16

Translating Prefrontal Cortex Insights to the Clinic and Society

James B. Rowe, Dibyadeep Datta, Christian J. Fiebach, Susanne M. Jaeggi, Conor Liston, Beatriz Luna, Steven A. Rasmussen, Angela C. Roberts, Rajita Sinha, and Suzanne N. Haber

Abstract

The prefrontal cortex (PFC) is implicated in a wide range of neuropsychiatric disorders. Many of these become manifest in adolescence (e.g., anxiety, obsessive-compulsive disorders, addiction, attention-deficit hyperactivity disorders) while others arise from selective neurodegeneration of the frontal lobe in later life. A major challenge to research into the disorders associated with the PFC has been the lack of one-to-one mappings between clinical syndromes, their underlying pathophysiology, and root neurobiological causes. Here, we propose a multilevel framework in which syndromes can be linked to symptom profiles, symptoms to cognitive processes, and cognitive processes to pharmacological and computational processes embedded in PFC and its associated networks. This approach explains the frequency of multi-morbidity of neuropsychiatric disorders. The multilevel framework has enabled animal models of underlying biology and psychological processes to inform the understanding and treatment of clinical disorders without necessitating full recapitulation of the complexity of human neurological and psychiatric disorders. Discussion include the causes and treatment potential of the prefrontal cortical circuit disorders, based on convergent evidence across animal and human studies of the mechanisms of action of lesion, stimulation, pharmacological and cognitive behavioral therapies. Challenges are emphasized in the development, validation, and precision-medicine application of such treatments and

Group photos (top left to bottom right) James Rowe, Suzanne Haber, Dibyadeep Datta, Rajita Sinha, Angela Roberts, Christian Fiebach, Steven Rasmussen, Susanne Jaeggi, Conor Liston, Beatriz Luna, James Rowe, Dibyadeep Datta, Christian Fiebach, Angela Roberts, Beatriz Luna, Suzanne Haber, Conor Liston, Susanne Jaeggi, Rajita Sinha, Beatriz Luna, and Steven Rasmussen

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

consideration given to the prefrontal systems and prefrontal disorders in the context of global opportunities for education, health and social policy.

The Challenge of Disorders of the Prefrontal Cortex

The PFC is implicated in many neurological and psychiatric disorders, arising from developmental variants, neurodegeneration and focal injury. Despite their diversity of etiology, the clinical manifestations and therapeutic strategies can be understood in terms of systems cognitive neuroscience. In this chapter, we illustrate this approach, drawing on examples from obsessive-compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), addiction, anxiety and depression, schizophrenia, stroke, and dementia.

We propose a layered dimensional framework to study the disorders and guide treatment approaches, mapping between diagnostic groups, underlying symptoms, core cognitive processes and their neuronal mechanisms (Figure 16.1). This provides a parsimonious explanation of multi-morbidity and the effects of stress and development on mental health while opening transdiagnostic insights and treatment potential. We also propose that each level of analysis is associated with gradients across the PFC and its connections. The core cognitive processes and their neuronal mechanisms enable cross-species comparisons and bidirectional translation between animal models and clinical disorders. An additional challenge, however, concerns a principled method to improve the effectiveness of treatments, or combinations of treatments, tailored to individual differences in symptoms and causes. Looking beyond individual treatment, we consider in the final section the advances in prefrontal cortical science in relation to wider societal issues of equity, public engagement, and education.

This approach to the disorders of PFC is agnostic to common but arbitrary professional boundaries (e.g., neurology, psychiatry, psychology, education). We advocate for an interdisciplinary approach, in which mechanisms and treatments in the context of one condition can facilitate the understanding and treatment of another. The benefits of this approach may be apparent especially in mental health and developmental disorders where the genetic, molecular, and lesion bases for disease are less well characterized than in classical neurological disorders.

Mapping Syndromes and Symptoms to Processes and Etiology

Syndromes are defined by a composite of symptoms and signs, each of which are a function of changes in one or more component cognitive processes. These component cognitive processes are in turn the result of, or moderated by, a complex array of underlying neural, metabolic, pharmacological or genetic

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

processes. Figure 16.1 summarizes this analytical framework, using distinct levels of analysis: syndrome, symptom, process, and mechanism.

Examples of the neuropsychiatric syndromes include ADHD, OCD, anxiety disorders, depression, and addiction. Their high rate of comorbidity is not the mere chance intersection of separate pathophysiologies. Rather, it emerges from a finite set of signs or *symptoms and signs* (e.g., anxiety or poor inhibitory and attentional control). Each of these symptoms and signs, in turn, can arise from relative impairments in a small set of fundamental cognitive *processes*, such as response inhibition, set shifting, action-reward association, and fear-conditioning. These cognitive processes are mediated by specific *mechanisms* which can be characterized in terms of neural circuits, neurotransmitters, and genetic variants.

In this multilevel framework, a one-to-one linear mapping from syndrome through to mechanisms is unusual; more commonly, there is divergence and convergence between each level. A structural change in the network mediating

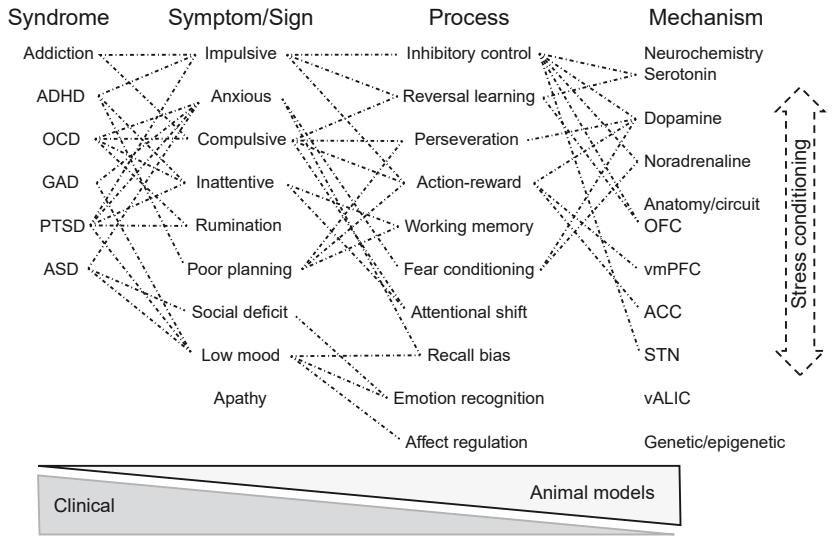


Figure 16.1 A multilevel framework for analysis of disorders associated with prefrontal cortical function. A syndrome (e.g., diagnosed clinically as generalized anxiety disorder, OCD, ADHD, addiction) can be mapped onto the constituent symptom/sign. Symptoms and signs are attributable to a finite set of underlying cognitive processes (e.g., inhibitory control, habit formation, attentional control, cognitive flexibility), which in turn are dependent on specific neurotransmitters and anatomical circuits. The exemplar symptoms, processes, and mechanisms, and their connections, are illustrative not exhaustive. The anatomical and neurochemical substrates are dynamic, with developmental trajectories through adolescence and vulnerability to conditioning effects of stressors, such that risk exposure creates a deferred as well as immediate risk of illness. Clinical studies and animal studies are differentially represented over these four levels, but not exclusively so.

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

a specific process, or a genetic variant affecting a given receptor type, will have its effect propagated up through the process level, so as to influence many symptoms and therefore contribute to many syndromes.

A corollary of this framework is that animal studies are more readily applicable to the levels of cognitive process and mechanism, whereas clinical studies are more readily applicable to syndromic and symptomatology descriptions. However, the formal linkage between levels increases the potential for translation: to pull preclinical insights forward to understand clinical disorders, and to select appropriate animal models, which we discuss further below.

The manifestations of adult neuropsychiatric disorders are influenced by multifactorial determinants, including processes during embryonic and postnatal development and environmental factors and stressors. These influences can be described by epidemiological associations at the upper levels (e.g., between a developmental exposure and prevalence of a given syndrome). However, to understand the mechanisms of developmental and environmental influences, it is necessary to examine their moderation of the lower levels - their influence on cognitive processes supported by specific circuits, cell types and receptors.

The emphasis on the process level of analysis, rather than by diagnosis or symptom, has some similarity to the RDoC initiative (Cuthbert 2014). Our proposal encompasses the RDoC concept of disease dimensions. One of the challenges, however, is to ensure that studies of human and animal PFC include data/assays on enough of the relevant processes in their task array to enable a systematic and comparative analysis.

Comorbidity

The neuropsychiatric syndromes associated with the PFC are highly heterogeneous. Accounting for this analytically is critical for understanding the role of PFC pathophysiology in modulating the underlying cognitive processes, behaviors, and symptoms. Comorbidities are the rule, not the exception, in population prevalence studies across the life span as well as disease-focused studies (Caspi et al. 2020; Kessler et al. 2003). Having multiple diagnostic labels does not imply the existence of separate diseases or distinct neuropathologies. Rather, multiple diagnoses can reflect different expressions of a single underlying disease entity within an individual (Crossley et al. 2014; Drysdale et al. 2017; Goodkind et al. 2015; Tokuda et al. 2021; Xia et al. 2018)

There are two main challenges to progress in understanding the mechanistic basis of multiple diagnoses. First, there is typically a gulf between studies with extremely large sample numbers but very limited phenotyping: genome-wide association studies often consist of $n > 10{,}000$ whereas studies with deep phenotyping consist of a much smaller number of cohorts, typically $n < 50$ for neuroimaging and bespoke psychophysical tasks. The former have the scale required to identify the cumulative effect of multiple weak risks, whether

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

genetic polymorphisms or environmental exposures, but often lack the range of questions or tasks required for deep characterization of the underlying cognitive processes and neural mechanisms. The latter use in-depth tools sufficient for mechanistic detail but lack the scale to identify small effect sizes of risks factors and moderators that underlie individual differences. In principle, large-scale deep phenotyping is possible. Detailed assessment of prefrontal structure and function has been attempted with $500 < n < 5000$ in studies such as the ABCD, ALSPAC, CamCAN, and IMAGEN (Barnett et al. 2007; Shafto et al. 2014; Volkow et al. 2018; Whelan et al. 2012). Still, new studies are required with even larger samples and deeper phenotyping to enable (a) data-driven approaches to resolve heterogeneity together with (b) theoretically informed hypothesis testing.

Second, there is a paucity of longitudinal studies of prefrontal cortical function and disorders associated with pathophysiology of PFC. Longitudinal rather than cross-sectional studies are less vulnerable to cohort differences such as intergenerational differences in schooling, nutrition, or social media. Longitudinal studies are also more suitable for the analysis of causality (e.g., via mediation analysis). These are particularly important given the dynamic nature of cognitive and neural development through adolescence and incidence of diagnostic expression of neuropsychiatric disorders. The influence of sex and gender differences on brain, cognitive, and clinical development through adolescence highlight the challenges for cross-sectional data in understanding the origins of neuropsychiatric disorders.

Larger studies increase the power of data-driven methods to study comorbidity. For instance, despite the multiplicity of neuropsychiatric diagnoses, psychopathology may have a very low dimensionality in the population. This can be summarized as a single dominant "P-factor" or small set of dimensions revealed, for example, by principal components analysis or confirmatory factor analysis (Sprooten et al. 2022). A core deficit (or psychopathology spectrum) would explain the clustering of disorders, within individuals as well as families. Where larger studies have gathered genetic or neuroimaging data, the dimensions of diagnostic comorbidity map onto common neural and genetic dimensions. Similarly, low dimensionality of neuropsychiatric symptom manifestations and corollary prefrontal structural change is observed with frontotemporal lobar degeneration syndromes (Murley et al. 2020). This calls for a transdiagnostic approach, to which we now turn.

Comorbidity and Transdiagnostics

The orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (vlPFC), and insula are strongly connected (Öngür and Price 2000), as part of a circuit that mediates value-encoding and goal-directed behaviors (Haber and Behrens 2014; see also Figure 16.2). Their association with these cognitive processes suggest that any of diverse pathologies affecting

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

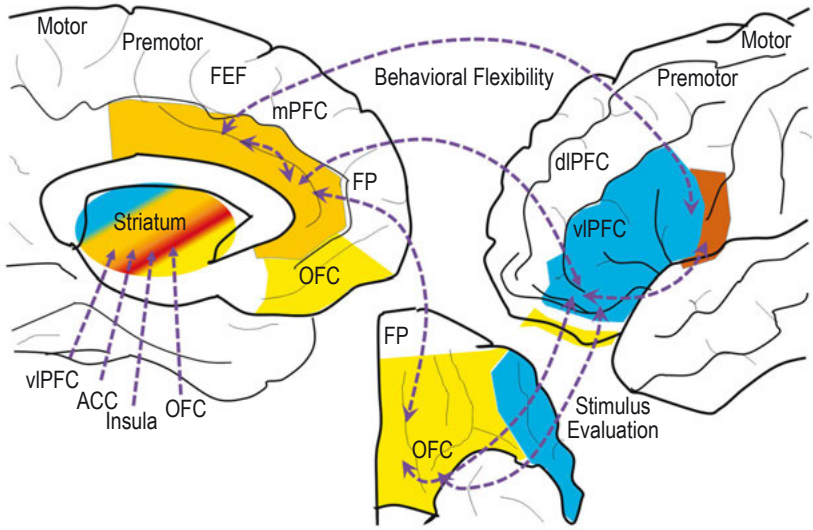


Figure 16.2 The network in which abnormalities are associated with several mental health disorders (Haber and Behrens 2014). OFC (yellow), ACC (orange), vlPFC (blue), and insula (brown) are strongly connected with each other directly and to the striatum. This network mediates value-encoding and goal-directed behaviors. Its association with these fundamental cognitive processes suggest that diverse pathologies impacting on these connections are likely to be associated with diagnoses with overlapping signs and symptoms.

these circuits are likely to be associated with overlapping signs and symptoms. A consequence of the disruption of such circuits is that insights into the mechanisms and cognitive processes associated with the circuit will be of relevance to multiple clinical disorders. This provides a strong motivation for the transdiagnostic approach to understand and treat disorders: clusters of diseases identified under "comorbidity" lend themselves to similar treatment with multiple benefits. The same drug (e.g., an SSRI), same target (e.g., noradrenergic alpha2 receptors), or same surgical site (e.g., capsulotomy) may have cognitive benefits for people with any of a wide set of diagnoses.

