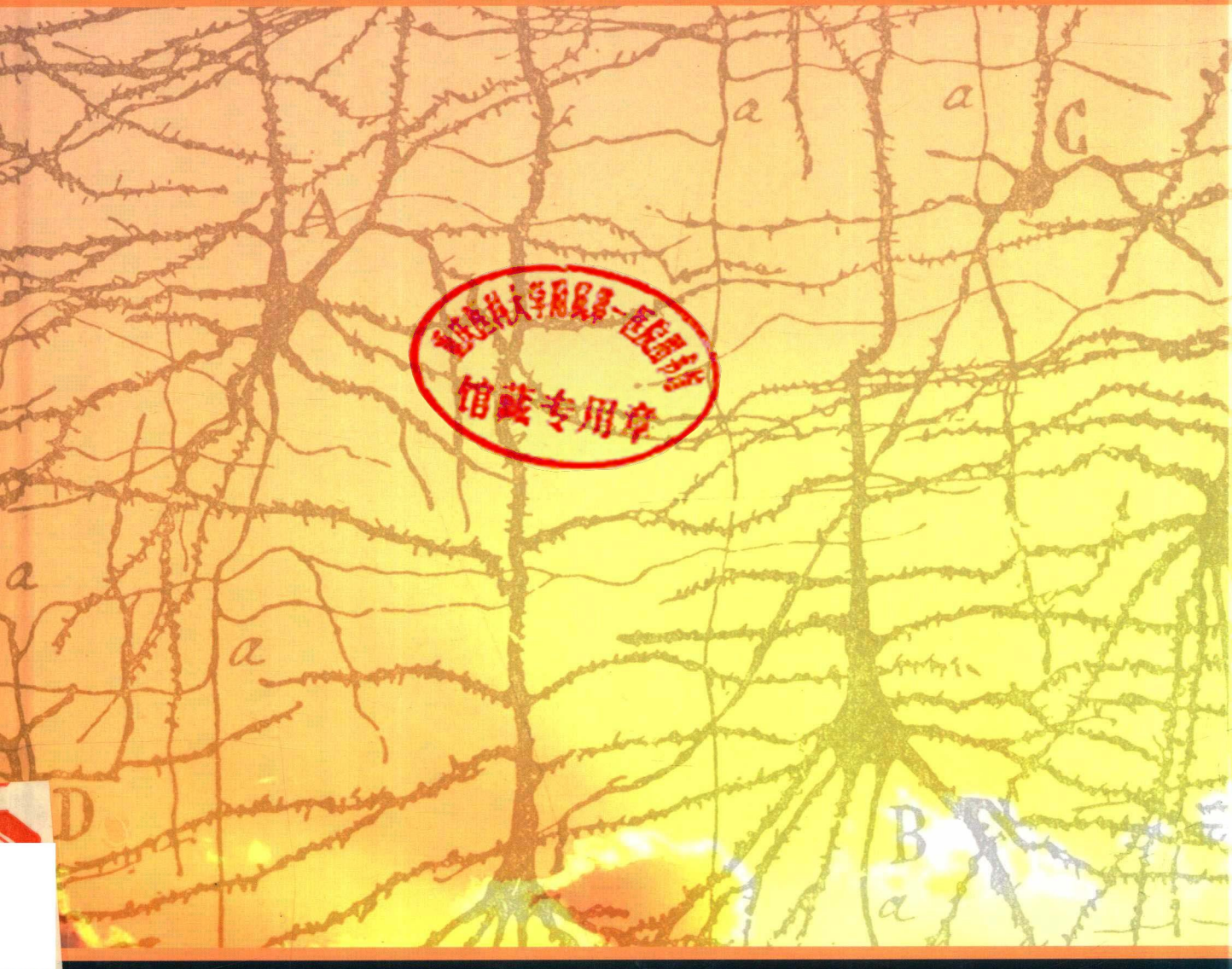
The Prefrontal Cortex

FIFTH EDITION



Joaquín M. Fuster

THE PREFRONTAL CORTEX

FIFTH EDITION

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THE PREFRONTAL CORTEX

"Joaquín Fuster has again done the field an invaluable service by synthesizing current scientific knowledge in the new edition of his classic book, *The Prefrontal Cortex*. Fuster's splendid book has been an essential reference for neuroscientists since its initial publication in 1980, elucidating the organization and function of the brain region that most makes us human. The new 5th edition has been updated with a wealth of new material from neurophysiology and neuroimaging on the executive functions of the prefrontal cortex, synthesized under the notion that the driving function of prefrontal cortex is to coordinate new sequences of purposeful action. It is a masterful accomplishment."
William Newsome, Director, Stanford Neurosciences Institute, and Harman Provostial Professor of Neurobiology Stanford University, USA.

"Joaquín Fuster has produced an extraordinarily insightful compendium of information about how the frontal cortex lets us develop new plans and sequences of thought and action— the heart of the behavior that makes us ourselves. Fuster makes us realize how important time is to the organization of our behavior, and that our mental and physical actions are guided by brain networks that have the frontal cortex as the master hub. Fuster gives us a rich and deep view of how our frontal cortex guides our mental life and lets us develop action sequences over time."
Ann Graybiel, Professor, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, USA.

"*The Prefrontal Cortex* is not only a classic, but also an essential book for anyone interested in higher brain function. One might think there's nothing left to say but Fuster proves that wrong. The latest edition is fresh and vibrant, and itself essential, destined to be a classic in its own right."
Joseph LeDoux, University Professor, New York University, USA, and author of *The Emotional Brain and Synaptic Self*.

"Once again, Dr. Fuster, the world's pre-eminent expert on the frontal lobes, has delivered an instant classic that should be read by everyone interested in understanding the link between brain and behavior."
