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Introduction

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It is generally acknowledged that understanding the human brain would represent a pinnacle of scientific achievement. A major part of that goal is to identify the causal relationships between neural mechanisms and behavior and cognition, the ultimate functions of the brain. Key to this crucial issue in mammalian cognition are the functions of the frontal lobes. These lobes, which are most expanded in humans as compared to other species, include the prefrontal cortex (PFC) and associated structures, such as anterior cingulate cortex (ACC), and are known to play a key role in higher-order thinking, executive function, and cognitive control, processes by which an organism can effortfully guide adaptive behavior.

Like most of the cerebral cortex, there is evidence of quite extensive specialization within frontal brain regions. The PFC is typically divided into subregions that mediate these functions (Friedman and Robbins 2022; Haber and Behrens 2014; Monosov and Rushworth 2022; Rudebeck and Izquierdo 2022). The orbitofrontal cortex (OFC) is involved in value encoding (revaluation and devaluation) of reward-related sensory input and outcomes. The caudal OFC and ventrolateral (vl) PFC have been implicated in a number of functions, including credit assignment (determining the previous events that resulted in a specific outcome) and behavioral flexibility. The dorsolateral (dl) PFC is in a central position to mediate cognitive control, working memory and higher-order thinking. Finally, frontopolar regions are linked to dlPFC and vlPFC regions and allow for meta-cognitive abilities. As such, there is a matrix of subregions and their interactions that characterize PFC organization.

Clearly these regions, which mediate goals, values, choices, and actions, interface extensively to develop appropriate adaptive behavior. Yet how the interactions between these complex frontal regions result in behavioral choice is less well understood, as research has become “siloed” with researchers focusing on a particular portion of frontal cortex. For example, several functions have been attributed to the ACC with theories ranging from

- conflict detection (Botvinick et al. 2004),
- interfacing between motivation, action, and effort (Rushworth 2008),
- detecting whether an action led to the expected outcome (Alexander and Brown 2011), and

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- late-stage selection, often motor response-related (Banich 2009).

However, since ACC is a rather large frontal subregion with complex connections, it is unlikely to have a single function (Tang et al. 2019). Likewise, computational models of PFC function often focus on a specific region or network and typically do not take into account interactions between and across multiple networks. Moreover, behavioral paradigms often fractionate underlying mental operations, each of which is often associated with specific brain regions or circuits.

We now know that a central feature of cognitive function is that behavior results from an intricate interplay between localized processing within specific brain regions and patterns of connectivity across regions (Geschwind 1965; Haber et al. 2022; Mesulam 1998). Networks are characterized by specialized subsystems as well as "hubs," which represent regions for integrating and distributing information from multiple cortical and subcortical regions. The ability for subsystems, hubs, and connectivity to be flexibly reorganized enables the brain to meet a wide variety of cognitive and computational demands.

Yet it remains unclear exactly how such higher-order cognitive processing is achieved by these organizational principles across heterogeneous PFC subregions and their connectivity between each other, as well as to more distant brain regions. Currently, a variety of methods across different levels of analysis, used singly and in conjunction, is starting to provide a framework for understanding this organization. These methods span anatomical approaches, including circuitry studies, to neurophysiological, neuroimaging and neurochemical studies of brain morphology and functional activation. To help better address how the complexity of cortical regions interact, computational methods such as Bayesian learning models and graph theory are being utilized to develop network interactive models.

However, the different approaches needed to address these interactions are, to some extent, species-specific (i.e., optogenetics in mice, resting-state MRI in humans, invasive electrical recordings in nonhuman primates). This leads to major issues when findings from animal models are extrapolated to inform drug discovery programs or identify better treatment targets for human mental disorders. Another major contemporary question is that of development: How does the PFC develop during human childhood and adolescence in relation to the rest of the brain?

This Forum was convened to examine the circuitry, neuronal mechanisms, computations, and potential treatment targets of different PFC areas that mediate key component operations (e.g., social, affective, cognitive, and motor control) and when and how such regions act locally or collectively. To address these goals, the Forum brought together scientists with expertise in different disciplines (ranging from psychology to computational modeling to all the main branches of neuroscience, including neuroimaging, neurophysiology

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and neuropharmacology) who work with different approaches (from animal models to humans and the clinic).