Therapeutically effective targeting does not necessarily require resolution of the "injury" or abnormality, merely the recovery of function of the system as a whole. Obsessions, for example, may have different neurocognitive antecedents in OCD and frontotemporal dementia, or depression may have different antecedents in stroke, adolescents, or aging populations (Costello et al. 2023). Nonetheless, there may be a common treatment for the symptom, despite variation in underlying processes or mechanisms, especially where the treatment targets convergent frontal cortico-subcortical circuits (Rasmussen, this volume; Greenberg et al. 2003).

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

Despite homologies in the anatomy and pharmacology of parallel frontal cortico-subcortical circuits, there is a rostro-caudal gradient in the local intracortical connections in PFC (see Murray et al., this volume). This means that information can transfer rapidly between the OFC, medial frontal, and lateral frontal areas of PFC and converge on polymodal areas of the PFC (Figure 16.2). The proximity and strength of connectivity among these regions means that the temporal separation of the signals is very short, approximately 20 msec. This short latency implies highly efficient parallel processing rather than sequential or independent functions. By these routes, information on object recognition can be associated with hippocampal, insular, and amygdala representations of current and past value experience. The expected and future value, encoded in ventromedial and orbitofrontal cortex, can be shared with dorsal ACC, whereby action selection and monitoring are influenced directly by emotion and expected action outcomes (Shenhav et al. 2016).

Stress and Trauma

The frontal lobes are critically involved in adaptive function, comprising the major foci for facing and adapting to challenging and novel environments. Focusing on a goal in the face of challenge and stress can draw on several strategies. To adapt to unstable environments and avoid dangers, one may use executive cognitive skills such as planning, problem solving, switching between subgoals and generating options, or redirecting attention. People may also take action to seek emotional support or reduce effort/costs by accepting things one cannot change. Each of these strategies has been associated with the PFC. Highly stressful situations and traumatic events may overwhelm this ability of the PFC and its networks to optimize goal-directed behaviors. Stress impairs dynamic flexibility and responsiveness, with a shift to habitual or sensorimotor responding (Roberts 2011). This may occur in acute events that are threatening, challenging, uncontrollable, and unpredictable and may include the maladaptive phenomenon of "shutting down." Similar failure of PFC adaptive mechanisms may occur in response to chronic adverse, uncontrollable, or volatile situations in which there are no clear options. High chronic stress goes beyond adaptive "healthy" stress responses with OFC and hippocampal changes that relate to physical and psychological health symptoms (Seo et al. 2014).

Stressful and traumatic events for humans are common including, for example, physical, sexual and emotional abuse and neglect in children (e.g., Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System[1]), domestic violence, assaults, loss of close relationships (by death or divorce), or loss of one's home due to war, migration, or climate change. In a general population survey of 24 countries, 70% of respondents reported having

[1] https://www.cdc.gov/brfss

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

experienced at least one traumatic event, and over 30% had experienced multiple events (Benjet et al. 2016).

To understand the impact of major stressors on the risk and expression of neuropsychiatric disorders, we need to consider their influence on the processes underlying symptoms and the neural circuits that mediate those processes. As illustrated in Figure 16.1, stressors may condition multiple PFC-mediated processes and therefore be indirectly manifest in the increased risk of multiple disorders.

Stressors in early development years, or in adulthood, change the structure and connectivity of PFC in terms of structural gray matter volume reductions and connectivity as well as functional brain responses to stress (Bartholomeusz et al. 2013; Chen et al. 2018; Goldfarb et al. 2020; Hanson et al. 2012, 2021). The effect of stressors is not uniform across regions: changes are especially common in OFC, ventromedial, rostral ACC, dlPFC, and their immediate connections to striatum and insula (Ansell et al. 2012). Animal studies of stress show consonant changes in homologous or analogous regions to the human studies (discussed further below). The global COVID pandemic provided a "natural experiment" to study the impact of compound stressors, and there is emerging evidence of post-pandemic increases in the rates of addictive behaviors (e.g., alcohol, cannabis, illicit drug use, gambling), anxiety, eating disorders, and other maladaptive behaviors. This may reflect the effects of stress on long-term function and plasticity of the PFC.

Different stressors may act divergently or convergently. Some of the clearest evidence comes from the effects of violence and trauma, with recent data on social deprivation (Dash et al. 2023; Pollak et al. 2010; Xiao et al. 2023). However, further characterization of other stressor effects is required. The greater the stress from an event or condition, in terms of uncontrollability, unpredictability, acuity/intensity, and chronicity (relentlessness), the greater the deleterious effect on the PFC. Moderate levels of stress can be advantageous for learning, memory encoding, and cortical plasticity. However, nonlinearity of dose-response relationships applies to the effect of stress as much as the effect of selective monoaminergic medications.

There are multiple mechanisms by which stress affects prefrontal processes, including changes in dopamine, noradrenaline, cannabinoids, and corticotrophin-releasing factor receptor modulators (Cools and Arnsten 2022; Datta and Arnsten 2019; Tomassini et al. 2022; Uliana et al. 2023). Physiological circadian oscillations in glucocorticoid signaling are critical for supporting developmental pruning and learning-induced plasticity (Liston et al. 2013; McGaugh 2004), whereas severe stressors and chronically elevated glucocorticoids in humans and animal models lead to excessive synapse pruning, dendritic atrophy, and associated cognitive deficits (Izquierdo et al. 2006; Liston and Gan 2011; Liston et al. 2011; Liston et al. 2009; McEwen et al. 2015). Macroscale human neuroimaging shows loss of prefrontal flexibility under

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

high acute stress, affecting ventromedial, orbitofrontal and dorsolateral cortices (Sinha et al. 2016).

Other monoamine neurotransmitter systems may mitigate the effects of stress. For example, serotonin is an important regulator of cognitive flexibility and adaptive responses to negative feedback in human, nonhuman primate, and rodent models (den Ouden et al. 2013; Roberts 2011). Serotonin also interacts with the HPA axis to regulate sleep, appetite, social interactions, and mood, thus indirectly influencing the response to stressors. However, individual differences in serotonergic mitigation of stress involve a complex interaction of genetics, neurochemistry, and behavior.

The prefrontal cortical consequences of stressors are linked to diverse rather than selective cognitive processes: each of these processes may, in turn, lead to a common set of symptoms, such as anxiety. For example, stress-related effects on PFC alter working memory, motor control, and cognitive control. The acute induction of stress in otherwise healthy individuals has been used in addition to the post-stress evaluation of chronically stressed individuals and those with established psychiatric disorders (Luo et al. 2018; Seo et al. 2013). Stress-related symptoms and signs can be classified as cognitive (forgetting, working memory, attention, rumination, negative bias), behavioral (habitual, maladaptive behaviors, avoidant and repetitive behaviors), emotional and affective (anxiety, hyperarousal), and physical health (e.g., sleep, food intake, pain, gastrointestinal distress). The mechanisms by which these signs and symptoms emerge are beginning to be characterized. Such circuit-level changes underlying anxiety (sACC), pain (vmPFC, dACC, insula), gastrointestinal symptoms (ventromedial and orbitofrontal), and behavioral decisions (ventromedial and orbitofrontal) (Dundon et al. 2021; Hollunder et al. 2023; Wood and Nee 2023; Zeredo et al. 2019). In the future, more mechanistic studies of this nature would be of benefit. The link to physical symptoms may be mediated by cognitive maladaptive changes, especially of functions related to PFC (Atlas et al. 2014; Eijsbouts et al. 2021; Woo et al. 2017).

The effects of stress on PFC function may not be immediately apparent. Stress may provide an enduring "first hit" that alters the future susceptibility to a "second hit," whether that second occurrence is another stressor or a distinct neurobiological injury. In other words, stress affects long-term resilience of the cortex. Multiple hits by cumulative or sequential stress exposure has dose-dependent effects on gray matter volume. It changes functional responsivity of PFC to adaptive stress with progressive loss of resilience and increasing risk for stress-related illnesses. A multiple hit may also be seen in gene-by-trauma exposure effects, such as on the depression and anxiety risks in response to stress (Caspi et al. 2010, 2003). The stress-signaling pathways may themselves be moderated by genetic variants. Further research on repeat or combined stressors is required, especially in relation to periods of higher vulnerability during child and adolescent development.

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

Summary

Many neuropsychiatric and neurodegenerative disorders are primarily associated with deficits in the function of PFC and its subcortical pathways. There is, however, no one-to-one mapping between syndromes and specific symptoms, specific cognitive deficits, and specific root biological causes in terms of gene, receptor, or anatomy. Instead, there is extensive comorbidity and overlapping etiology. This can be understood in terms of a multilevel approach to disease, with convergence and divergence across a wide spectrum of syndromes, in terms of their underlying symptoms, processes, and etiology. This approach accommodates not only the complexity (and weakness) of clinical-pathological correlations, but also the diverse effects of development and stressors.

Gradients across Prefrontal Cortex in Health and Disease

Gradients of the PFC

The structure and functional organization of the PFC is not merely a juxtaposition of discrete entities. Instead, there is a set of intersecting spatially distributed gradients that can be characterized by their direction, content (Badre, this volume; Vertes et al., this volume), or the mechanisms underlying cognitive processes. The content of a gradient may be described in terms of the progression or hierarchy of cognitive processes based, for example, on their complexity, abstractness, or temporal scale. The gradient may also express differences in physiological properties of the neurons, cytoarchitectonic difference, or connectivity patterns, or the spatial patterns of gene transcriptomic variance and receptor density, as illustrated in Figure 16.3.

There is an advantage to analyzing gradients rather than discrete functions of structures, in part due to spatially smooth variance in the biological substrates of prefrontal function, rather than discontinuities. In addition, the effects of common developmental, neuropsychiatric, and degenerative disorders are typically spatially distributed rather than discrete (in contrast to stroke or surgical lesions). The historical emphasis on discrete regions made an important contribution to understanding cortical and subcortical inhomogeneity and maximized the insights from sparse data. It may be tempting to follow Plato, for whom "…our best theories will be those which carve nature at its joints." However, the brain and its disorders are complex. Reducing natural gradients to arbitrary categories is to disregard much of the variance in the biological information used to understand risk and expression of disease. As for other modeling methods, when trying to identify statistical dependencies among continuous variables, it is preferable to retain variance in the model rather than the error terms. Thus, it is important to consider gradients of PFC: how they relate to each other as well as to the dimensions of disease.

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

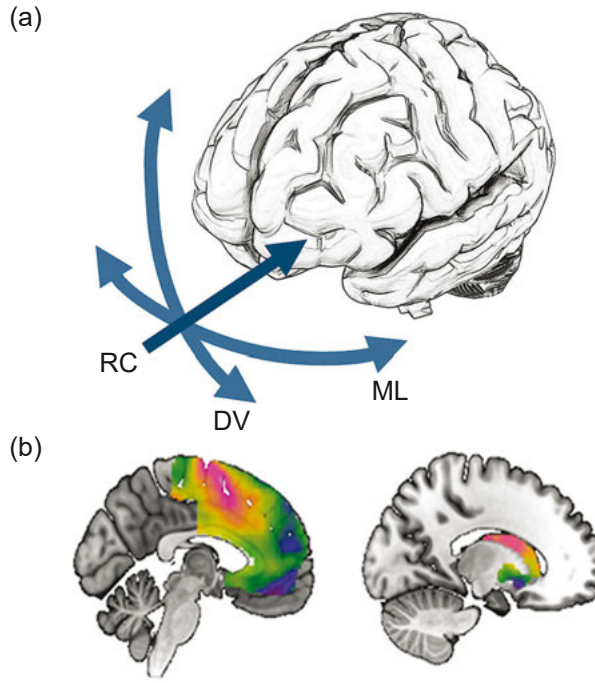


Figure 16.3 Prefrontal gradients are observed receptors, cytoarchitecture, connectional patterns, function, and transcriptomics. (a) Spatially distributed gradients in mechanisms and processes may have rostro-caudal, medial-lateral, and dorsal-ventral directions. (b) Functional gradients may result, for example in representation of switching (hot) and repetition (cool) of abstract and concrete rules in frontal cortex and striatum respectively (Kehagia et al. 2017). Figure 16.3 continues on pp. 330–331.

