Prospection and the Integrative Capacities of the Prefrontal Cortex: A contemporary synthesis

The Prefrontal Cortex (Fifth Edition)

By Joaquín Fuster, Academic Press, 2015

The fifth edition of *The Prefrontal Cortex* provides a synthesis of the structure and functions of the brain region for which it is named. Joaquín Fuster's extensive academic history elucidating the brain mechanisms of cognitive functions once again contributes to this insightful overview of the neural underpinnings of prefrontal function, the contributions of the prefrontal cortex to whole brain function, and the methodological advances that allow research in these areas to progress. The magnitude of this undertaking is reflected in the volume of articles concerning the prefrontal cortex. However, the end product highlights the discerning eye that only an expert can bring to not only filter out the most relevant empirical evidence for inclusion but to incorporate this evidence into his overarching theoretical view for the book. As a result, *The Prefrontal Cortex* is accessible both to the casual reader, as well as experts in the fields of neuroscience, psychology, and others.

Through my own endeavors in elucidating the contributions that prefrontal neurobiological mechanisms make to behavior, I have come to appreciate the importance of establishing a solid theoretical foundation for research of this kind. Although it is easy to be captivated by the latest results and cutting-edge research techniques, perspective is critical to incorporating empirical novelty into a meaningful model of the brain and behavior. Fuster provides exactly this perspective by providing a historical purview of the prefrontal cortex that details how the field arrived where it is today. This book also serves as a reminder of the symbiotic relationship between the facts that inform a theory and the theoretical extensions providing the impetus for further research. Indeed, in the same way that the relevance and impact of *The Prefrontal Cortex* draws from contemporary literature, Fuster's overview of the

topic has contributed to advances in prefrontal research. Fuster acknowledges that theories must be flexible, and able to incorporate new facts as well as new interpretations of facts. This is evident by the evolution of the editions of *The Prefrontal Cortex,* motivated early on by prefrontal contributions to motor functioning, later by prefrontal function and dysfunction influencing cognition and behavior, and most recently regarding the prefrontal capacity to organize new goal-directed actions in the time domain. In Fuster's own words, *this cortex opens the brain to the future, giving it the ability both to predict and to invent that future* (p. xiii).

Establishing a basis of prefrontal function

A dominating theme in contemporary neuroscience research is the integrated nature of functionality within individual brain structures, as well as throughout the brain as a whole. Furthermore, empirical support for integrative brain functioning has increased exponentially in recent years. In line with this, Fuster suggests that all prefrontal functions are to some degree interdependent, and furthermore, that the prefrontal cortex performs its executive control of temporal organization by orchestrating activity in other neural structures that participate in executive function. From a neuroanatomical perspective discrete regions can be associated with discrete functions. However, the canonical discrete functions are components of a more global function (e.g. the design and implementation of novel, complex, goal-directed actions). Fuster adeptly incorporates this perspective into in every topic covered in his book; integration can be found from the level of chemical messengers within a single neuron to the complete perception-action circuit of executive function. Furthermore, every methodological innovation seems to provide an additional level of support for this framework of cortical function. Relatedly, I found it very fitting that the book itself manifests as a hierarchical integrated set of ideas. Indeed, component "populations" of empirical data are grouped into discrete sections, but are also emphasized as contributing to the overall impetus of the book. Additionally, many chapters include a similar distribution of introduction, historical background, development and aging, etc.

This structure effectively orients the reader towards the nature of each chapter, as well as how each theme fits into the book as a whole, and thus prefrontal function as a whole.