We felt that it was especially beneficial to convene this Forum for several reasons. Research on the frontal lobes is an active area of research across various fields, yet interdisciplinary interactions have been minimal as there has been no major meeting on the frontal lobes since the five-day Baycrest-Rotman/Berkeley conference held in 2010 (Stuss and Knight 2012), which followed on from an earlier meeting in 2002 (Stuss and Knight 2002). Despite the enormous conceptual and technical advances that have been made over the last decade, no further meetings were planned in that series. Smaller symposia or meetings have focused on restricted issues (e.g., the OFC, dlPFC, cortico-striatal systems, rodent prefrontal function) or some of the processes implemented by frontal regions, such as cognitive control (e.g., the Control Processes meeting held at Brown University in 2019). None, however, has addressed specifically how the organization of the frontal lobe enables such processing nor attempted an integrative approach, such as proposed in this volume. Since the Royal Society meeting in the mid-1990s (Roberts et al. 1998), the community has lacked a published discussion among the main leaders of the field. Hence, to realize the important implications of this knowledge for health and disease, effective discussion and collaboration across fields was required and could readily be provided by the Ernst Strüngmann Forum.

Framework for Discussion

The unique aspect of an Ernst Strüngmann Forum lies in its think-tank approach. For a week, experts from around the world interact in a residential setting to scrutinize issues and questions posed in advance by the organizing committee. To initiate this discourse, the committee commissioned papers to introduce key topics. Then, during the week, intense interactions emerged between the invited, multidisciplinary experts, centered around the following themes:

Group 1: Evolutionary Perspectives: Homologies and Analogies

Discussion in the first working group examined key principles that determine homologies and cross-species functional similarities of PFC. Aided by Chapters 2 (A. Izquierdo) and 3 (R. P. Vertes et al.), the group addressed the following questions:

- What are the major regions and circuits observed across species within PFC?
- What are the structural and functional homologies of the PFC across species?

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- How did the PFC evolve and how has this evolution led to produce higher-order cognition, including social and moral reasoning elements in humans?
- What are the mechanisms by which these major circuits exert control? By patterns of anatomical connectivity, neural synchronization and oscillations, chemical neuromodulation, excitatory/ inhibitory balance, plasticity and long-term potentiation, or other mechanisms specific to the prefrontal cortex?
- How can the functions of micro-circuit approaches defined by optogenetics and multiple unit electrophysiology be linked to macro-circuits as revealed by human imaging modalities?

The resulting discussion was informed by experts from behavioral neuroscience, cognitive neuroscience, cross-species comparisons, evolutionary neuroscience, neuroanatomy, neurophysiology, neuropsychology, neuropsychopharmacology, and systems neuroscience: Bernard Balleine, Michael Halassa, Alicia Izquierdo, Nicola Palomero-Gallagher, Trevor W. Robbins (moderator), Peter Rudebeck, Jeroen Smaers, and Kevin S. Weiner (rapporteur). Together, they worked toward generating a consensus statement regarding the ambitious goal of determining the homologies of PFC, as well as functional similarities across species, providing evolutionary, cognitive, and translational insights (see Chapter 4 by K. S. Weiner et al.).

Group 2: Functional Fractionation and Integration: Physiology, Networks, and Behaviors

The second working group focused on the functions of subregions of the PFC, their associated circuitry, and interactions. Three papers were commissioned—Chapter 5 (E. Rich and B. Averbeck), Chapter 6 (J. D. Murray and C. Constantinidis), and Chapter 7 (D. Badre)—to initiate the debate, which addressed the following issues:

- To what degree is the PFC composed of discrete functional regions, and if so to what degree do they overlap?
- How can interactions between PFC regions best be understood (e.g., are there specific hubs that coordinate PFC function)?
- Is the organization of these functional regions hierarchical or can it be conceptualized in some other organizational mode?
- To what degree do subcircuits within the PFC converge map onto non-frontal regions?
- How are PFC circuits modified by genetic expression and environmental input?

Input from behavioral, cognitive and systems neuroscience, including neuroimaging, neurophysiology and neuropsychopharmacology, informed the debate

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between Bruno B. Averbeck, David Badre, Christos Constantinidis, Roshan Cools, Clayton E. Curtis, Mark D'Esposito (Moderator), Lesley K. Fellows, Anna S. Mitchell, Elisabeth A. Murray (Rapporteur), John D. Murray, and Erin L. Rich. Together, they considered evidence for functional fractionation of the frontal lobes, discussed whether the organization of the frontal lobes should be conceptualized in terms of functional and anatomical gradients, instead of discrete areas with well-delineated boundaries. Their report also highlights critical gaps in knowledge for future research (see Chapter 8 by E. A. Murray et al.).