Mark D'Esposito, Director, Henry H. Wheeler Jr. Brain Imaging Center, Professor of Neuroscience, University of California, Berkeley, USA.

"A classic that has graced the library of many of us since its first edition appeared 35 years ago now returns, splendidly updated. As a result, this book will continue to be the go-to reference on the prefrontal cortex as we strive to understand more fully its critical role in brain function."
Marcus E. Raichle, Professor of Radiology and Neurology, Washington University School of Medicine, USA.

"The frontal lobe serves the highest cognitive functions of the brain, including symbolic representation of the world, decision making, and planning for the future. Arguably, the enormous development of these functions distinguishes the human from other species. Joaquín Fuster has devoted his life to studying the many complex roles of the frontal cortex in behavior and cognition. This book is the product of his efforts to make these issues comprehensible in an exciting and fast-growing field. Even if you possess earlier editions of his book you should have this one to stay informed about the brain structure that makes us human. For that, this vastly updated edition is a must-have, whether you are a specialist or not."
Pasko Rakic, Chairman, Department of Neurobiology, and Director, Kavli Institute for Neuroscience, Yale Medical School, USA.

"The *Prefrontal Cortex* is a classic, and the classic has just been updated, expanded and thought anew, with the depth and wisdom that characterize Fuster's work. As before, this is an indispensable volume for neuroscientists."
Antonio Damasio, Dornsife Professor of Neuroscience and Director, Brain and Creativity Institute, University of Southern California, USA.

"The frontal lobes are central to cognitive neuroscience. The revision of this important volume provides the crucial background needed to grasp their role. In the final chapter Fuster brings together all that is known by emphasizing the temporal course of brain networks in a way which serves to illuminate action, consciousness and free will."
Michael I. Posner, Professor, Department of Psychology, Institute of Cognitive and Decision Sciences, University of Oregon, USA.