Morphology and Pharmacology

There are important differences in neuronal morphology, circuit architecture, and physiological properties across the cortical hierarchy (Gilman et al. 2017; Wang 2020). These include factors that promote the persistent neuronal firing that benefits some forms of higher cognitive functions, such as increasing local recurrent circuits with corresponding spine density and increasing numbers of regulatory interneurons (Elston 2000; Elston et al. 2006; Gonzalez-Burgos et al. 2019; Torres-Gomez et al. 2020). Whereas MRI macroscale imaging gradients are associated with transcriptomic variance, there are also transcriptomic gradients across cortical hierarchies of genes that have prima facie relevance to synaptic transmission and plasticity. There is increased reliance on magnified calcium signaling (e.g., calbindin, NMDA GluN2B) as one moves up the neurocognitive hierarchy (Burt et al. 2018).

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

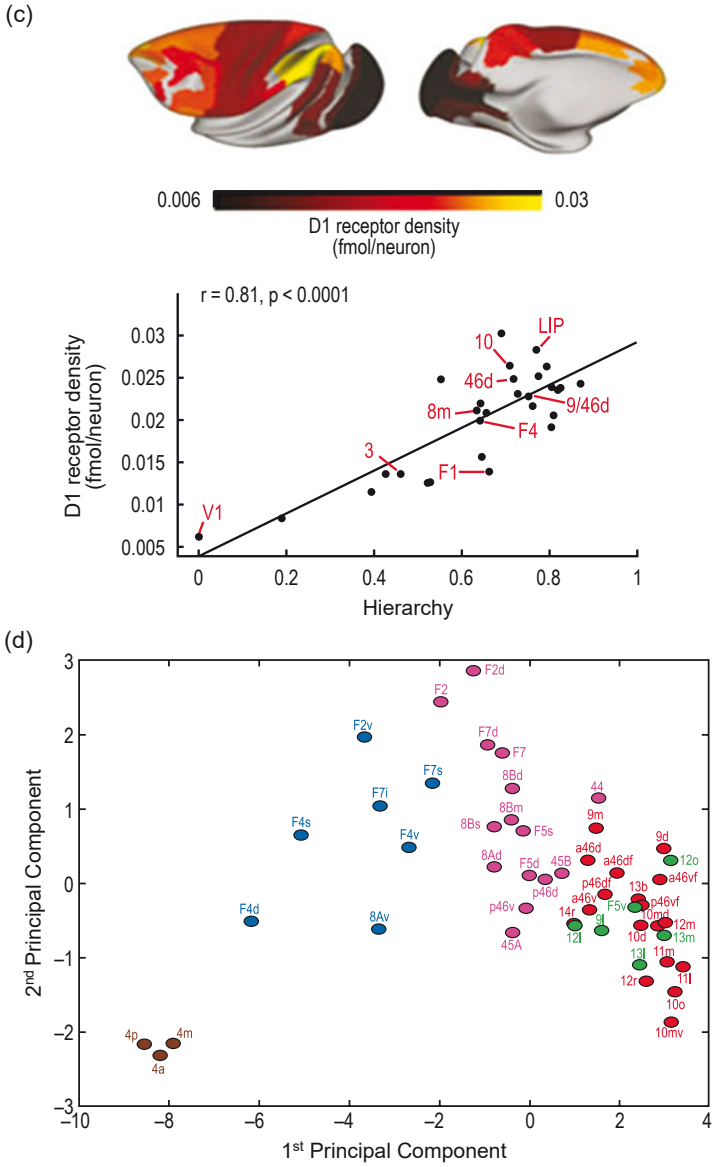
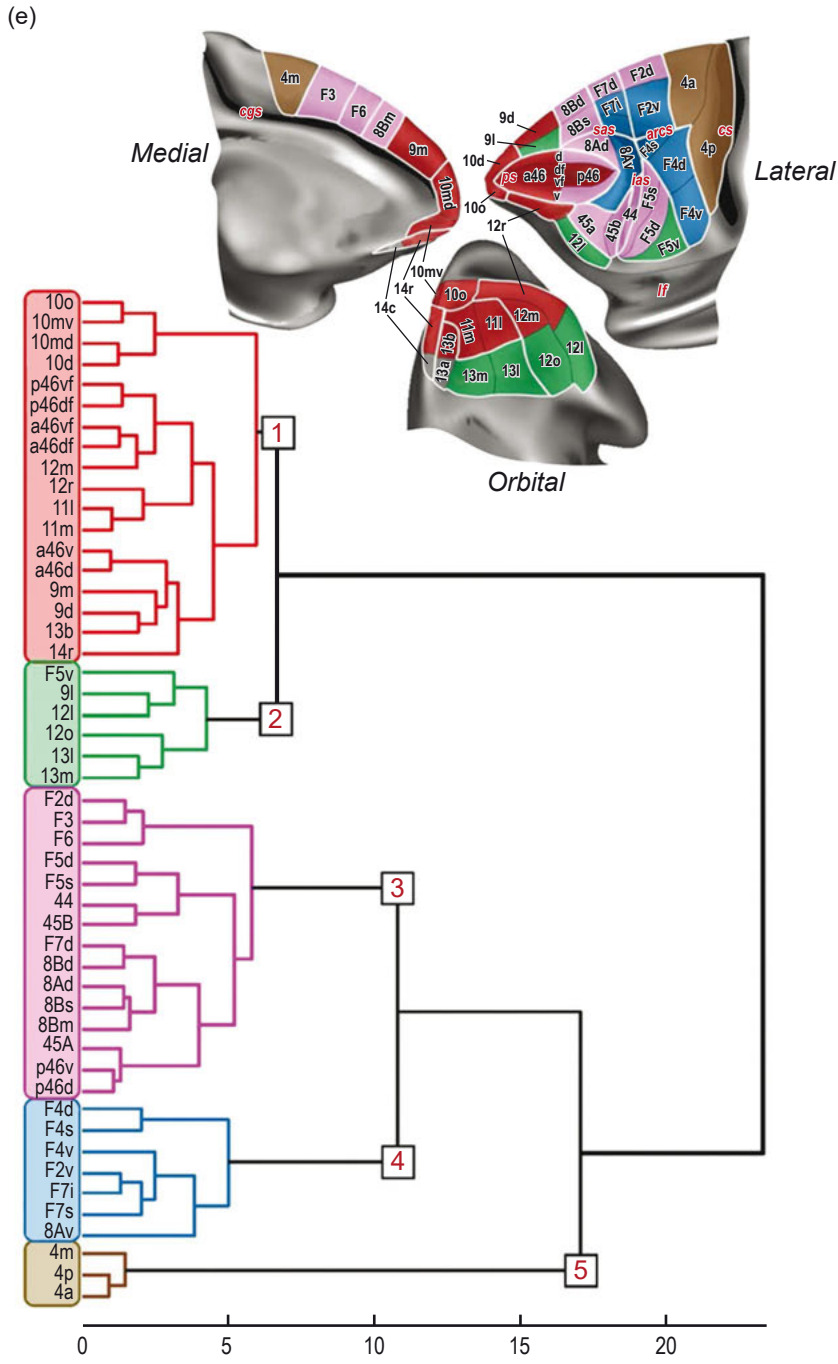


Figure 16.3 (continued) Prefrontal gradients are observed receptors, cytoarchitecture, connectional patterns, function, and transcriptomics. (c) Anatomical gradients of receptor density can be seen across the frontal lobe, illustrated with D1 receptors that control a working memory hierarchy (Froudist-Walsh et al. 2021). From multiple receptor densities (e.g., AMPA, kainate, NMDA, $GABA_A$, $GABA_B$, M1, M2, M3, α1, α2, 5-HT1A, 5-HT2, and D1), multidimensional scaling (d) and hierarchical clustering (e) of "receptor fingerprints" reveal a rostro-caudal gradient over prefrontal cortex (Rapan et al. 2021, 2023).

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530



From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

Similarly, the D1-receptor distribution shows gradients across PFC (Froudist-Walsh et al. 2021). These gradients encompass the multivariate fingerprint based on a large panel of receptors (Rapan et al. 2023), whereby there is a gradual progression of neurochemical functionality from central sulcus to frontopolar cortex (Figure 16.3). Such neurochemical gradients shape the anatomical mediation of psychopharmacological treatments for cognitive and psychiatric disorders and modulate the connectivity of regions.

Connectivity Gradients

PFC does not operate in isolation but acts via partially dissociable cortical-subcortical-thalamo-cortical loops for which the functional properties also form a gradient. These large-scale functional networks vary between individuals (Gratton et al., this volume), and the integration of network perspectives with the processes associated with symptoms can elucidate individual differences in vulnerability, resilience, or treatment opportunities. Connectivity gradients have been demonstrated at different levels of analyses:

1. Cortico-cortical connections based on cytoarchitectonic organization (Goulas et al. 2018),
2. Spatial gradients in which there is high connectivity between adjacent cortical areas that decreases with distance, and
3. Anatomic functional connectivity, which creates links, for example, limbic to cognitive to motor regions (Tang et al. 2019; Trambaiolli et al. 2022).

An example of the latter is the ACC, an area of particular interest for its association with depression, anxiety, and OCD. The ACC is anatomically heterogeneous and can be divided into subgenual (sACC), rostral (rACC), and dorsal (dACC) regions (Morecraft et al. 2012; Öngür and Price 2000). The sACC and vmPFC, which also includes ventral area 10 and 14m, are a central part of the motivation network. The vmPFC is strongly connected to OFC, amygdala, rACC, and the shell of the nucleus accumbens (Haber and Behrens 2014). It supports visceral and emotional functions in motivation (Alexander et al. 2019, 2020; Woods et al. 2023) and is critical for determining value (Camille et al. 2011a; Jocham et al. 2012; Kolling et al. 2016b). The sACC is tightly connected to the rACC, which in turn is connected with the dACC, dlPFC, and vlPFC (Tang et al. 2019). The rACC is associated with cognitive control and choice of action (Kolling et al. 2018). Caudally, the dACC is connected with the action network consisting of motor control areas, including frontal eye fields and premotor areas (Morecraft et al. 2012; Öngür and Price 2000). The dACC is associated with motor planning and action execution (Caruana et al. 2018; Picard and Strick 1996). Thus, through these anatomic connections, the ACC can use value-based information to

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

help regulate flexibility, adaptation, and top-down control (Etkin et al. 2015; Kolling et al. 2016b; Shenhav et al. 2016).

Importantly, there are no clearly defined borders between these three anterior cingulate divisions based on their anatomical connections. Instead, there is a gradual transition in the information content in the projections, gradually changing from limbic to cognitive and finally motor systems (Tang et al. 2019). Cortico-striatal and cortico-thalamic connections follow a similar gradient. Thus, although frontostriatal projections are organized in a general functional topographic manner, forming a ventromedial/dorsolateral gradient, there is a great deal of overlap between projections from these different areas. For example, inputs from OFC, sACC, and rACC converge extensively in the medial striatum. rACC, dorsal ACC, and OFC fibers converge with those from the dlPFC and vlPFC in more central caudate and putamen regions, particularly at rostral levels. Hence, cortical connections from distant regions converge within the striatum (Averbeck and Costa 2017; Giarrocco and Averbeck 2023). These areas of convergence are likely important regions for integrating information across diverse functional domains.

The concept of functional networks predate modern-day technical developments and maps. In the 18th century, Franz Joseph Gall recognized the importance of white matter connectivity between brain regions that were assigned specific functions (Zola-Morgan 1995). In the 19th century, Carl Wernicke thought the connectivity between brain regions, rather than location, was central to function (Catani and Ffytche 2005). In the mid-20th century, Norman Geschwind supported the notion that higher cognitive functions depended on a combination of localized function and their connectivity, leading to the idea that the brain was comprised of complex anatomic networks supporting cognitive and emotional processes (Geschwind 1965). More recent advances in neuroimaging have been combined with graph theory approaches to define brain networks. Whole-brain functional magnetic resonance imaging (fMRI) networks have been subdivided into functionally specialized resting-state networks, many of which include the PFC such as the default mode network, frontoparietal control and attention networks. Within such networks, a subset of regions serve as "hubs" to bring information together, either within or between networks. The term "hub," first coined by Marsel Mesulam to describe transmodal cortical areas that serve as anatomic and computational epicenters for large-scale cognitive networks, is now used in human network analyses to describe specific regions that serve as information integration centers (for review, see Haber et al. 2022). Such hubs are dynamic over the life span, with prefrontal hubs stabilizing in adolescence in concert with maturation of many cognitive systems (Hwang et al. 2013; Marek et al. 2015; Satterthwaite et al. 2013). Although important for efficiency of integrative processing, hubs also create vulnerability for dysfunction (Bassett et al. 2018; Crossley et al. 2014).

