascular responsivity to both proximal and distal threat, opposite to that reported in rodent IL. This suggests that IL and A25 may act similarly within reward networks but their roles may have diverged within threat networks illustrating the complexity of cross-species functional comparisons. Roberts and colleagues also showed (b) that IL/A25 and PL/A32 predominantly serve distinct and separable functions, with A25 mainly involved in cardiovascular and affective functions and A32 in cognitive functions. A cytoarchitectonically informed meta-analysis of functional imaging studies in humans provides further evidence for this functional segregation of A25 and A32 (Palomero-Gallagher et al. 2015). For instance, with respect to differences between A25 and A32, Wallis et al. (2017) demonstrated that inactivation of A25 produced pronounced cardiovascular changes, whereas inactivation of A32 had no cardiovascular effects, and further that A25 and A32 mediated opposite effects on a Pavlovian fear conditioning and extinction paradigm: A25 inactivation decreased fear-elicited behavior responses

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promoting extinction, whereas A32 inactivation enhanced these responses thereby suppressing extinction.

Lastly, Diehl and Redish (2023) have performed comprehensive recordings across the rat mPFC in the context of a foraging task termed "restaurant row." This task combines multiple cognitive elements including associative learning, working memory, switching, and value-based judgments. Although they found that all prefrontal areas encode the various relevant task variables, there was clear specialization, with the IL clearly encoding more value-related cognitive variables than executive or sensorimotor ones. This is consistent with an earlier report, in which Hardung et al. (2017) examined the neural substrates for response inhibition across areas of the rodent frontal cortex using both optogenetic inactivation and electrophysiological recordings. Strikingly, inactivation of the PL and IL had opposite effects on the behavior, where PL inactivation increased and IL inactivation decreased premature responses. Electrophysiological recordings were also consistent with opposing roles for these two subregions, again, consistent with the idea that PL shares functional homology with the primate lateral stream whereas the IL is medial (and evaluative).

Conclusions

Building on the two-stream notion of human (or generally primate) PFC, the collective evidence reviewed in this chapter argues for homology with the two major divisions of rodent PFC: the PL and IL. The argument implicitly makes a prediction about how the rostrodorsal PL may have disconnected from the IL throughout evolution, and subsequently pushed laterally to form what is currently recognized as dlPFC of primates. The fact that *T. belangeri* MF is granular is consistent with this idea. Overall, we hope this synthesis will stimulate further discussion and motivate the design of new experiments to test this hypothesis directly.

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