"Joaquín Fuster is one of the leading scientists in the field of cognitive neuroscience. He is famous not only for his discovery of "memory cells" in the frontal lobe of the monkey, but also for his excellent books. Among them the most famous and influential is *The Prefrontal Cortex*. I remember the first edition of it back in 1980. It was a mere intellectual pleasure reading it. The book reviewed an amazing amount of data from anatomy, ontogeny and physiology to the effect of lesions on innate and conditioned behavior and synthesized them in a coherent theory. In this new completely re-written edition of the book, Fuster has been able to repeat the enterprise. In spite of the enormous amount of new data, many coming from the rather messy field of brain imaging, he has been able to review them and put them in a clear theoretical frame. I am sure the new generation of neuroscientists will be influenced by this book in the same way as I was more than 20 years ago and will receive, by reading it, the same intellectual pleasure."
Giacomo Rizzolatti, Professor of Human Physiology, Department of Neuroscience, Section of Physiology, University of Parma, Italy.

"This is a superb, fresh, in-depth, review of one of the most complex and fascinating topics in cognitive neuroscience. In this, the latest edition of his excellent book, Fuster further substantiates the general proposition that the prefrontal cortex serves the organization of goal-directed actions in the most human of all action domains. Based on a wealth of recent empirical evidence, he places the temporal integrative functions of the frontal lobe – including working memory and planning – at the summit of the perception-action cycle. There, with access to myriad signals from the internal and external milieus, the prefrontal cortex attends to the orderly pursuit of rational, linguistic, and social goals. It is a must read for all interested in neuroscience."
Richard Thompson, William M. Keck Chair in Biological Sciences and Professor of Psychology and Biological Sciences, University of Southern California, USA.

To the memory of my father – physician, educator, historian, and man of infallible common sense

Preface

Since 2007, when the previous edition of this book went to the printer, the electronic database of PubMed has accumulated more than 14,000 additional articles related in one way or another to the book's subject matter. To bring the book up to date, I had to review much of that massive material, although I did it with a critical discriminating eye, attempting to highlight the substantive new knowledge. I also made use of recently published reviews by others. Naturally, the interpretation of new data may have been subject to my own theoretical biases. Indeed, Friedrich Hayek is reputed to have wisely said that, "without a theory the facts are silent." But, of course, theories are based on facts, which can oblige us at any time to change or discard an outdated theory. This is not always easy, especially when the interpretations of facts contradict one another or a faulty theory is deeply entrenched in collective thinking. In any case, as a result of my effort I had to modify some of my previous ideas.

Since the last edition, what is new in the field of the prefrontal cortex seems to be *novelty* itself, or at least a renewed emphasis on it and on the *future orientation* of prefrontal functions. There is a growing recognition that the cardinal function of this part of the brain, which is the latest to develop in evolution and in ontogeny, is the design and implementation of novel, complex, goal-directed or purposeful actions. In other words, we are dealing primarily with a prospective function of creating new forms of action. This is especially true for the cortex of the lateral convexity of the frontal lobe, which is the one to have developed to a maximum in the human brain.

In previous editions, novelty of action was couched in the more general concept of a prefrontal role in the temporal organization of all modes of behavioral action. The latest studies, however, oblige us to place the emphasis on what for the organism is not only new behavior, but also new perception, new language, and new reasoning. By so doing, we attribute to the prefrontal cortex imagination in addition to predictive and creative capacity. Indeed, it appears that this cortex opens the brain to the future, giving it the ability both to predict and to invent that future. If the human brain is the ultimate adaptive system to emerge from evolution, the human prefrontal cortex, which is the latest structure to evolve within it, gives it the power to *preadapt* the organism to its environment and to prepare it for future adaptive actions.

That environment is not only external, made of the world that surrounds us, but internal as well, consisting of what has been called the *internal milieu*. The latter is the aggregate of biological conditions of the body served by "biodrives" (hunger, sex, avoidance of pain, and others); these drives ensure internal chemical equilibrium or homeostasis, physical pleasure, defense, survival, and procreation. All biodrives are led or accompanied by emotion and closely intertwined with social behavior. A large body of recent evidence implicates further the prefrontal cortex, especially its internal or medial and inferior (orbital) aspects, in emotion and social behavior, thus complementing and expanding much of the evidence previously inferred from clinical and neuropsychological observations.