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

Cognitive Gradients

PFC can be viewed as a gateway to therapeutic interventions. Behavioral, pharmacological, and target-specific invasive and noninvasive interventions, such as deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS), need to be understood in terms of the mechanisms and circuits of underlying cognition. For example, executive functions can be summarized as belonging to three principal groups:

1. Working memory: the ability to maintain task-relevant information over brief periods of time and manipulate this information if necessary
2. Cognitive flexibility: the ability to switch flexibly between tasks and/or goals
3. Inhibition: the ability to resist interference and inhibit inappropriate actions and behaviors

Despite behavioral evidence for such a functional fractionation, functional neuroimaging in humans remains equivocal on the strength of a corresponding functional-neuroanatomical dissociation. For example, large-scale quantitative meta-analysis of 193 functional neuroimaging studies indicated largely overlapping brain systems for these three "core" executive functions, spanning wide areas of lateral and medial PFC and their subcortical connections (Niendam et al. 2012). This does not mean that the PFC is undifferentiated. Behavioral evidence suggests that inhibition may contribute to tasks primarily designed to probe working memory and cognitive flexibility, and such a common executive function might be captured by prefrontal multiple demand systems (see Duncan and Friedman, this volume). Gradient models offer a parsimonious account of PFC that accommodates both task commonalities (the apparent co-localization in multiple demands) and smooth functional variation along axes of anatomical organization, with heterogeneity associated with variation in cytoarchitecture, connectivity patterns, and neurochemistry.

The direction of a cognitive gradient may lie along dorso-ventral, rostro-caudal, or medio-lateral axes (see Figure 16.3). For example, on lateral PFC, there is a gradient of organization as one records progressively more rostrally, in terms of activity or connectivity (Badre, this volume; Badre and D'Esposito 2007). The cognitive processes associated with this rostro-caudal gradient in response and connectivity have been described in several terms. Hierarchical control models have been proposed for lateral PFC, according to different types of representations or control signals that vary in the degree of abstraction (Badre 2008). The rostro-caudal gradient may also reflect a functional hierarchy in the timescales across episodic, contextual, and event-based determinants of behavioral decisions. While posterior regions control behavior and actions driven primarily by direct motor affordances of a current stimulus, mid-rostral regions are associated with more abstract cognitive control (e.g., contextual control of stimulus-driven behaviors according to transient abstract

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

task sets), and more rostral regions mediate controlled behavior depending on past experiences or future long-term goals (episodic control; Koechlin and Summerfield 2007). The highest level of behavioral control, often attributed to the frontopolar cortex, has been associated with the management or monitoring of multiple goals and subgoals in parallel (Mansouri et al. 2017).

The temporal scale of cognitive processes also maps onto a spatial gradient of PFC. This is seen in the temporal dynamics of intrinsic fluctuations in neuronal spiking in nonhuman primate and human cortex, whereby sensory cortical areas have shorter timescales and PFC association areas have longer timescales (Demirtas et al. 2019; Murray et al. 2014). Such a gradient in temporal dynamics influences the cognitive-physiological properties supported across the gradient. For example, primary visual cortex (V1) requires a short timescale to accurately decode the onset and offset of a visual stimulus, while sensory association cortices (e.g., MT/V5 or LIP) use longer timescales to integrate and analyze information to facilitate recognition, and dlPFC uses still longer timescales to maintain and manipulate information for many seconds without sensory stimulation (Funahashi et al. 1993b; Leavitt et al. 2017; Wang and Krystal 2014). Lateral and medial prefrontal rostro-caudal gradients also reflect the temporal span of task-relevant representations (e.g., immediate action, contextual task set, episodic influence and enduring normative social rules) and temporal extent of influence of motivational signals (immediate rewards, context-dependent motivational signals, longer-term episodic goals) (Kouneiher et al. 2009; Wood et al. 2023).

Control demands may vary along the ventral-to-dorsal axis. The classical proposal of the organization of working memory systems in lateral PFC is that ventral regions host the sustained maintenance of task-relevant information, whereas dorsal regions are engaged when cognitive load increases beyond capacity limits or when actions are required on working memory contents (manipulation, updating, selection; cf. D'Esposito et al. 1998b). A dorsal-to-ventral axis is observed along the medial prefrontal cortex, as tasks or their underlying representations vary in the degree of emotional control (vmPFC, sACC, and pregenual ACC) or cognitive control including the monitoring of conflict and uncertainty (dorsal ACC) (Bush et al. 2000; Sheth et al. 2012).

The lateral-to-medial axis has correlates in the processing of value signals, with differential responses to negative (punishment) versus positive (reward) value (Kringelbach and Rolls 2004), that may guide avoidance versus approach behaviors. A medial-to-lateral gradient has also been proposed for the degree to which lateral regions are oriented toward external states and goals while medial PFC is oriented to internal states (e.g., Denny et al. 2012). On this basis, frontopolar cortex might be involved in switching between such externally versus internally guided controlled behavior (e.g., the gateway hypothesis; Burgess et al. 2007).

The existence of orthogonal gradients creates a "matrix" of PFC functions with which to understand the nature of prefrontal deficits in neuropsychiatric

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

disorders. A very large set of regions with specific properties can be efficiently created from a small set of macroscopic gradients: each conjunction of gradients defines areas with apparent "localization" of functions, leading to apparent localization of the correlations with symptom, such as contextual control signals in lateral prefrontal cortex (Barbalat et al. 2011). A hierarchical organization of cognitive control may result in asymmetric deficits, such that impairments in episodic control (e.g., due to traumatic experiences) may indirectly impact hierarchically "lower" stages of contextual or sensory control, even though these in themselves could be unaffected (e.g., at the level of brain-structural integrity or neurochemical modulation). Understanding cognitive contributions to psychiatric disorders at such a fine-grained level of resolution requires a systematic approach to experimental psychopathology research with new classes of experimental paradigms built on cognitive control theory. It has the potential to link cognitive phenotypes of a disorder to underlying mechanisms, not only in terms of local effects but in terms of the statistical dependency between cognitive, physiological, and pharmacological gradients.

Brain imaging by structural and functional MRI often contains graded information, with graded rather than discontinuous variation in activity or connectivity. Unfortunately, published brain imaging maps are typically thresholded, creating the impression of discrete functional areas. To get around this limitation, the raw data or unthresholded maps should be shared. An alternative approach is to use statistical tools that express gradients in structural and functional imaging data (Bethlehem et al. 2020). Such system-level gradients are not restricted to atrophy or fMRI connectivity but can be generated for microstructural differentiation so as to reveal the pattern of change in adolescence or aging (Bethlehem et al. 2022b). These gradient mapping methods are well suited to characterize multidimensional hierarchical functional systems. These gradients are not restricted to imaging modalities but can be directly linked to spatial variation in receptor density or gene expression, linking the macroscale imaging of disorders to genetic regulators of neurons, glia or endothelium (Altmann et al. 2020). Across multiple neuropsychiatric disorders, the spatial patterns of cortical anatomy changes in adolescence correlate with spatial expression of copy number variation genes in neurotypical adults. Such genetic gradients provide a mechanism to mediate the mapping of genetic risk onto regional brain changes in neurogenetic disorders (Seidlitz et al. 2020). They are likely to contribute to the strong polygenetic influence on developmental trajectories of brain structure and connectivity (Bethlehem et al. 2022a) and establish developmental gradients.

Developmental Gradients and Critical Periods

The dynamic nature of PFC during development confers a particular risk to disruption and, in turn, increased risk for psychopathology. The developmental timing of stress exposure is similarly important. These prefrontal cortical

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

circuits are undergoing significant specialization during adolescence, including decreases in frontostriatal (Parr et al. 2021) and fronto-amygdala connectivity (Jalbrzikowski et al. 2017) and increases in fronto-hippocampal connectivity (Calabro et al. 2020). Given the sex differences in adolescence and brain development, the age of stress may lead to differential risks of psychopathology in later life. The dynamic nature might also confer resilience to recovery, following the termination of stressors (McEwen 2013).

Development can be seen as a process of accumulation through childhood and long into traditional definitions of adulthood. Cell division, migration, and axonal connections are well established by birth. The brain achieves 95% of adult size and weight by 7–11 years of age, and full adult weight by adolescence (Caviness et al. 1996; Giedd et al. 1996). However, developmental trajectories are not equivalent across the PFC, with peak cortical thickness achieved last in vmPFC and insula/vlPFC (Bethlehem et al. 2022a). During postnatal development synaptogenesis, synaptic pruning and myelination become the dominant means of plasticity (Huttenlocher 1990). Synaptic pruning in PFC begins in childhood and continues into the 30s (Petanjek et al. 2011, 2023). Functional connectivity decreases in frontostriatal and fronto-amygdala systems (Jalbrzikowski et al. 2017; Parr et al. 2021) reflective of dampening of activation from subcortical regions (Murty et al. 2018). Myelination begins during gestation and continues through adulthood. Myelination of sensorimotor tracts is in place by childhood but major tracts that provide connectivity for lateral PFC regions, such as the superior longitudinal fasciculus, mature throughout adolescence. Those providing connections to ventral PFC systems, including the cingulum and uncinate fasciculus as well as myelination of endpoints in the gray matter, continue to mature into adulthood (Lebel and Beaulieu 2011; Simmonds et al. 2014). Myelination is not confined to white matter tracts: using magnetization transfer ratio, layer 5 and 6 of human cortex reveals increases in intracortical myelination up to 24 years of age (Whitaker et al. 2016).

With neuronal maturation comes the development of cognitive abilities. For example, the trajectory of executive function from childhood through to adulthood mirrors anatomical maturation (Luna et al. 2015; Tervo-Clemmens et al. 2023). The efficiency of executive systems increases in parallel: activations of ACC and lateral PFC decreases from childhood to adolescence during inhibitory control and working memory tasks (Ordaz et al. 2013; Simmonds et al. 2017). By adolescence, essential neural systems are in place, with spatial gradients and specialization finessing performance toward the adult level of executive function. A corollary of this development of cognitive abilities associated with PFC is the development of the risks for major psychopathology (see Figure 16.4) (Gogtay et al. 2004; Han et al. 2021; Paus et al. 2008; Solmi et al. 2022; Uhlhaas et al. 2023). Understanding the neural mechanisms of maturation of prefrontal cortical systems may explain the emergence of mental

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

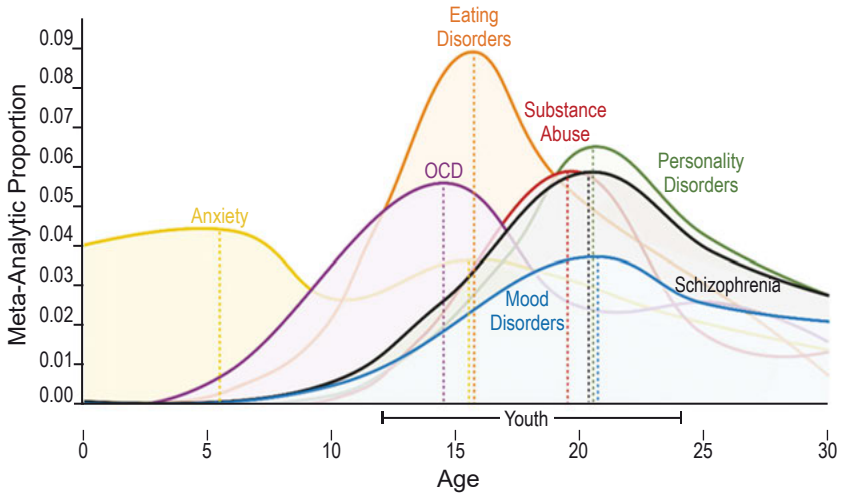


Figure 16.4 The risk of developing neuropsychiatric disorders varies with age and peaks during adolescence as the neural systems underlying the relevant cognitive processes themselves reach maturation (based on a meta-analysis by Solmi et al. 2022).

illness as an expression of a neurobiological predisposition or an impairment of normal developmental plasticity.

The phased maturation of cortical and subcortical circuits creates critical periods for the neural risks of mental health disorders. The expression of psychopathology emerges at different developmental periods: with ASD emerging in infancy, ADHD and initial OCD in early childhood, anxiety in mid-childhood, and psychosis, bipolar, and mood disorders in adolescence. This temporal sequence is influenced by the hierarchical maturation in terms of neurogenesis, synaptogenesis, synaptic pruning, and myelination, thus creating critical windows. The neurobiological basis of critical windows in development has been established most comprehensively for the visual system (Toyoizumi et al. 2013) but similar principles apply to prefrontal cortex. Critical period plasticity is underscored by increases in glutamatergic excitatory function, breaking its balance with inhibitory GABAergic function. This triggers change in inhibitory circuitry, such as parvalbumin neurons that dampen spontaneous excitatory neural activity returning excitatory-inhibitory balance (Dorrn et al. 2010; Hensch and Fagiolini 2005; Toyoizumi et al. 2013). Similar processes occur in animal and human postmortem studies. In adolescence, for instance, GABAergic parvalbumin cells increase (Caballero et al. 2014; Larsen and Luna 2018) in parallel with decreases in prefrontal glutamatergic signaling (Henson et al. 2008; Hoftman et al. 2018). *In vivo* high-field 7T MRI spectroscopic imaging has identified the progression of prefrontal glutamate-GABA balance into adulthood, supporting an adolescent critical period of plasticity (Perica et al. 2022).