Early in the book (Chapter 2), Fuster outlines the anatomical connectivity of the prefrontal cortex. The evidence presented in this chapter both maintains and fortifies insight from the fourth edition regarding the hierarchical cooperation of the prefrontal cortex with other brain regions to yield structured behavior, reasoning, and language. Briefly, sensory information processed by widespread cortical areas is passed to the prefrontal cortex where this information is interpreted with regard to the motivational significance of external stimuli. The localized convergence of distinct, multimodal sensory tracts, which are relatively independent of one another until they reach the prefrontal cortex, highlights the integrative, associational, nature of the prefrontal cortex. Importantly, this chapter is of immense relevance to the population of researchers utilizing animal models. I have personally experienced the challenges of determining translational implications from research done with animals. However, Fuster details cortico-cortical connectivity that supports comparable roles in the fundamentally associational character of the prefrontal cortex in a number of species. In particular, connectivity provides an important indicator of homologies between rats, cats, monkeys and humans. Evidence of functional homologies, even in the absence of anatomical homologies, may very well increase as we progress our understanding of the relationship between neurobiology and behavior.

In order to understand the nuances of behavior (in any species) it is often necessary to allot executive function into discrete and measurable components. However, in doing so, it is important not to sacrifice the overlaying coordination of these components. Fuster accomplishes this by taking a hierarchical perspective: that one component of executive function takes precedence at a given time. Relatedly, the dominant function of subregions of the prefrontal cortex can also be inferred in this manner. The six executive functions cited as cardinal for the temporal organization of behavior are planning, attention, working memory, decision making, error monitoring and avoidance, and inhibitory control. Fuster's research regarding "memory

cells," the physiological substrate of working memory, has made seminal contributions to the field. Thus, it is warranted that this topic receives extensive coverage, both as an individual executive function as well as a contributor to goal-directed behavior as a whole. In keeping with the impetus of the book, Fuster assimilates each executive function into a larger model of goal-directed behavior. To this end, working memory is intrinsically linked to attention; in this case attention directed towards an internal representation of a long term memory network that is updated in order to organize actions in the present, or near future. Relatedly, attention is described as the heart of cognitive function, as it is integral to priming sensory and motor neural structures to elicit action. This can contribute to decision making, which results from the computation of several synergistic factors of different weight and requires cooperation between the prefrontal cortex and the rest of the brain. Finally, many executive functions require not only the focus on what is relevant and necessary, but also the inhibition of what is irrelevant and unnecessary. Thus inhibitory control is immensely important for regulating impulses that may impede or derail temporal organization of actions in the pursuit of goals. These examples are among many outlined by Fuster throughout the book to highlight the complex nature of prefrontal function.

In line with the extensive overlap between prefrontal functions, the neural circuits underlying these functions also intersect and interact profusely. In recent decades, Fuster has developed the theory of "cognits", or distributed cognitive networks, each acting as a unit that represents knowledge and memory. A cognit is the result of linking simultaneous stimuli or actions into a stored network by connective associations. These networks can subsequently be retrieved by encounters with environmental or internal events that have been previously associated with them. Fuster posits that synchronous synaptic convergence is critical to cognit formation, similar to Hebbian principles of association formation in perceptual networks of the posterior cortex (Hebb, 1949; Hayek, 1952). Fuster has proposed that all cognitive functions are based on neural transactions within and between these cognits (e.g. Fuster & Bressler, 2012).

As such, the theory that the nature of each cognit is subject to individual variation based on the interactions of an organism with its environment (Edelman, 1987) may explain, at least in part, the wide variety in cognitive tendencies observed between individuals. An additional facet of these cognitive networks is the idea of heterarchy, or interactions between hierarchical layers. Specifically, that networks representing simple percepts or motor acts are nested within more complex networks representing abstract perceptual or executive information. The result is a lack of clear cut separation between cognit content categories, consistent with the lack of discrete functions or anatomical specificities of the prefrontal cortex.