Because of its key position in making us agents of free choice, planning, and decision-making, the prefrontal cortex has lately entered the debate on issues of free will and ethical responsibility. In this latest edition these issues had to be dealt with somewhat more extensively than in previous ones, although I have treated them separately in another text (Fuster, 2013).

Animals possess intelligence, working memory, perception, attention, and practically every other cognitive function known to humans. It is by studying the prefrontal cortex of animals that we have come to understand some of the principles of operation of these functions in the human prefrontal cortex as well as the cortex at large. For example, we would know next to nothing about the mechanisms of working memory and the role of the prefrontal cortex in it had it not been for the research of these matters in the non-human primate. Meanwhile, however, we have been neglecting the fact that working memory is a prospective function like all other so-called executive functions of the prefrontal cortex. It has a future dimension that is part of its definition: working memory is short-term memory *for* a prospective action.

Language is a uniquely human form of communication and behavior. It is also a vehicle of cognitive expression as well as social and emotional interaction. All novel and rich spoken language is a most complex form of organized action. On these grounds alone, the prefrontal cortex plays a critical role in language. The latest data, mainly from neuroimaging studies, point to a dual basis for that role. One is the capacity of the prefrontal cortex to predict (from Latin *praedicere*, to foretell), and thus to make new proposals, "to propositionise," as John Hughlings Jackson (1958) called it; language serves the formulation of new plans of future action, a basic prefrontal function. The other is the temporally organized nature of language; like all forms of organized goal-directed action, it depends critically on the prefrontal cortex, especially if the language is novel and elaborate. A plausible argument can be made for considering the syntax of language a special case of the syntax of action, and as such, dependent on the lateral prefrontal cortex. For that syntax, working memory is essential.

There are two fundamental principles in the previous edition that the present one not only upholds but also strengthens. One is the intimate hierarchical *cooperation* of the prefrontal cortex with other cortical and subcortical regions of the brain in the structuring of behavior, reasoning, and language. The other is the controlling position of the prefrontal cortex at the summit of the *perception–action cycle*, the cybernetic loop of information processing between the cortex at large and the environment, which adapts and *pre*adapts the organism to that environment. What needed emphasis before, and now receives it, is that much of that environment is internalized in the cortex, in the form of widely distributed cognitive networks or *cognits* that represent the memories, knowledge, and culture of the individual. All of that, forming part of the perception–action cycle, has been acquired by prior experience in the course of life and is ready for recall to be engaged in that cycle at any new round of adaptation.

Now, more than in 2007, the prefrontal cortex is penetrating our clinical reasoning and agenda. A prefrontal disorder is implicated in several pathological conditions with psychiatric manifestations, ranging from the attention deficit/hyperactivity disorder of childhood to drug addiction, obsessive–compulsive disorder, autism, schizophrenia, depression, and dementia. Rarely is the prefrontal cortex disturbed alone in any of these conditions, which usually also affect other brain structures and several neurochemical systems. Furthermore, some of these conditions are subject to genetic factors, the influence of which is likely to transcend the prefrontal structure or functions. There is no doubt, however, that all of them manifest as cognitive, social, or emotional disorders

that are squarely attributable to prefrontal dysfunction.

This foreword cannot come to a close without my recognition of the help that many fellow scientists have extended to me in the writing of the various editions of this book, including the present one: Amy Arnsten, Lewis Baxter, Susan Bookheimer, Carmen Cavada, Norman Geschwind, Patricia Goldman-Rakic, Patricia Greenfield, Eric Kandel, David Lewis, Donald Lindsley, James Marsh, John Mazziotta, Mortimer Mishkin, Walle Nauta, Carlos Otero, Karl Pribram, Javier Quintana, Donald Stuss, and John Warren. To all of them, I am deeply indebted. I also owe special thanks to Carmen Cox, who assisted me in assembling an exceptionally copious bibliography.