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

The presence of plasticity through adolescence creates a particular susceptibility to environmental influence. For example, a genetic neurobiological predisposition for psychopathology may be more strongly expressed within a stressful environment so as to foster the phenotypic behaviors of diverse mental illnesses. In this way, the mechanisms underlying plasticity need not be impaired as such; they merely need to adjust to experience. Critical periods may vary in duration, with prolonged critical period plasticity or precocious termination, according to glutamatergic and GABAergic systems status and external factors such as stress. Chronic stressors during adolescence decrease excitatory activity and plasticity in frontal cortex in animal models (Novick et al. 2016; Urban and Valentino 2017; Yuen et al. 2012). Similarly, chronic stress in adolescence destabilizes and dampens inhibitory activity and peri-neuronal nets (Bicks et al. 2020; Tzanoulinou et al. 2016).

Stressors in the fetal period reduce critical GABAergic processes (Suwaluk and Chutabhakdikul 2022a, b) and protein phosphorylation affecting prefrontal cortical maturation. This is associated with anxiety and depression as well as risk for mental health disorders later in life. Stress during infancy and childhood also affects prefrontal circuits, such as fronto-amygdalar connectivity (Morin et al. 2020), and altered expression of immediate early genes and myelin-related genes (Blaze et al. 2013; Teissier et al. 2020). By adolescence, stress, especially social stress, affects cortico-limbic regions involved in emotion and stress regulation, including amygdala structure and social circuitry (Godfrey et al. 2023; King et al. 2023). Not all stressors are equivalent in their consequences: rodent and human studies show that short-term acute stress can have enhancing effects on cognition and excitation, whereas long-lasting chronic stress generally dampens excitatory and inhibitory processes undermining critical period plasticity and increasing the risk for psychopathology.

Gradients of Disease Expression and Treatment Outcome

The evidence of cognitive gradients comes from human functional neuroimaging and therapeutic lesion outcomes. The evidence of morphological, receptor, and transcriptomic gradients in nonhuman primates suggests the likely existence of analogous functional gradients. However, the type of gradient based on abstraction hierarchies has yet to be demonstrated in nonhuman primates. This partly reflects the challenge of training and performing multiple tasks in other species. So, while animal models have established the molecular, pharmacological, and microanatomical underpinnings of critical cognitive processes, we can also learn from the syndromic associations of regionally defined disorders and focal interventions.

How do gradients in cognitive hierarchies across the PFC link to neuropsychiatric syndromes? Consider the rostro-caudal gradients in lateral, medial, and cingulo-opercular networks described above. The temporal scaling property along this axis is ideally suited to support the gradient from simple

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

Pavlovian stimulus-bound value (caudal) to value associated with local context (mid) and to enduring representations of prospective expected value associated with episodic future thinking (rostral). Symptoms related to OCD and anxiety disorders may mirror this spatiotemporal gradient and distinguish, for example, those present at the stimulus level (e.g., a contaminated object), the local contextual level (e.g., holding a knife in the presence of a child associated with aggressive obsessions), or an extended abstract future-oriented consequence (e.g., my parents might go to hell if I don't complete this ritual). The neurobiological basis of symptoms can, in principle, be mapped onto the rostro-caudal gradient, either in the OFC representation of expected value or medial cingulate monitoring of action outcome.

The contiguity of such gradients through cortico-striato-thalamo-cortical circuits can inform the selection of sites for therapeutic surgery or focal stimulation by DBS or TMS. By this means, a very focal lesion may affect the function of a much larger swathe of PFC.

Neurodegenerative Gradients

Thus far we have focused on disorders that emerge during adolescence and young adult life, including the clustered psychopathologies of autism syndrome disorders, ADHD, anxiety, OCD, and addiction. However, phenomenologically analogous syndromes can arise from focal neurodegeneration. Developmental and degenerative disorders are not exact homologues, but they are mutually informative and have critical cognitive and behavioral similarities. This is most evident in the family of syndromes caused by frontotemporal lobar degeneration. This leads to a progressive rostro-caudal gradient of synaptic and neuronal loss, beginning in mid-to-later life. In the behavioral variant of frontotemporal dementia (FTD), for example, there is early synaptic and neuronal loss in insula, orbitofrontal, and ventromedial regions with later progression to ventrolateral and anterior cingulate cortex. Symptoms include repetitive and obsessional behaviors, poor executive function, impulsivity, risk-taking, and cognitive inflexibility. There are additional changes to affective cognition, with loss of social cognitive skills, poor empathy and a reduction of goal-directed behaviors (i.e., apathy). The autosomal dominant genetics, molecular pathology and prominent atrophy in these associated disorders has contributed to their classical designation as "neurological" rather than "psychiatric" disorders. This professional distinction can obscure the phenomenological similarity between behavioral variant FTD and developmental or young adult psychiatric and neuropsychiatric disorders. The genetic risks and structural change may be more subtle with the latter group, but despite the scarcity of autosomal dominant etiology of psychiatric disorders, the heritability of cortical, subcortical gray, and white matter volumes is very high (Bethlehem et al. 2022a).

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

Other focal and multifocal "neurological" disorders affecting the frontal lobe can lead to similar cognitive and behavioral change, whether from leukodystrophy, stroke, tumors and their excision, inflammatory lesions, or traumatic brain injury. Despite myriad etiologies, the lens of systems cognitive neuroscience can be used to understand the clinical presentations and guide therapy (Passamonti et al. 2018). Not all therapeutic approaches have been through disease-specific randomized controlled trials, but anecdotal reports, case series, and early phase trials support the translational relevance of the schema illustrated in Figure 16.1 to dementias (Holland et al. 2021; Murley and Rowe 2018).

The impulsivity and cognitive inflexibility arising from behavioral variant FTD has several contributory factors. The FTD-related atrophy of ventrolateral and orbitofrontal cortex is associated with impulsivity (Lansdall et al. 2017, 2018), while the loss of induced beta-power from lateral prefrontal cortical microcircuits correlates with everyday challenging behaviors (Hughes et al. 2018). There is also a severe loss of serotonergic innervation of the PFC (Murley and Rowe 2018), resonant with the serotonergic role in perseveration and impulsivity in marmoset and rodent models (Clarke et al. 2004, 2005, 2007; den Ouden et al. 2013). Although the atrophy cannot yet be rectified, serotonergic reuptake inhibition has been shown to partially restore neurophysiological functions of the PFC in FTD (Hughes et al. 2015). Serotonergic reuptake inhibition is widely used in the clinic for challenging behaviors, even in the absence of depression or anxiety. A related frontotemporal lobar degeneration syndrome of note is progressive supranuclear palsy (PSP). In addition to motor deficits, people with PSP are impaired in response inhibition (Zhang et al. 2016), cognitive flexibility (Robbins et al. 1994), social cognition (Ghosh et al. 2012), and goal-directed behavior (Murley et al. 2020). People with PSP have modest atrophy of medial PFC but severe atrophy of subcortical nuclei (locus coeruleus and subthalamic nuclei and pallidum) and severe synaptic loss across the PFC that correlates with clinical decline (Holland et al. 2023). PSP causes early and severe noradrenergic deficits arising from degeneration of the locus coeruleus, leading to impulsivity and apathy (Kaalund et al. 2020; Ye et al. 2023a), in part by loss of noradrenergic-dependent connectivity between prefrontal cortical regions and their subcortical pathways (Tomassini et al. 2022). Given the robust noradrenergic influence on inhibition and set shifting across species (Bari et al. 2011; Chamberlain et al. 2006; Rae et al. 2016; Robinson et al. 2008; Ye et al. 2023a), noradrenergic strategies are now in clinical trials for cognitive and behavioral consequences of neurodegeneration. The noradrenergic hypothesis provides an example of the value of cross-species and transdiagnostic approaches, based on systems cognitive neuroscience: bootstrapping noradrenergic therapies for attentional and cognitive control in ADHD (Elliott et al. 2020), addiction (NCT00218543), Alzheimer disease (David et al. 2022; Eudract 2016-002598-36), and parkinsonism (ISRCTN99462035). Future

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

studies in neurological disorders can draw on new insights into the regulation of PFC and look to ameliorate symptoms through restorative pharmacology aimed at the range of processes outlined in Figure 16.1. The noradrenergic hypothesis also illustrates the direct line of sight from rodent and NHP models through psychopharmacological probe studies in humans with neuroimaging support, and then to clinical therapeutics.

Summary

Much of the complexity of PFC function can be explained in terms of the intersection of gradients. Individual gradients may reflect fundamental neural variance (e.g., receptor density, anatomical connection patterns, and myelination). They may also reflect information content of encoded information and the temporal scales to which they refer. The trajectory of development of these gradients gives rise to critical windows for the risk and manifestation of psychopathology. An important corollary of prefrontal gradients is their cross-species homologies that can inform therapeutic strategies and prediction of outcomes.

Animal Models Related to Human Disorders

Role

There are two broad aims for animal models of human disorders. First, they may seek to recapitulate the pathology (e.g., through genetic manipulation, cytotoxic lesions, pharmacology or environmental insults such as stress). Second, the animal model may seek *construct equivalence*, to study specific symptoms related to particular parts of the pathophysiology or psychopathology of the disease. Gaining such an understanding of the basic neurobiological mechanisms of specific processes, the dysregulation of which lies at the core of clinical symptoms, is of enormous value.

Animal models can be designed and used so as to aid the understanding of human disorders. However, responsibility lies in both directions. Those studying clinical phenotypes also need to ask the right questions and record the right variables with human volunteers so one can learn from the insights emerging from the animal literature. This is especially important for the neuropsychiatric disorders associated with the PFC, where cross-species homologies can be challenging.

There are clear examples of animal models that are helpful in understanding the prefrontal circuitry and its dysregulation associated with neuropsychiatric symptoms:

- The disruptions in goal-directed behavior in rats (Balleine 2019), marmosets (Duan et al. 2021) and macaques (Murray and Rudebeck 2018) that are also seen in people suffering from OCD.

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

- The effect of cingulate lesions in macaques on monitoring of social consequences, relevant to social phobia (Rudebeck et al. 2008a, b).
- The platform avoidance task of Quirk and colleagues related to OCD and other anxiety disorders that manifest active avoidance as a prominent symptom (Martinez-Rivera et al. 2023).
- Impaired inhibitory control in stop signal reaction time, related to impulsivity seen in ADHD (Eagle et al. 2008a).

Such experimental studies in animals are often better placed to determine whether alterations in activity associated with a particular disorder are compensatory or causal to the disorder and its symptoms: the hyperactivity of orbitofrontal cortex in OCD or hyperactivity of subcallosal cingulate cortex in depression. Overactivation of subcallosal cingulate cortex can induce behavioral changes in monkeys similar to symptoms of anxiety and anhedonia reported in depression (Alexander et al. 2019). Similarly, overactivation of OFC has been shown in rodents to cause compulsive-like grooming behavior of relevance to the compulsivity seen in OCD (Price et al. 2021). Evidence that hyperactivity in a disorder is compensatory may require an experimental second hit (e.g., lesion or inhibitory stimulation), which is usually clinically not advisable.

As stress is a known contributor to the onset of many clinical disorders, another approach in experimental studies in animals has been to study the impact of stress on prefrontal function. For example, diverse types of psychological, social, or physical stressors affect the prefrontal physiology underlying clinically relevant cognitive processes. These include plasticity mechanisms and related behaviors including cognitive flexibility, goal-directed behavior, working memory, and reactivity to negative and positive reinforcers (see Roberts and Liston, this volume). These stress manipulations can recapitulate some of the clusters of symptoms seen transdiagnostically. The psychological or physical nature of the stressor may differentially influence specific prefrontal circuits (Bondi et al. 2008; Danet et al. 2010). Moreover, when these stressors are induced during development, the pattern of behavioral changes seen can also vary depending upon the timing of the stressor. For example, in rats, maternal deprivation in infants produces a different phenotype to social deprivation in juveniles/adolescents, indicating distinct neurobiological substrates for stress-related disorders, depression, and ADHD (Matthews and Robbins 2003; Robbins et al. 1996). This highlights the contribution that animal studies can provide to our understanding of neurodevelopmental processes in general and effects of stress in particular.

We discussed the developmental trajectory of the human frontal lobe, with respect to myelination, synaptic pruning, and circuit connectivity. Analogous trajectories are seen in animals, particularly nonhuman primates (Sawiak et al. 2018; Scott et al. 2016). Even in marmosets, the neural substrate of individual differences in cognitive development can be seen in the trajectories of prefrontal gray matter volume (Sawiak et al. 2018).

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

There are, however, limits to cross-species comparisons. For example, the sex differences in brain development that are evident in humans have not been reliably replicated in marmosets. This may be true null result in a species or may reflect the obstacles to large studies of nonhuman primates: compare $n > 130{,}000$ humans scanned individuals collated by Bethlehem et al. (2022a) with nonhuman primates studies typically $n < 10$ and rarely $10 < n < 50$.

Animal studies can also provide insight into the prefrontal mechanisms that confer vulnerability or resilience to brain disorders. For example, with respect to vulnerability, distinct behavioral traits, such as hyperactivity, poor flexibility, or impulsivity in rats, can lead to different aspects of drug-seeking, drug-taking, and drug-dependency behavior and related prefrontal disturbance, which is of relevance to our understanding of addiction (Belin et al. 2016). On the other hand, rats or mice which fail to display anxiety-like or depression-like symptoms following chronic social defeat stress have the potential to provide insight into mechanisms of resilience (Krishnan et al. 2007). Further insights into resilience can be gained by not excluding non-responders. Some studies may exclude animals that do not express psychopathological responses to stressors, such as social stress. Such natural variation in trait vulnerability offers an important opportunity to determine the mechanisms of vulnerability and resilience (Lorsch et al. 2021; Nasca et al. 2019).