Group 3: Integrative Psychological, Computational, and Mechanistic Approaches to Frontal Lobe Function

In this working group, experts considered whether the frontal lobes have a unitary function that works across multiple demands or has a set of more diverse functions, and the computational bases of such PFC function(s). Aided by three papers—Chapter 9 (J. Duncan and N. P. Friedman), Chapter 10 (X.-J. Wang and E. Koechlin), and Chapter 11 (C. Gratton et al.)—group discussions centered around the following questions:

- To what extent is there unitary versus diversity of fronto-executive functions?
- Are concepts of cognitive or executive control outmoded? Should there be a new taxonomy?
- How can computational approaches enhance our understanding of the concept of cognitive control or executive function?
- How can such computational approaches be linked to PFC function?
- How best can information about PFC anatomy, function, connectivity, and computational modeling of behavior be combined to produce new insights into how the PFC enables higher-level cognition?

Informing the debate were experts from cognitive and computational neuroscience, as well as functional neuroimaging and neurophysiology: Marie T. Banich, Christian Beste, Timothy J. Buschman, Naomi P. Friedman, Caterina Gratton, Etienne Koechlin, John O'Doherty (Moderator), Nicolas Schuck, Amitai Shenhav (Rapporteur) and Xiao-Jing Wang. In their report (Chapter 12), Shenhav et al. propose a new neurocomputational modeling framework for conceptualizing PFC function and discuss critical directions needed to validate or falsify this account. They also considered whether neurocomputations are processed at a lower (cellular) level or emerge from network organization.

Group 4: How Can Understanding of the PFC Be Translated to the Bedside and Society?

In the fourth working group, participants considered important clinical, translational, and societal issues that arise from our understanding of the PFC and

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its networks. Informed by three background papers—Chapter 13 (A. Roberts and C. Liston), 14 (S. M. Jaeggi et al.) and 15 (S. A. Rasmussen)—the group explored the following questions:

- How can an understanding of the functional anatomy of the PFC inform our understanding of psychiatric and neurological disorders, including comorbidities?
- How can animal models involving PFC function be enhanced to address salient clinical issues?
- What are the surgical, pharmaceutical, or cognitive-behavioral interventions that can produce improvements in cognitive control and executive function?
- What are the mechanisms by which such interventions are likely to act?
- What general principles can we learn about the functions of the PFC that have broader societal implications (e.g., philosophy of volition).

Experts in the group included behavioral, cognitive and systems neuroscientists, as well as clinician-scientists (neurologists, psychiatrists and psychologists): Dibyadeep Datta, Christian J. Fiebach, Suzanne N. Haber (Moderator), Susanne M. Jaeggi, Conor Liston, Beatriz Luna, Steven A. Rasmussen, Angela C. Roberts, James B. Rowe (Rapporteur), and Rajita Sinha. Given the lack of one-to-one mappings between clinical syndromes, their underlying pathophysiology, and root neurobiological causes, Rowe et al. (Chapter 16) propose a multilevel framework in which syndromes can be linked to symptom profiles, symptoms to cognitive processes, and cognitive processes to neurochemical, neurophysiological, and computational processes embedded in PFC and its associated networks. They also consider prefrontal disorders in the context of global opportunities for education, health, and social policy.

Moving Forward

The issues presented in this volume have enormous societal implications. Understanding PFC function is highly relevant to many neurological and psychiatric diseases and disorders, including anxiety, obsessive-compulsive disorder, posttraumatic stress disorder, depression, frontal lobe dementia, schizophrenia, addiction, and autism. Virtually all neuropsychiatric disorders involve malfunctioning of PFC circuits as core impairments, yet currently we do not know whether general fronto-executive impairments contribute to these clinical phenotypes or whether each have a distinct "signature." This distinction has implications for treatments based on circuits or neuromodulation. How nature has solved the problems posed by executive control may also inspire new approaches to artificial intelligence and business organizations.

The final step of any Ernst Strüngmann Forum involves turning over the ideas that emerged from the debate to others for further consideration. To this

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end, the invited papers and group reports have been reviewed, finalized, and carefully edited to provide an account of where the debate stands. In addition, in Chapter 17, we have attempted to synthesize and draw together the main themes.

We cannot assert that answers to each and every one of our questions were provided definitively with consensus in these discussions. Most certainly, some controversies persist! It is our hope, however, that this volume captures some of the excitement of the interactions we experienced at the Forum, facilitated by the excellent infrastructure provided by Julia Lupp and her team.

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