Joaquín M. Fuster
Los Angeles, California
December 2014

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5. Human Neuropsychology

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7. Neuroimaging

CHAPTER

1

Introduction

OUTLINE

I. INTRODUCTION

The prefrontal cortex is the cortex of the anterior pole of the mammalian brain. In characterizing the anterior part of the frontal lobe with the adjective *prefrontal*, we make loose, if not improper, use of the prefix *pre* (literally we place that cortex in midair!). Nevertheless, that designation has been condoned by so much usage that it seems unwarranted to discard it for semantic reasons.

Here, the prefrontal cortex is defined as the part of the cerebral cortex that receives projections from the mediodorsal nucleus of the thalamus. This anatomical definition is applicable to all mammalian brains. It takes into consideration the possibility that the relationship with a well-defined thalamic nucleus reflects an identifiable function or group of functions. Of course, such reasoning is based on analogy with specific thalamic nuclei and their cortical projection areas, an analogy that may not be entirely appropriate. Furthermore, the functions of the mediodorsal nucleus are not well known, and the prefrontal cortex is also connected to many other cerebral structures.

On the other hand, the definition by relationship has here the merit of obeying the reasonable principle that the physiology of a cortical region can be meaningfully studied and understood only in the context of its anatomical connections with other structures (Creutzfeldt, 1977). In this respect, however, the connectivity of the prefrontal cortex with other parts of the cortex may be more important than its thalamic connectivity.

The basic function of the prefrontal cortex is *the representation and execution of new forms of organized goal-directed action*. All the so-called executive functions of the prefrontal cortex serve that superordinate function in one way or another.

The goals of an organism, especially the human organism, can vary immensely, and so do the timescale and means to achieve them. Also variable are the motives for action and the emotions that accompany it, as well as their influence at any step in the pursuit of a goal. Depending on these factors, each of the executive functions of the prefrontal cortex may be brought into play at one time or another. In the human and non-human primate, as in

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other animals, each one of these functions has a dominant if not specific regional location in the prefrontal cortex. In any event, the diversity of regional commitments, as well as of the connectivity of different prefrontal areas, has to be analyzed in depth, because therein lies the key to their function. We shall never understand fully the functions of the prefrontal cortex if we neglect the operations of its components.

At the same time, we must keep in mind the wider structural and dynamic context in which those operations take place. This context is defined by two basic biological principles that set the background for any discussion of this cortex. One is the evolutionary *hierarchy* of cortical and subcortical structures dedicated to the organization of goal-directed actions. The other is the *perception–action cycle*; that is, the cybernetic circulation of information processing that governs the interactions of the organism with its environment. Both principles are structurally and dynamically intertwined.

The first, the hierarchical vision of the neuroscience of action, has its origin in the writings of John Hughlings Jackson (1958), a scholarly physician who practiced neurology in London's Queen Square Hospital at the end of the nineteenth and beginning of the twentieth century. Based on his studies of motor functions and their disorders, Jackson advanced the idea that the structures of the central nervous system, its motor structures in particular, were hierarchically organized in the order determined by evolution: structures representing and coordinating simple movements at the bottom (basal ganglia, pyramidal system, cerebellum), and those representing and coordinating new complex behavior at the top (prefrontal and premotor cortices). As clinical observations clearly demonstrate, lesions at a particular level of the motor hierarchy lead to paralyses of movements organized at that level and, at the same time, to the release of simpler, automatic movements from lower levels of the hierarchy. Jackson characterized such a pathological disorder as "dissolution," a term he coined as an opposite to evolution, since the disorder indicated that upon failure of higher levels of the hierarchy, the nervous system regressed to the performance of movements that are more primitive from an evolutionary point of view.

An evident corollary of Jackson's theory, which he drew quite early (Jackson, 1882), is that the evolutionarily lower structures and their functions are nested under the higher structures and functions, which they normally serve. When the higher ones fail, the lower are released from their control. This is true in all cortical hierarchies of action, but is most obvious in the hierarchy of areas dedicated to the phylogenetically most advanced cognitive activity, the spoken language. At the lowest cortical level of the speech hierarchy is the sensorimotor cortex, which controls the representation and articulation of simple speech utterances. By high-resolution methods in humans, precise temporal patterns can be recorded in that cortex that correspond to the successive activations of oral and laryngeal muscles during the articulation of vowels and consonants (Bouchard et al., 2013). Words are made of phonemes and morphemes, which are organized into sentences in hierarchically higher cortical regions, such as the premotor cortex and Broca's area.

