



EDITORIAL

# The prefrontal cortex

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The prefrontal cortex (PFC) is essential for developing action plans, driven by the coordination of cognitive and emotional processes, that relies on both current goals and future plans. Importantly, behavioral flexibility is necessary for successfully reaching goals in a changing environment. To accomplish this, the PFC comprises several regions, each of which is associated with various functions. It is the product of evolution that has resulted in a complex set of inter-related structures or regions with networks of connectivity to wide-spread brain regions. These regions are organized into networks to mediate different aspects of behavior. Indeed, it is now well accepted that circuit dysfunction between regions and/or networks underlie most mental illnesses. The goal of this special issue of *Neuropsychopharmacology Reviews* is to highlight key structural and functional features of PFC that are particularly relevant to the mechanisms that underlie normal and abnormal behaviors.

This is the first multidisciplinary volume on the PFC since the monumental publication of *Principles of Frontal Lobe Function (2nd edition)*, Stuss and Knight, editors, Oxford University Press, 2013). The 23 contributions include cross-species comparisons, electrophysiology, circuit and network analyses, computational modeling, neuroimaging, and therapeutic approaches. We have tried to serve this multi-disciplinarity by commissioning fresh teams of authors – authors who had hitherto never worked together – to tackle different facets of the functions of the PFC, from their complementary perspectives. The first section of the volume, “The Fundamentals”, covers general principles of structure and function. The next section, “Structure and Function Interactions”, considers in more detail the interactions between PFC components or PFC and key subcortical structures. The third section, “Clinical-Translational Perspectives”, discusses PFC dysregulation in several major neuropsychiatric disorders. Finally, the fourth section, “Modulation and Treatment”, addresses current therapeutic approaches to psychiatric illnesses that target the PFC mental health disorders arising in part from PFC dysfunction. Many articles take a cross-species approach including work on humans, nonhuman primates and rodents.

“The Fundamentals” begins with a critical cross-species evaluation of the PFC. Preuss and Wise focus on the cytoarchitectonic definition of PFC, demonstrating the comparative granular and agranular anterior cortical structures in rodents, nonhuman, and human primates. Although the PFC enlarged greatly throughout evolution and underwent profound modifications of cortico-cortical connectivity and gene expression, they show how it is unlikely that a substantial number of new PFC areas emerged since the human lineage diverged from the chimpanzees and

bonobos lineages. Haber et al. focus on translational approaches to linking PFC anatomical and functional connectivity by combining nonhuman primate anatomy and imaging with human neuroimaging. The article addresses PFC anatomic connectivity, neuroimaging methods, and network analyses based on graph theory. It then highlights recent analyses that combine anatomy with neuroimaging data to demonstrate the correspondence between structural and functional imaging for specific PFC connections. Kolk and Rakic review recent advances in understanding PFC development. Although PFC neurons are generated before birth, their differentiation and connectivity continue in the case of humans into the third decade of life. They consider the role of specific genes, non-coding regulatory elements and signaling molecules in control of neuronal production, phenotypic fate, and migration to the PFC. They also show how subtle deficits in developmental processes can result in lifelong cognitive impairment. Soltani and Koechlin argue that adaptive, flexible behaviors rely on different computational models. These are based on learning in terms of internal models associating stimuli (including contexts), actions and outcomes. They show how the model components map onto specific PFC regions and how this framework helps understand the neural computations and cognitive architecture that guide adaptive behavior. The last four articles focus on important functions of the PFC, cognition, executive function, decision-making, and moral and social consciousness. Friedman and Robbins review the role of PFC in cognitive control and executive function from a cross-species, neuropsychological and psychometric perspective. They argue for a diversity as well as unity of PFC functions. They then consider how such factors contribute to neuropsychiatric disorders. Menon and D’Esposito relate how executive function is mediated by PFC networks. Their review emphasizes primarily human neuroimaging studies to illustrate the potential of a network analytic approach to PFC connectomics. Collins and Shehavi also consider various means of computational modeling, with a particular focus on decision-making and learning. They relate how models have developed from basic algorithms for updating and action selection to the enhanced depth in processing required for learning and decision-making. Zoh et al. review the PFC neural mechanisms of moral behavior. They take a comparative approach in considering shared and normative, and unique aspects of cooperative behavior in humans relative to nonhuman primates. They specifically highlight a common medial PFC network supporting a foundational process in cooperative decision-making. This medial network interacts with lateral PFC areas that

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represent cooperative norms and modulate value to guide appropriate behavior and with the anterior PFC for arbitrating across social contexts.