In introducing this systems level structure Fuster is able to provide a reasonable neural framework for the integrative functional capacity of prefrontal cortex emphasized throughout the book. However, an additional integral component must be included to complete the theoretical backdrop against which functions of the prefrontal cortex can be viewed: the “perception-action cycle”. Briefly, the perception-action cycle embodies the circular flow of information processing linking an organism with the environment in the course of goal directed behavior. The pathways of this cycle have no true origin, and instead consist of feed forward and feedback signals between cortical and subcortical structures. For example, processing sensory inputs from the environment generates actions that can contribute to changes in the environment, and these changes can lead to new sensory input. The outcome is both to adapt and pre-adapt the organism to an environment. Fuster states that the prefrontal cortex constitutes the highest stage of neural integration into the parallel and circular pathways of the perception-action cycle. Both the cognitive cycle, which courses through the sensory receptors and associative areas of the neocortex, as well as the emotional cycle which collects information from the internal, visceral, and emotional receptors, converge on the executive cortex. Emotional and cognitive cycles work in parallel and close interaction with each other to guide the organism to its biological and cognitive goals. Importantly, the dynamics of these cycles rely heavily on coordination of the cognits outlined above.

In the past two decades, the network dynamics of Fuster's perception-action cycle have gained substantial neurobiological support from both physiological and neuroimaging studies. For example, during the earliest stages of implementing a behavior, functional imaging methods have shown a cascade of processing downward in the executive hierarchy of the frontal lobe. Widely distributed cognits at the higher hierarchical levels of the perception-action cycle integrate highly complex perceptual experiences and actions. However, at every stage of the temporal organization of behavior executive networks of the prefrontal cortex are linked with subcortical structures and with perceptual networks of posterior cortex. Thus, these abstract cognits give way to activation of networks localized to sensory or motor cortices, in accord with the anticipated perceptual environment and requirement for action. In this way, brain activation patterns reflect the prospective function of the prefrontal cortex and prepare for feedback from the environment to be seamlessly incorporated into the hierarchical representation of a behavior.

Incorporating methodological advances

In order to establish as well as update existing theories, additions must be made as new methodologies and techniques are developed and refined. Throughout the editions of *The Prefrontal Cortex* technological advances have made major contributions to guiding revisions. In particular, the development of electrophysiological and brain-imaging techniques, methods for studying chemical neurotransmission, structural and functional neuroconnectivity, and computational modeling have been integral to the empirical basis of previous editions. In the present edition, Fuster incorporates evidence resulting from refinements in each of these areas.

Much of what has been established regarding the major functions of the prefrontal cortex and the compilation of these functions into an interdependent "executive set" has resulted from brain lesions (both experimentally induced ablation and disease-related damage; Chapters 4 and 5). Damage to the prefrontal cortex often produces groups of symptoms that occur together,

and that differ depending on the location and magnitude of the damage. The characteristic abnormalities that result from damage to a particular region can be used to infer the dominant (but not necessarily exclusive) role of that region in neuropsychological functioning. I found these sections striking as they exemplify how far the field has come, and how far it will still go. Indeed, there are methodologies in current laboratory use that allow for precise and minimally invasive regulation of activity in discrete brain regions, as well as individual neurons. Fuster limits his discussion of reversible lesions to electrical stimulation and hypothermia, but future compilations of prefrontal functioning will no doubt be shaped by insight from increasingly targeted methods of neural manipulation.

In the latter chapters of the book, Fuster discusses how brain activity at a regional (Chapter 7; neuroimaging) as well as cellular (Chapter 6; neurophysiology) level can be used to elucidate the neural dynamics of goal directed behavior. A major benefit of techniques in these categories is that they allow researchers to establish real time correlations between brain activity and observable behaviors. Fuster makes particular note of diffusion tensor imaging (DTI) and near-infrared spectroscopy (NIRS) as these methods for studying anatomical and functional connectivity have burgeoned since the fourth edition. He also points out that an exciting product of research using neuroimaging techniques is that they allow for the extension from studying "executive functions" per-say to complex products of executive functions such as planning and language. Fuster also presents evidence from both single unit and local field potential recordings to reiterate the symbiotic nature of the prefrontal cortex, in this case within anatomically distinct but functionally interdependent neuronal units. A major theme in Chapter 6 is that prefrontal neurons incorporate multisensory information from the environment in order to attribute value to external stimuli. This information is integrated with signals from neighboring neurons involved in motor command, in order to elicit behavior. By way of relevant empirical examples, Fuster reiterates the idea that the kinds of behavior for which the prefrontal cortex is essential require continuous integration of sensory input with action output. As a final note,

Fuster is also very candid in the limitations of these methodologies, including difficulties in establishing an operational definition of what activity in a given brain region or circuit really means with regards to function. Increases in our knowledge of the physiological relations between blood flow, neuron discharge, and energy metabolism should help address this issue.