As a result of his clinical research, Jackson reserved for the prefrontal cortex the representation and organization of what he called "propositional" language. It should not escape us that, in logic and linguistics, the term *propositional* implies novelty, complexity, and even a future dimension – which all proposals have. At the same time, these are the characteristics that make language a uniquely human activity (Berwick et al., 2013) and place its most novel and complex aspects in the prefrontal cortex, at the summit of the evolutionary hierarchy of neural structures for action.

The concept of the perception–action cycle also has a deep root in biology. Prefrontal areas, networks, and functions are not simply

interdependent; they are cooperative. The temporal organization of complex and novel actions toward their goal is the product of the dynamics of the perception–action cycle, which consists of the coordinated participation of neural structures in the successive interactions of the organism with its environment in the pursuit of a goal. Thus, the perception–action cycle is the cortical substrate for the processing of information between the organism and its environment; the prefrontal cortex constitutes the highest stage of neural integration in that cycle. In the course of a goal-directed sequence of actions, signals from the internal milieu and the external environment are processed through hierarchically organized neural channels and lead into the prefrontal cortex (internal signals into orbitomedial, external signals into lateral prefrontal cortex). There, the signals generate or modulate further action, which in turn causes changes in the internal and external environments, changes which enter the processing cycle toward further action, and so on until the goal is reached. At each hierarchical level of the cycle, there is feedback to prior levels. At the highest level, there is re-entrant feedback from the prefrontal cortex to the posterior association cortex, which plays a critical role in working memory, set, and monitoring.

Those two general concepts, hierarchy and the perception–action cycle, mark the theoretical backdrop in the cerebral cortex at large against which the functions of the prefrontal cortex must be viewed. Both cortices, posterior and frontal, are hierarchically organized. Whereas the posterior cortex is devoted to perceptual and mnemonic functions, the entirety of the frontal cortex, including its prefrontal region, is devoted to action of one kind or another, whether it is skeletal movement, ocular movement, the expression of emotion, speech, or visceral control. The action can even be mental and internal, such as reasoning. The frontal cortex is therefore "doer" cortex, much as the posterior cortex is "sensor" cortex (both reflecting up in the cortex the polarity of functions existing in the anterior and posterior horns of the spinal cord). In sum, the posterior cortex and the frontal cortex constitute the cortical infrastructure for the perception–action cycle.

The frontal cortex does nothing by itself. It works in the perception–action cycle with other cortices, with subcortical structures, and with certain sectors of the sensory and motor apparatus and of the autonomic system. There is, however, considerable specialization of action within it. Accordingly, there are frontal areas for eye movement, for skeletal movement of various body parts, for speech, for emotional expression, and so on. More importantly in what concerns us here, the specialized areas within the prefrontal cortex, whatever the action domain they represent, contribute their share to the common cognitive and emotional functions that drive the neocortex as a whole. Those functions are essentially integrative and goal directed. They are also, as we will see, new for the organism; they are new as that organism has to meet new circumstances, now or in the future, and has to adapt to them. In that sense, the prefrontal cortex is not only adaptive, but also *pre*adaptive.

As organisms evolve, their actions become more complex and idiosyncratic, their goals more remote in space and time, and their reasons or motives for attaining them less transparent, more based on probability and prior experience than on peremptory instinctual need. Furthermore, action in general becomes more deliberate and voluntary. With this evolution of biological action, and presumably because of it, the most anterior sector of the frontal cortex, which we call the prefrontal cortex, grows substantially – in relative size – as evolution progresses, and so does its functional role. Its growth reaches a maximum in the human primate. The prefrontal cortex of the lateral or outer frontal convexity, which is essential for cognitive functions and intelligent behavior, undergoes greater development than that of the