Selection of Models and Tasks to Support Translation

Different species may be better suited to translate specific aspects of disorders associated with prefrontal function, their etiology, and treatment. There are critical decisions for the research team regarding the processes and regions of interest and the nature of any intervention. The complementarity of models rests in part on the intrinsic capacity of species to support a cognitive process in a recognizably homologous cortical area. For example, an animal study of hierarchical representations across the prefrontal gradient, akin to that described by Badre (this volume), requires a species with a highly differentiated dlPFC; in other words, a macaque and less so a marmoset, where the dlPFC is less differentiated, and not a rodent, where it appears nonexistent. By contrast, a study of auditory social interactions may be more appropriate with marmosets. This does not mean a lack of ambition for animal models. Even rats can be used, for example, to study confidence estimates, previously suggested to require "metacognition" and conscious awareness. The decision of species and task to study the relevant process are intimately connected. Complementarity also extends to the mode of intervention: skull morphology, brain size, or nucleus volume may critically determine the feasibility of focal surgery.

The availability of established models of behavior, disease, and risk is an important consideration. For example, the degree to which a physical or psychological stressor is recognized for a given species and the degree to which the animal behavior is interpretable for a given species varies. Even where

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

models (e.g., for stress) exist and are transferable across species, the optimal readouts of the model may differ between species.

A further choice lies in the selection of a task to compare across species. Some tasks have been extensively studied and validated across species, such that the task can be run with formal equivalence in animal and human laboratories. Examples of this type of task are the stop signal task of inhibitory control (Eagle et al. 2008a) and intra/extra-dimensional shift tasks (Chamberlain et al. 2021). These can be operationalized with equivalence across species and have major homologies in terms of functional anatomy and psychopharmacology across mice, rat, marmoset, macaque, and human species. Care is still required to determine the possible differences in cognitive strategies by which an animal or human might approach the same task, because even within a species, there can be differences in the strategy used by an individual. Nonetheless, these tasks have shown how comparisons can be sustained, and they support translation of pharmacological interventions, such as the noradrenergic hypothesis discussed above.

Despite limitations of cross-species homology, animal models offer many advantages. These include experimental methods that are not practical or ethical with human participants, such as the ability to systematically manipulate genetic variants by breeding of traits or CRISPR technology as well as the control of neuronal function by optogenetics or pharmacology using DREADDs (designer receptors exclusively activated by designer drugs). A much wider range of pharmacological interventions is available for animal research, relevant to prefrontal function, such as selective D1 agonists that are not yet available for human use to study working memory systems. Animal models also enable a wider range of readouts than is available for clinical studies, both *in vivo* (e.g., physiological recording or calcium imaging) and postmortem (at any stage of development).

This experimental control over the baseline state of the PFC, before a stressor or drug, is a powerful tool to study and accommodate baseline dependency. For many stressors and pharmacological interventions, response depends markedly on the baseline state of the organisms. For example, the effect of dopaminergic manipulations of impulsivity, risk-taking, and working memory depends on the individuals' baseline performance and baseline dopaminergic function. This contributes to nonlinear dose-response curves and heterogeneous responses to standardized interventions. It may fully obscure the group-wise effect of intervention, unless one controls for individual differences. Such baseline differences are quantifiable in humans but are less easy to control experimentally.

Selection of Clinical Evidence

Animal studies demand critical decisions regarding the selection of model, task, and intervention for them to be relevant to human prefrontal function and

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

its disorders. Likewise, critical decisions are also required of human normative and clinical studies; however, this challenge arguably receives less consideration. Are human studies recording the information required to make use of the data emerging from animal models? We need to rethink not only the approach to animal models of biological processes and behaviors that are relevant in PFC-related neuropsychiatric disorders. It is equally important to optimize clinical trials and human neuroscience studies to ensure that they are recording the information and data types required for integration with insights from animal models. Three principles should guide this work in the future.

First, it will be critical to refine clinical ratings scales to maximize data quality. Clinician-rated scales have some advantages over self-report assessments of psychiatric symptoms, but they typically depend on rigorous training to ensure robust and reproducible results. Conversely, the validity of patient-rated scales may not hold in the context of some PFC-related disorders (Williams et al. 2023). The field would benefit from a greater understanding of the factors that influence data quality, validity, and reliability.

Second, it is important to optimize clinical scales and trial designs to ensure they are quantifying the right variables, especially those that can also be studied in animal models. For example, there has been significant progress in recent years toward understanding the prefrontal circuit mechanisms that regulate reward-seeking, motivation, incentive salience, and effort valuation. These constructs are, however, rarely assessed in detail in large-scale clinical studies. Similarly, it would be valuable to quantify symptoms in multiple domains in a standardized way across different clinical disorders rather than diagnosis-specific rating scales; for example, to assess OCD symptoms, compulsive behaviors, and cognitive flexibility in studies focused on depression, and vice versa.

Third, studies should not rely unduly on subjective clinical scales but also include objective behavioral assessments. These can complement clinical symptom measures. The advantage of the objective behavioral assessments is that they can be designed to capture similar functions across species. This will greatly strengthen the translational bridges across species and models and accelerate the development of clinical therapeutics informed by preclinical model systems with a wider range of methods than can be applied in human studies. One needs to remain mindful of the fact that a human might solve the same problem differently than a mouse or marmoset.

Limitations

Animal models of clinical disorders do not need to be exact homologies to be useful. The closer the approximation to critical clinical phenomenology, the easier it may be to see a pathway for translation from laboratory model to clinical therapeutics. This, however, is not essential, provided that researchers avoid naive interpretations of tasks and look behind the superficial interpretations of

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

clinical phenomena. For example, challenging behaviors from prefrontal cortical degeneration in FTD may be called impulsivity or disinhibition, when in fact they arise from a loss of contextual knowledge to indicate social norms (O'Callaghan et al. 2016; Restrepo-Martinez et al. 2023). In other words, a semantic deficit may be misinterpreted as impulsivity. Similarly, apathy as an observed deficiency of goal-directed behavior may be misinterpreted as depression, even in the absence of a mood disorder. Training and cross-disciplinary collaboration mitigates this risk.

Are any cognitive processes and domains off-limits in animal research? At first glance, it may seem that some human cognitive functions cannot be studied in rodents or even primate models. However, through the adoption of construct equivalences and new model-based approaches, few cognitive domains are out of bounds.

Language may at first seem exclusively human, yet critical aspects of language are amenable. For example, marmosets can be used to study the vocal sensorimotor integration in real time (Pomberger et al. 2020; Takahashi et al. 2015). Also, in nonfluent aphasia, the excessive precision of speech priors in ventral PFC undermining comprehension is part of a wider deficit in predictive coding, which in turn is amenable to preclinical models (Cope et al. 2017; Kocagoncu et al. 2021). While social behaviors may not be manifested in the same way in humans and macaques, there are close similarities in the underlying constructs to enable detailed assessment of PFC regions in social cuing, inference, and behavior. The representations and functional anatomy of face identify, face emotion, eye gaze, rewards associated with social partners, and social decisions establish strong equivalent constructs across species. Moreover, the cooperative breeding style and allomaternal care of marmosets mirrors that of humans, as distinct from other primate species (e.g., chimpanzees and macaques), and is an excellent model for studying sociocognitive brain development (Hrdy and Burkart 2022). To understand the representation of events that have not happened is challenging. However, this challenge is not limited by species. Prefrontal representation of counterfactual events and their value can be studied in macaques as well as humans (Fouragnan et al. 2019).

Summary

There is a balance to be struck between the simplicity of a model whose components are readily understood and the complexity of a model that may afford greater ecological relevance. Progress in translational neuroscience is facilitated by the use of complementary models, and tasks, referring to a common set of underlying constructs. We have illustrated how trans-species constructs at the level of processes and mechanisms can be used to understand the symptoms and syndromes associated with human prefrontal function. Whether this

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

approach is robust enough to understand the mechanisms of psychotherapy, via animal models, remains to be seen but should not be ruled out.

Improved Targeting of Treatments, with Combinations and Prediction

The treatment of disorders associated with PFC and its associated circuits (e.g., frontostriatal and fronto-amygdala) might seek to reverse the deficit directly, for example, by replacing deficient neurotransmitters and improving symptom severity in an individual, thereby improving their quality of life. This chain of therapeutic effects cannot be assumed, even where the intervention engages the intended target. Moreover, reversal of the pathophysiological deficit itself may not be required. Instead, an effective treatment may engage other areas of the cortex or frontostriatal circuits, so as to compensate for the deficit rather than reverse it. Many individuals with neuropsychiatric syndromes struggle with prefrontal-related cognitive tasks (e.g., executive functions), which may underlie and/or exacerbate other problems (e.g., emotion regulation) and functional disadvantages (e.g., scholastic achievement). There is a pressing need for interventions that address and remediate cognitive processes and psychiatric illness. Both curative and symptom-mitigation treatments aspire to improve quality of life for the affected individual.

Treatments can be considered as focal or diffuse in their mode of application. Focal treatments in clinical use include neurosurgery, TMS, focused ultrasound stimulation, and DBS. Their benefit may nonetheless be mediated by diffuse systems, in the case of wide projections from the site of intervention. The effects of diffuse treatments, including pharmacology and cognitive behavioral therapies (CBTs), may nonetheless be exerted by their action on a focal system or circuit (see Roberts and Liston, this volume).

Psychological and Behavioral Therapies

As discussed by Jaeggi et al. (this volume), CBTs are representative of a wider body of evidence-based psychological interventions for psychiatric disorders and behavioral health symptoms. Here we set them in context of PFC circuits and other interventional approaches. Note that some are inherently diffuse in their cognitive processes and in the presumed functional anatomical associations (e.g., mindfulness) while others are cognitively and by extension anatomically constrained (e.g., cognitive training, exposure therapy, or goal management training). Classical CBT methods lie midway in this spectrum.

CBT methods share a structured, time-limited, problem-focused, and goal-oriented form of psychotherapy, through partnering with the client for symptom reduction. This includes a detailed assessment of the key symptoms, their antecedents and consequences of the symptoms or problems, and the contexts

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

in which they occur. CBT has a strong evidence base in depression (Hofmann et al. 2012a). A common clinical model is to have an 8–12 weeks course that focuses on patient-specific symptoms. Specific interventions are adjusted to the problem, but they use a common underlying methodology: monitoring, tracking, antecedents, behavior, and consequences. Specific sessions and interventions may be implicitly or explicitly focused on processes associated with PFC such as self-monitoring; chain analysis of thoughts; feelings and actions in context; goal setting, planning and problem solving; and developing new strategies with greater cognitive control. In other words, CBT is goal directed, seeking adaptive strategies, reminiscent of the functions of the PFC itself. CBT may also include relaxation training, participating in pleasant activities, exposure to contexts and situations causing distress, the toleration of distress, and other exercises. The goal is to target maladaptive cognitive and behavioral processes and achieve a better understanding of one's symptoms and their drivers, together with training to reduce symptoms via adaptive cognitive, emotional, and behavioral responses. CBT protocols and their variations have been adapted for specific psychiatric disorders (e.g., major depression, anxiety disorders, OCD, addictions) and management of health symptoms such as insomnia, chronic pain, stress and anxiety management, binge eating, and weight gain may occur in isolation or co-occur with neurologic and other medical illnesses. There is extensive support of efficacy of CBT approaches in the treatment of these conditions, with response rates in the range 30–60%, depending on the illness, condition, and severity.

Prefrontal involvement in the working of CBT interventions has been shown via functional neuroimaging and cognitive testing. For example, neuroimaging studies have shown improvement and normalization of amygdala-prefrontal activation and connectivity during exposure to sad versus neutral faces, when comparing pre- to posttreatment in major depressive disorder. Such task-specific improvements are seen after treatment of posttraumatic stress disorder (Malejko et al. 2017), OCD (Cyr et al. 2020), social anxiety (Whitfield-Gabrieli et al. 2016; Young et al. 2019), and addiction disorders (Yip et al. 2019). Collectively, these studies provide evidence that CBT improves prefrontal neural circuit function along with symptoms.

Other psychotherapeutic approaches have been developed and tested with similar positive efficacy to CBT in the treatment of neuropsychiatric disorders and health symptoms. Examples include mindfulness training based on mindfulness-based stress reduction, acceptance and commitment therapy (Hayes 2019), prolonged exposure (Foa and McLean 2016), and cognitive processing therapy. These approaches maintain the principle of focusing on the present symptoms and context and typically use sensory, emotion, interoceptive, and behavioral stimulation with the reexperiencing of subjective states so as to promote adaptive functioning. From a neural circuit perspective, they may be seen as bottom-up approaches configured to revisit the symptoms and context in different ways to promote new, more adaptive learning and functioning. When

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

combined with MRI, they suggest that ACC changes in response to fear images but to date, the neural evidence is less developed than for standard CBT.