In the next section, "Structure and Function Interactions", specific consideration is given to particular PFC interactions. The first article by Rudebeck and Izquierdo focuses on the orbitofrontal cortex in an innovative analysis of foraging behavior. They take a cross-species approach to examine how PFC contributes to reward procurement in rodent and primates, pointing out the importance of considering both the environment in which the animal forages and the similarities and differences in PFC structure and function. An important aspect of this review is the emphasis on where translation between species can be made, where cannot, and where more work is needed. O'Doherty and Averbeck review current knowledge on computational and neural mechanisms of reinforcement learning with a focus on fronto-striatal circuitry. The review focuses on five broad themes that address learned values, how these are turned into choice and action, and how the brain arbitrates control over sub-systems of reinforcement learning. Murray and Fellows examine interactions of the primate amygdala and PFC. They show how interplay between these regions may contribute to adaptive behavior and survival. In this cross-species review, the authors discuss foraging, predator defense and social signaling in rodents and primates (both nonhuman and human). Anderson and Floresco integrate animal and human research on extinction and memory retrieval. They hypothesize, based on recent evidence, that controlled suppression of activity in the hippocampus and amygdala by the PFC inhibits fearful thoughts. Finally in this section, Monosov and Rushworth review the evidence that two highly inter-connected frontal regions, the anterior cingulate and ventrolateral PFC, provide a biological substrate for linking two crucial aspects of hypothesis formation and testing, the control of information seeking and credit assignment. Using neuroimaging, targeted disruptions, and neurophysiological studies, they demonstrate how information seeking and credit assignment are neuronally linked and why this circuit is important for ensuring the ability to be flexible and adaptive.

The third group of articles under "Clinical-Translational Perspectives" exemplify the notion that virtually all of the major neuropsychiatric disorders implicate PFC dysregulation in one way or another. Thus, Ahmari and Rauch describe how neuroimaging studies of obsessive-compulsive disorder (OCD) combined with symptom provocation and neurocognitive tasks have consistently implicated PFC and associated circuitry. They consider how these functional mappings may relate theoretically to OCD symptoms and consider possible treatments. Roberts and Pizzagalli relate human depressive symptoms to functioning of specific PFC regions and circuitry, with a focus on primate area 25, and a reappraisal of cross-species, especially nonhuman primate, models of depression. The article by Kredlow et al. interprets post-traumatic stress disorder as one of fear dysregulation and harness novel techniques ranging from brain stimulation in humans to optogenetics in rodents to probe the role of the PFC. Neural mechanisms of more general anxiety disorders are covered by Kenwood et al. They advance the premise that expansion of the primate PFC has led to an increased capacity to formulate strategies for coping with anxiety and to regulate autonomic drive, via specialized PFC pathways that interface with inhibitory mechanisms in the cortex, amygdala, and thalamic reticular nucleus. Cecili et al. review the burgeoning evidence that drug addiction involves impaired top-down response inhibition and salience attribution as well as reward based decision-making deficits commonly mediated by disruptions of PFC circuitry. They consider the causal nature of these disruptions and the extent to which they are actually caused by drugs of abuse or are pre-existing. They integrate human neuroimaging evidence and

experiments studies in animals, including nonhuman primates, to suggest that both abstinence and treatment may lead to recovery of function through changes in plasticity. Finally, Smucny et al. focus on cognitive deficits in schizophrenia and present evidence suggesting that many of these, including working memory, are underpinned by molecular, cellular, and electrophysiological changes in the functioning of the dorsolateral PFC. They also consider potential avenues for future treatment of these disabling symptoms.

The last section, Modulation and Treatment, contains contributions that address current therapeutic approaches to mental health disorders arising in part from PFC dysfunction. Cools and Arnsten review neurochemical modulation of PFC function, from the point of view of monoaminergic (i.e., dopamine, norepinephrine and serotonin) and cholinergic influences. They convey a central message of the narrow-inverted U dose response curve that characterizes most drug effects, primarily in considering studies of nonhuman primates and human volunteers. They also integrate findings from pharmacological studies with those of neuroimaging and genetic investigations. Zamani et al. add a review of the current status of psychedelic drug effects in an experimental and therapeutic context; they also consider the new paradigms that may be necessary for measuring conscious experience following such interventions and the role of PFC regions in mediating these experiences. Rasmussen and Goodman review the rather different approaches associated with neurosurgical intervention, in the specific contexts of their generally successful outcomes in OCD. Effects of cingulotomy, capsulotomy and deep brain stimulation are all considered as possible manipulations of activity in defined PFC-striatal circuitries. Finally, a complementary article by Regenold et al. surveys non-invasive neuromodulatory strategies including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), for the treatment of mental health disorders, again from the perspective of circuit approaches involving the PFC.

Collectively, these articles provide an up-to-date account of our present knowledge of the PFC as well as a glimpse into future directions of research. It progresses from our basic understanding of the PFC to specific component interactions that underlie the behavioral flexibility required to modify goals based on a changing environment. Finally, this volume addresses some of the PFC abnormalities associated with psychiatric illnesses and new innovative therapeutic approaches. Taken together, this volume captures the momentum and acceleration in this field and provides insight into the circuits and networks underlying neuropsychiatric disorders.

## AUTHOR CONTRIBUTIONS

Both authors (SNH and TR) contributed equally to the Editorial.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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