A final area that has progressed in great part due to methodological advances is the study of prefrontal microcircuitry. The advent of neuroanatomical, immunological and antibody-based assays has been pivotal in establishing the distribution patterns of neurotransmitters (Glutamate, GABA, Norepinephrine, Dopamine, Serotonin, and Acetylcholine) and neuropeptides in the prefrontal cortex as well as their major roles and interactions with one another (the focus of Chapter 3). Again at this level, Fuster presents evidence that indicates the integrative nature of the prefrontal cortex. Indeed, the influence of a transmitter on a given facet of executive function depends on the location of action and abundance of transmitter, the brain structure, and the underlying connectivity of the structure. Furthermore, the co-localization of transmitters or receptors in the same pre- or postsynaptic units indicates numerous interactions between neurotransmitter systems at the root of probably all prefrontal functions. Finally, although neuropeptides are significantly less studied, and their functions are more obscure, they still play important roles in prefrontal and whole brain functioning. Thus, it is worthwhile to note Fuster's inclusion of neuropeptides, as it reflects his foresight that a current dearth of understanding in no way negates the significance that may be established by future research.

Implications for contemporary research

Much of the book focuses on the function of a canonical prefrontal cortex, but Fuster also includes evidence related to development, aging, and prefrontal dysfunction. These topics provide insight into how the brain develops, how brain regions contribute to behavior, and how the former influences the latter. For example, patterns of cognitive and behavioral consequences of damage during development (e.g. attention deficits and learning disabilities)

suggest that different functions develop at different times, and that some functions are more vulnerable than others. Interestingly, although the prefrontal cortex is one of the last regions of the brain to reach maturity, it is one of first regions to deteriorate with senescence. Finally, Fuster focuses on how diseases are more than just one neurotransmitter malfunction or one region. Together, Fuster utilizes these topics to emphasize the circuit/system nature seen with normal prefrontal function.

Fuster concludes the book by discussing the implications of prefrontal function for contemporary topics of relevance. Fuster explains that complex functions such as imagination, creative intelligence, and language are iterations of the same temporal organization of behavior outlined for prefrontal executive functioning. The basis for this comes from the vast combinatorial power of cortical networks, allowing for countless new cognits or representational circuits. In this way, creative intelligence is composed of basic perception, attention, memory, and language functions, restructured and developed into action in the form of innovative use of language, tools, and instruments. Finally, the prefrontal cortex has recently entered debate on issues of free will. These debates utilize the notion of consciousness, or awareness of one's self, that can only be studied in humans using introspective methods and personal inquiry. Much of the debate centers around the notion that consciousness is not localized anywhere in the brain, but rather is a phenomenon of neural activity in several regions of the brain, especially the neocortex.

Concluding remarks

In conclusion, this edition of *The Prefrontal Cortex* reconciles insight from previous editions with a contemporary body of empirical support. The book provides meaningful examples from Fuster's comprehensive and unifying analysis of the existing literature regarding contemporary prefrontal research. The product is a monograph emphasizing the temporal integrative functions of the prefrontal cortex that merge the past with the future of a behavioral

structure. Importantly, the prefrontal cortex is not assumed to be the source of volition and decisions, but rather to enable the perception action cycle, at levels at which novel and complex action is organized. In other words, Fuster establishes the prefrontal cortex as providing the cognitive infrastructure of goal-directed action. Finally, research with the most impact will result from integrating multiple methodologies, as well as remaining open to the possibility of adjusting a theoretical framework. In this way, an integrative perspective is key to science, just as it is key to prefrontal function.

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