There is increased activation of ventromedial and anterior pregenual cortex in OCD and depression, which is diminished following successful pharmacologic or behavioral treatment. These findings, as well as previous stereotactic neurosurgical interventions, support the use of ventral anterior limb of the internal capsule (vALIC) and subgenual targets to treat refractory OCD and depression, respectively. In spite of the relatively large size of the cingulotomy and ventral capsulotomy lesions as well as wide electrical fields affected by DBS in the capsule and subgenual regions, few neuropsychological deficits have been reported. This reflects the highly distributed nature of PFC and its functional resilience to focal injury. In OCD and depression, lesions and DBS target ventromedial OFC and ACC hyperactivity and the longitudinal white matter pathways that connect these top-down cortical control regions with thalamic, subthalamic, and brainstem structures as well as the reciprocal connections to PFC. Ongoing studies are in progress to identify the fiber tracks that are most predictive of a positive treatment outcome. These refinements in individual lesion targeting are facilitated by improvements in the resolution of diffusion imaging and the ability to image patients safely with implanted DBS devices. There appear to be few major adverse neuropsychological effects on prefrontal function from modern lesion or DBS procedures. Careful assessment is needed, however, of real-life tasks, particularly in the social and planning realms, as deficits in these areas may be overlooked by traditional methods of assessment.

Cognitive interventions can also be focused (for detailed discussion, see Jaeggi et al., this volume). Typically, they are designed to target a specific process (e.g., working memory, inhibitory control) with the idea that training such tasks or processes strengthens the underlying circuitry or systems. In ADHD, where targeted (computerized/app-based) executive function training is often implemented (mostly to supplement pharmacological treatments), training-specific executive function tasks aim to improve not only those trained cognitive domains, but ultimately to have a broader impact on domains that rely on the integrity of those cognitive functions (e.g., ADHD symptoms, well-being, self-efficacy, scholastic achievement), thus benefitting the quality of everyday life.

Despite growing popularity, not all individuals benefit from these approaches and often, the benefits are more proximal (restricted to the trained domain). The heterogeneity of outcomes likely reflects individual differences in cognitive strengths and needs, the heterogeneity of symptoms (Nigg et al. 2020) as well as the heterogeneity of approaches (Pergher et al. 2020a, b). As such, we need to increase understanding of the underlying mechanisms of an intervention (i.e., mechanisms of action) and individual differences in patients/participants to stratify treatment and improve efficacy (personalized medicine). A growing literature focused on improving understanding of individual

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

differences, mediators, and moderators can inform efforts to determine training efficacy at the cognitive level, thus illustrating how baseline cognitive ability as well as training engagement and improvement are powerful predictors for training benefits and treatment response (Karbach et al. 2015, 2017). Other work has focused on biomarkers, such as brain modularity (Gallen and D'Esposito 2019), which might reflect the brain's "readiness to learn," as an example of the potential for the development of personalized approaches.

A key issue is the motivational readiness to engage in treatment, which itself is a function associated with PFC. Here, combined interventions that include a focus/supplement on motivation and participant buy-in could be particularly powerful (e.g., Jaeggi et al. 2023), as could those that include pharmacological components to get participants to a level where they are ready to engage (e.g., with exposure therapy, CBT) and work synergistically. Such combined approaches may results in broad impacts (due to multiple targets) and more sustained effects, since individuals have the chance to capitalize on what is learned and continue to "practice" in various environments/circumstances, which would promote long-term learning or the process of "learning to learn" (Beck 2011).

Focal Lesions and Stimulation

The therapeutic response to focal lesions may not be immediate: for OCD, it can take 6–12 months to fully respond to DBS or lesions of the vALIC (Rasmussen et al. 2018). Qualitatively, individuals experience a gradual lessening of the anxiety associated with obsessions and the corresponding urge to complete compulsions (Barrios-Anderson et al. 2022). This is accompanied by a recognition that the extensive effort needed to undertake a compulsion may not be worth it. This sets in motion a process that enables individuals to approach stimuli and contexts, which they previously avoided at all costs, and to engage in exposure-based treatments (see Rasmussen, this volume). This learning process, however, takes time.

There is converging evidence that the addition of exposure-based CBT to pharmacologic or neuromodulatory interventions in OCD and other anxiety/depressive disorders leads to the improved outcomes (Franklin et al. 2011; Strawn et al. 2022). As for capsulotomy, the benefit of combination may take several months to emerge and be influenced by baseline clinical severity. One reason for the therapeutic delay is that these interventions lead to a greater willingness to approach feared stimuli or contexts; still, they cannot replace the action-outcome effect of being exposed to the feared consequence followed by not experiencing the feared consequence. In other words, pharmacologic and neuromodulatory interventions may enable learning to take place, and it is the effect of learning that reduces symptoms. Again, this learning process takes time.

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

A focal treatment alternative to neurosurgical lesions is high-intensity ultrasound, which has been FDA approved for the treatment of essential tremor (Martinez-Fernandez and Pineda-Pardo 2020). It has also been tested in the vALIC as the target for OCD with promising preliminary results on clinical OCD benefit without major cognitive side effects (Davidson et al. 2020a). Focality of the target has been limited by attenuation and dispersion of the beam through the skull, making the total energy delivered to the target and therefore the size of the lesion variable (Davidson et al. 2020b). Technical limitations in targeting and regulatory concerns, however, present significant challenges for blinded treatment trials for neuropsychiatric conditions.

TMS modulates neurons in a relatively focal, superficial area of cortex by delivering potent, high-frequency magnetic field pulses that elicit electric field fluctuations and depolarize neurons at the target site. TMS is already used to treat a variety of neuropsychiatric conditions, such as depression, OCD, addiction, and chronic pain (Zhao et al. 2023). Understanding of its therapeutic mechanisms has evolved rapidly over the past two decades, particularly from work in depression, and provides insights in three main areas. The first concerns the success of cross-species modeling. Early TMS treatment protocols emerged from insights derived from patients with left dorsolateral prefrontal strokes and analogous studies in marmosets. For example, left dlPFC inactivation increases anxiety, which may be due to interhemispheric imbalance, that can be mitigated by TMS (Lefaucheur et al. 2014).

Second, TMS has confirmed the hypothesis that depression is a network disorder. Functional connectivity between subgenual cingulate and a dlPFC target site modulates the TMS response and connectivity, such that therapeutic effects are driven in part by effects on downstream targets. Although connectivity in a single circuit account for only a small percentage of variance, the combination of prefrontal circuits mediates additive benefits (Elbau et al. 2023). These effects of TMS accord with lesion mapping studies to suggest that network-level functional connectivity patterns are important to predict depression after stroke, as well as to identify TMS targets (Hollunder et al. 2022; Siddiqi and Fox 2023). It is not fully understood how TMS engages downstream areas that are remote from the local prefrontal target, and animal models together with concurrent TMS/fMRI/EEG studies are required to selectively manipulate neuronal responses and determine causal mechanisms.

Third, TMS studies highlight the individual variation in response to treatment, which may be explained, and predicted, in terms of network connectivity. For example, functional mapping has revealed robust and reproducible individual differences in the topology of functional networks in the human PFC (Fox et al. 2012; Gratton et al. 2014; Siddiqi et al. 2020). Personalized approaches can be attempted that allow investigators to determine the optimal TMS target site and coil orientation to engage selectively a specific network while avoiding others (Lynch et al. 2022).

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

Further studies are needed to develop accelerated protocols and enhance responses with optimal dosage. This is likely to require large clinical studies using systematic approaches to target stimuli and readouts so as to optimize and individualize treatments over a high-dimensional parameter space. The degree to which TMS "rescues" or "compensates" for biological and behavioral deficits remains unresolved, both at the physiological and process level. The functional connectivity features that predict treatment response may not be abnormal; rather, variance of intact functional connectivity of the TMS site may determine the capacity to engage downstream targets and to manipulate systems that mediate one cognitive domain (e.g., primary sensory motor representations of pain) in order to improve another (e.g., depression).

Pharmacological Approaches

Drug interventions in humans are macroscopically diffuse, even though they are pharmacologically specific and thereby microscopically restricted to specific cell types and, in some cases, highly restricted receptor distributions. Experimental studies in animals shed light on the underlying mechanisms of drug treatment, focused on the basic molecular, cellular, network, and behavioral analysis of chemical systems in the PFC on which pharmaceutical treatments, such as guanfacine and ketamine, act (Robbins and Arnsten 2009). This not only indicates the likely targets of current treatments but also potential novel targets for treatment. In addition, fundamental neuroanatomical studies have provided insight into the neural pathways likely to be affected by DBS or ablative lesions, used for treating disorders such as depression or OCD (Rasmussen and Eisen 1997; Rasmussen and Goodman 2022). Moreover, DBS or tract lesions in animals can provide further insight into the underlying functional networks that are engaged. Other animal studies have used stressors (in development or adulthood) to elicit symptom-relevant behaviors (e.g., anhedonia or anxiety) and reveal the physiological and behavioral mediators of pharmacological treatments, such as serotonin reuptake inhibition or ketamine (Roberts and Liston, this volume). A recurrent theme of these animal-pharmacology studies is the prefrontal plasticity that follows treatment.

Evolutionary Expansion of mGluR3-NAAG-GCPII Signaling

Based on decades of research in rhesus macaque dlPFC, the prevailing notion is that intracellular calcium–cAMP–PKA–K^+ mechanisms must be tightly regulated to maintain network connectivity and cognitive function (Arnsten 2009; Arnsten et al. 2021, 2022). Their biochemical feedforward nature can otherwise rapidly generate elevated levels of cytosolic calcium and cAMP, with deleterious effects. Specifically, the receptors that inhibit cAMP production via $G_{i/o}$ signaling (e.g., mGluR3 and noradrenergic α2A-AR) are localized on dendritic spines in layer III of dlPFC, and both enhance delay cell firing

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

and working memory performance via inhibition of cAMP–PKA–K^+ channel signaling. Genetic predispositions in *GRM3*, which encodes metabotropic glutamate receptor type 3, are associated with elevated risk of schizophrenia based on genome-wide association studies. The mGluR3 receptors are selectively activated by NAAG, which is a highly prevalent neurotransmitter co-released with glutamate. NAAG is catabolized by glutamate carboxypeptidase II (GCPII). The mGluR3s are also localized on astrocytes, where they augment glutamate uptake through excitatory amino acid transporters (Neale et al. 2011). Based on experiments in rodents, mGluR3s reside on presynaptic terminals and reduce glutamate release, playing key a role in neuronal microcircuits. They have traditionally been seen as providing negative feedback on glutamate signaling and protective against excitotoxicity (Cao et al. 2016). Recent studies, however, support the hypothesis that their action in pyramidal neurons has changed and expanded with cortical evolution across phylogeny. In rhesus monkey dlPFC, for example, mGluR3 and GCPII have an evolutionarily novel role in higher cortical circuits: strengthening the connectivity of layer III dlPFC circuits that mediates working memory (Jin et al. 2018; Yang et al. 2022). This may partially explain their genetic predilections to human cognition and cognitive disorders.

Ultrastructural studies using immunoelectron microscopy of the rhesus monkey layer III dlPFC show that mGluR3s are concentrated postsynaptically on dendritic spines, which is strikingly different from their classic location on presynaptic terminals in rodent circuits. The mGluR3s are also localized on astrocytes in primate dlPFC, but the presynaptic receptors on glutamate axon terminals are exclusively mGluR2 rather than mGluR3 (Jin et al. 2017, 2018). Relevant to therapeutics is the finding that NAAG-mGluR3 signaling in primate dlPFC can enhance neuronal firing related to working memory by attenuating cAMP–PKA–K^+ channel signaling (Arnsten 2015; Arnsten et al. 2021; Birnbaum et al. 2004; Gamo et al. 2015). Therefore, NAAG–mGluR3 signaling strengthens the connectivity of higher cortical glutamatergic circuits and increases dlPFC neuronal firing in primates, opposite to the decrease in glutamate release typically associated with mGluR3 presynaptic actions in rodents. These mechanisms influence prefrontal cortical function and provide a further mechanism for the effect of stress on cognition via exacerbated catecholamine release (Jin et al. 2018; Yang et al. 2022).

Noradrenergic Therapeutic Strategies for PFC-Associated Cognitive Impairment

Studies across many species highlight the critical role for noradrenergic neurotransmission in prefrontal function, and have, for example, resulted in

- the selective norepinephrine (NE) α2A-adrenoceptor (α2A-AR) agonist, guanfacine (Intuniv™),

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

- selective noradrenergic reuptake inhibitor, atomoxetine (Strattera™), and
- the nonselective modulator of noradrenaline and dopamine, methylphenidate (Ritalin™).

These drugs provide a clear example of translational success (Holland et al. 2021; Robbins and Arnsten 2009): based on clinical trials that followed preclinical studies of noradrenergic attentional and inhibitory control in animal models and preclinical human studies, they are approved in many countries to treat ADHD. They are also widely used off-label to treat additional mental disorders that involve impaired functioning of PFC, including stress-related disorders such as substance abuse (Levin et al. 2009), schizotypal cognitive deficits, and traumatic brain injury (NCT00702364; Ripley et al. 2014). Clinical trials in neurodegenerative disorders such as Alzheimer disease and PSP are underway (e.g., NCT03116126, ISRCTN99462035). At the level of neuronal microcircuits, pioneering work has revealed that guanfacine acts within the PFC via postsynaptic α2A-AR on dendritic spines to inhibit cAMP–PKA–K^+ channel signaling, thus consolidating network connectivity, improving prefrontal cortical neuronal firing, and enhancing prefrontal cognitive functions (Hains et al. 2015). Although guanfacine's beneficial effects on attentional and inhibitory control are present in rodents, they are especially evident in primates where the PFC greatly differentiates and elaborates during evolution. Therefore, NE α2A-AR-mediated actions by guanfacine or atomoxetine can fine-tune top-down control by prefrontal networks, which may explain their therapeutic efficacy in a variety of mental disorders (Arnsten 2020; Hains et al. 2015). It is interesting to note that the use of the drugs in this context is to improve symptoms and function, not to resolve the root mechanisms underlying risk or vulnerability to illness. The normalization of function does not necessitate normalization of the underlying neurobiology. This distinction is relevant to drug and nondrug interventions, whether the intention may be curative (e.g., phobias) or ameliorative (e.g., OCD severity).

An important caveat for pharmacological strategies to target prefrontal networks is drug dosage. For example, both NE α1-AR and DA D1R have a nonlinear inverted-U dose-response effect on dlPFC persistent firing and working memory function. Mediated by activation of calcium–cAMP signaling in dendritic spines, moderate levels are essential; excessive levels significantly reduce firing and cognition by opening nearby K^+ channels (Datta and Arnsten 2019; Datta et al. 2019; Jin et al. 2018; Wang et al. 2019). Optimal levels of stimulation may strengthen persistent firing by magnifying calcium near the postsynaptic density and/or by phosphorylation of NMDA receptors to amplify their synaptic actions (Li et al. 2010b; Skeberdis et al. 2006). Paradoxically, higher levels of stimulation as a result of uncontrollable stress or medication reduces neuronal firing and impairs working memory by opening HCN and KCNQ channels (Birnbaum et al. 2004). Excessive levels of catecholamines

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

strengthen more primitive circuits, such as the amygdala (Ferry et al. 1999), switching control of behavior to more unconscious habitual and instinctive responses. With chronic stress exposure, sustained weakening of network connections by calcium–cAMP–PKA–K^+ signaling leads to removal of spines and dendrites (Hains et al. 2009; Moda-Sava et al. 2019; Radley et al. 2006), an observation seen in humans (Ansell et al. 2012). Clinical applications of diffuse drug treatments are made more complex by these nonlinear dose dependencies, thus requiring stratified or even individualized dosing decisions for comparable effects. Higher doses may not only fail to confer added benefit, they may be counterproductive. The nonlinear dose-response relationships and baseline dependency of effects may explain a proportion of apparent non-responders.

Summary and Future Considerations

Combination treatments are often used in practice, by either combining a drug with a behavioral therapy or through the use of two or more drugs. A systematic approach to combinatorial therapies is required in preclinical and clinical studies, but it has proven challenging to implement in practice. From a theoretical perspective, drug combinations might be rational: one drug may open a patient's receptiveness to another treatment or amplify efficacy. However, clinical polypharmacy is often not a combinatorial science. It is highly complex in view of the multiplicity of neurotransmission and deficits in the PFC.

Looking ahead, we see four areas for research focus in therapeutics. First, rigorous placebo-controlled studies are essential, whether in clinical trials of humans or animal studies. This requires animal models of the pathophysiological processes of the disorder as well as the candidate intervention.

Second, the systematicity of pharmacological interventions, and their combinations, needs to be linked to systematic phenotyping of patients with heterogeneous syndromes. Only this type of systematic, inclusive approach to disorders will resolve the dimensional complexity of neuropsychiatric illness. Within such systematic phenotyping, sex differences should be a factor of special interest, not merely a confound.

Third, there is a pressing need for targeting or precision medicine, based on models that predict response to a given treatment. These models might include genetic, phenotypic, neurochemistry, activity, or connectivity imaging data, or even the response to a test dose. Computational psychiatry approaches (see Koechlin and Wang, this volume) are attractive foundations for such predictive models, although simpler modality-specific data may be sufficient to predict, for example, remission from depression in response to diverse treatment approaches, according to PET or MRI measurements of overactivity in area 25 (McGrath et al. 2014).

Finally, to improve the understanding of underlying biological mechanisms disease, heuristically predictive models should be compared with biophysical or neurocognitive informed models. This necessitates a cross-disciplinary

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

approach to research, unfettered by historical professional boundaries or historical boundaries between funding bodies and healthcare services. Precision medicine in the future should aspire to be informed by mechanisms of disease, adapted to developmental stages, and attentive to individual differences, including their "windows of opportunity" for maximal therapeutic efficacy.

Focal lesions and pharmacological treatments provide complementary and additive clinical benefit for a range of neuropsychiatric syndromes. By targeting specific neurochemical mechanisms and prefrontal networks, they can influence the core cognitive processes underlying multiple symptoms. As shown in Figure 16.1, this leads to potential clinical benefits in multiple diagnostic groups, while remaining subject to individual differences in severity, demographics, and comorbidity. Looking ahead, a systematic approach is required to guide therapeutic combinations and participant phenotypic variation, and enable accurate prediction models as a foundation for precision medicine.

Prefrontal Cortex and Society

How can insights about PFC function and its contribution to mental health be harnessed for the benefit of our global society? Mental health, climate change, conflict, and communication: these are all areas of intersection between the neuroscience of PFC and society.

Executive functions of the PFC may provide a highly effective, sensitive singular marker of brain health—a sort of "canary in the coal mine" for societal brain health. Basic markers of executive function could identify people at risk of diverse mental health disorders, akin to the century-old height and weight growth charts for children, or blood-pressure and cholesterol surveillance in mid-life. Growth charts and developmental milestones are sensitive to myriad risks, diseases, nutrition, and stress and provide early warnings for investigation and treatment. Many psychiatric conditions involve PFC dysfunction, with deficits acting as a powerful early warning system (e.g., Diamond 2013). Since major psychopathology emerges during adolescence (Paus et al. 2008), monitoring PFC development may provide a strong risk marker for atypical development and pathways toward psychopathology. To determine the integrity of PFC function at a large (societal) scale, executive functions that require just a few minutes to complete (e.g., on mobile devices) could provide an initial screening, for example, of motor skills, vision and hearing, and social skills, which are tested at regular intervals in children. Similar approaches, for example by the Brain Health Project at UT Dallas,[2] are being evaluated at scale in adults. If screenings indicate impaired maturation against a "cognitive growth chart" of normative development, additional assessments may be warranted. Further psychological measures and interviews may then be targeted

[2] https://centerforbrainhealth.org/project

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

to identify problems and, if appropriate, lead to interventions to improve resilience and decrease the risk for adverse developmental trajectories. Increasing resilience as well as an individual's chance for successful school outcomes would be a major step forward in tackling the disastrous effects of socioeconomic inequality on individual developmental opportunities.

Such neurocognitive screening needs to be accompanied by appropriate and personalized interventions that are accessible to individuals and communities (e.g., leveraging school and family support). To realize this at scale, a new range of education technologies may be required (e.g., the "EF+Math" program[3]) as will novel ways to engage and prioritize traditionally underserved populations. Education technology offers a powerful means to improve the accessibility of assessments and interventions, yet have historically been preferentially accessible to high socioeconomic groups that are disproportionately white and geographically uneven. Examples for interventions that might be implemented at scale include web-based CBT and app-based computerized intervention "games" that can be played on low-cost devices (Iyadurai et al. 2018). Preliminary evidence indicates that remote interventions and assessments can work as well as in-person interventions, and they have the potential to be more cost-effective and accessible.

The challenge is to make them also equitable and purposefully designed by being sensitive to and taking into account of the relevant cultural background of the target population. This benefits from a co-design approach, as implemented in the "EF+Math" program mentioned above: a focus on strengths rather than deficits, while capitalizing on patient resources to maximize participant buy-in and agency (Fluckiger et al. 2023). Lessons need to be learned from historical misuse and divisiveness related to IQ testing, systemic disadvantages, and loss of trust arising from a failure of cultural embedding of assessments. Better cultural embedding is one means of linking neuroscience advances to global challenges.

Climate change and massive population displacements from war and famine represent major global challenges. They are a cause of chronic stress for many individuals, with enduring consequences for neuropsychiatric health. They also represent a collective failure of control, restraint, forward planning, and value-based decision making (cf. functions of our prefrontal cortex). For decades, we have failed to adjust our decisions and actions in in the service of global goals, despite the existence of abundant knowledge about the potential risks of global warming. Immediate adjustments ranging from individual actions to political regulatory measures may seem obvious, yet the majority of the world's population has problems overcoming long-established patterns of behavior. Lack of behavioral regulation continues to happen across levels: from individual consumer behaviors to large-scale commercial organizations to governmental policy. Beyond an analogy with the functions of PFC:

[3] https://aerdf.org/programs/ef-math

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

- How can understanding the brain basis of decision making contribute to resolving obstacles to behavioral change?
- To what extent is it valid to map decision making across levels (i.e., from individual consumer decisions to organizations and policy), with geographically and temporally distant consequences?
- Can we improve current behaviors based on an understanding of long-term goals of future generations, making them more motivationally relevant for current decisions and actions?

Such broad-scale questions go beyond the traditional scope of neuroscience, but cognitive neuroscience can contribute to an interdisciplinary research agenda that promotes adaptive and anticipatory behavior at large scales, in response to global challenges (Aron et al. 2020; Castiglione et al. 2022).

To study and engage population-based approaches to health and mental health, the language of neuroscience may need to change. Words matter as we consider communicating about the role of frontal cortex and prefrontal processes in neuropsychiatric and other brain disorders. Mental health disorders are already associated with stigma (Rose et al. 2007). Do we help or hinder patients when the terminology of our research framework is based on phrases that have strong negative connotations, such as "cognitive control," "suppression," or "management"? Such phrases can alienate the public and get in the way of a research-based approach to illness and health conditions by reducing engagement in prevention and treatment strategies (Bailey 1999; Burns and Rapee 2006; Volger et al. 2012; Young et al. 2008). It should be possible to use terminology acceptable to individuals from diverse backgrounds, races, ethnicity, and cultures. Identifying people as patients, defined by their illness, is often perceived as pejorative, stigmatizing, or less desirable. It may push individuals away from engaging with information about the illness, their associated underlying mechanisms and participation in treatment and prevention efforts (Volkow et al. 2021). For example, there is broad-based consensus across diseases and medical conditions for the use of *first person* language when describing individuals with an illness: *persons with depression* or *individuals with obesity* are preferred and not "depressed patients" or "obese people" across clinical, scientific, or public health contexts (Volkow et al. 2021). Furthermore, words such as "mental" or "mental health" may convey emotionality and mental weakness; "suppression," "control," and "management" may convey messages of colonial or social dominance. Alternative term such as "self-regulation," "stress," or "resilience" are regarded more favorably and may denote higher acceptability in conveying concepts PFC function to a wider audience.

Together, these issues of education, resilience, global policy and inclusive language are important to advance global health and economic well-being. They speak to social determinants of brain health, and therefore public policies to improve brain health. They speak to ways to reduce illnesses associated with

From "The Frontal Cortex: Organization, Networks, and Function," edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530

prefrontal function, reducing trauma, stress, and developmental risk. They also speak to active steps that can be taken through education and health services to prevent, detect, and treat disorders associated with prefrontal cortical function.

Conclusion

In this chapter, we began with consideration of the complexity of the PFC, and the many levels at which its function and disorders can be analyzed. We proposed a way through this complexity that involves (a) multiple explanatory levels with divergence and convergence between syndrome, symptom, process, and biological mechanisms, and (b) spatial and temporal gradients across the PFC. Together, the levels and gradients provide an explanatory framework that links animal and human studies in such a way as to inform therapeutic strategies.

The recent evolutionary expansion of the PFC in humans and nonhuman primates has been subject to natural selection for a relatively short time period, from an evolutionary perspective. This expansion of neocortical regions and their subcortical connections has clearly led to selective advantages but may also have created vulnerability to mental health disorders. Converging evidence implicates PFC circuitry and its connections in many neuropsychiatric conditions. Basic cognitive functions such as working memory, decision making, selective attention, and executive control depend on the same prefrontal regions and associated circuits that are abnormal in psychiatric and neurological disorders.

Theoretical, laboratory, and clinical neuroscientists can work together to understand prefrontal function and its deficits. New models of computational psychiatry (Wang and Krystal 2014) as well as advances in experimental tools and big data will further help establish a solid biological foundation for the diagnosis and treatment of diseases of PFC. To realize the full potential of this endeavor requires highly cross-disciplinary collaborative and translational research, with improved career pathways, regulatory recognition, and training. With this success, insights about prefrontal cortical function can be harnessed for the benefit of our global society, with equity of access to evidence-based health and education.

From “The Frontal Cortex: Organization, Networks, and Function,” edited by Marie T. Banich, Suzanne N. Haber, and Trevor W. Robbins. 2024. Strüngmann Forum Reports, vol. 34, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 9780262549530