The Prefrontal Cortex

FIFTH EDITION

Joaquín M. Fuster

THE PREFRONTAL CORTEX

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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 But, of course, theories are based on facts, which can oblige us at any time to change or discard an outdated theory.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.

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Los Angeles, California
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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 medial and inferior (orbital) surfaces, which are critically involved in emotional behavior. Although their functions are interdependent and integrated in the behavior of the organism, lateral and orbitomedial cortices require somewhat different methodologies for their study.

In this book, we shall examine the prefrontal cortex by systematically reviewing data from each of the contributing methodologies. As we proceed from the basic facts of anatomy to neuropsychology, to neurophysiology, and to neuroimaging, my own conceptual point of view will become progressively more explicit. This introduction outlines it in broad strokes and the last chapter describes it in detail.

In the 33 years since the first edition of this book, my theoretical position on the prefrontal cortex has changed considerably as new facts have demanded it, but some of the basic elements of my initial view are still valid. To begin with, there is now wide agreement with the concept I held then, that the lateral prefrontal cortex is critical for the cognitive functions that mediate the temporal organization of actions. These functions include planning, decision-making, and top–down attention, the latter with its three subcomponents of working memory, set, and inhibitory control. Another surviving view is that the limbic, "dysgranular," cingular, medial, and orbital areas of the prefrontal cortex, while also involved in those functions, modulate their emotional and affective components. Those areas can even initiate goal-directed actions in the *emotional* perception–action cycle, which runs parallel to the cognitive one and interacts with it – in orbital prefrontal cortex. We also know, as we knew then, that two specialized regions at the transition between prefrontal and premotor cortex serve the coordination of eye movements (area 8) and speech (areas 44–45, Broca's area).

With continuing research, other views on the prefrontal cortex have emerged in later years, which, without substantially modifying the previous ones, add to them two essential accents: one on novelty and the other on the future. Any series of purposive actions that is new and thus deviates from rehearsed or automatic routine or instinctual order necessitates the lateral prefrontal cortex. The longer the series, and therefore the further it extends into the future, the greater the need for that cortex. Time is only one factor, however, among those determining that need; other factors include the complexity of the actions and of the information on which they are based, and still another the uncertainties or ambiguities in that information. There is considerable trade-off between those factors. For example, a monkey with a prefrontal deficit may fail at a simple and thoroughly rehearsed task, such as delayed response, not only because of the interval of time between cue and response, but also because of the competitive interference – a source of uncertainty and ambiguity – between two alternative cues that succeed each other at random from one trial to the next. Still, the question may be asked, what is *new* for the prefrontal cortex in a task as stereotypical as that one? The answer to that question is that the cue for every trial, although part of an old repertoire, is unpredictable and *new for that trial*. This critical element of built-in novelty is ignored by many studies using delay tasks.

Yet time is probably the single most important attribute placing a complex and novel sequence of behavior under the physiological purview of the lateral prefrontal cortex (Fuster, 2001). Only this part of the cerebral cortex can provide that "temporal gestalt" with the coherence and coordination of actions that are essential for the organism to reach its new goal. Both coherence and coordination derive from the capacity of the prefrontal cortex to organize new goal-directed actions in the time domain, which in my view is the most general and characteristic of all prefrontal functions in the primate. The importance of this temporal-organizing function in mammalian behavior cannot be overstated. Without it, there is no execution of novel, elaborate behavior, no speech fluency, no higher reasoning, and no creative activity with more than a minimal temporal dimension; only temporal concreteness is left, the here and now.

For it to function properly, however, the overarching prefrontal function of organizing new goal-directed actions in time necessitates two essential elements: (1) a cortex-wide infrastructure for the representation of knowledge and memory in the form of distributed cognitive networks, which I have called *cognits* (Fuster, 2009); and (2) a number of executive integrative functions that will manipulate those cognits in temporal integration. There are essentially five of these functions: planning, decision-making, working memory, preparatory set, and inhibitory control. Note that they all have a future perspective and that they interact with one another in the organization of goal-directed actions.

Indeed, all the cognitive functions of the cortex take place on a neural substrate of neural representation. That substrate is made of a vast neuronal network that is the repository of permanent, though modifiable, long-term memory, and knowledge (knowledge is semantic memory). That substrate extends to the hippocampus, which is a portion of ancient cortex that is essential for the consolidation of all explicit/declarative memory and knowledge. Individual memories or cognits are subcomponents, also network-like, of that vast network. They can be perceptual, acquired through the senses and spread in posterior cortex, or executive, acquired through action and spread in frontal cortex; or they can be mixed and spread in both cortices. Cognits overlap, intersect, and interact profusely. One neuron or group of neurons almost anywhere in cortex of association can be part of many cognits, part of many memories or items of knowledge.

Cognits are made by association of simultaneous stimuli or actions, stored in networks by connective associations, and retrieved by association with environmental or internal events that have been previously associated with them. All cognitive functions – attention, perception, memory, language, and intelligence – consist of neural transactions within and between cognits. Because these are made of associations, the cognitive "code" is essentially a relational code.

The representational substrate of the prefrontal cortex, in particular its lateral sector, is made of networks or cognits of *executive memory*, which have been formed by prior experience and extend into other cortical areas. The *executive functions* or operations of the prefrontal cortex essentially consist of the utilization of that substrate (1) *for* the acquisition of new perceptual and executive memory; and (2) *for* planning, decision-making, and organizing new behavior, reasoning, or language.

My use of the preposition *for* in the last sentence points to the central position of *teleology* in the physiology of the prefrontal cortex. Teleology is anathema in any scientific discourse, if nothing else because it blatantly defies the logic of causality. Yet in the discourse about prefrontal physiology *goal*, like *purpose*, is of the essence. All cognitive functions of the lateral prefrontal cortex are determined, we might say "caused," by goals. If there is a unique and characteristic feature of that part of the brain, it is its ability to structure the present in order to serve the future, in this manner inverting the temporal direction of causality. Of course, this inversion is not real in physical terms. It is only real in cognitive terms inasmuch as the *representations of goals* antecede the actions to pursue them through the agency of the prefrontal cortex. Furthermore, all representations of the future, in the brain as in the mind, are reconfigurations of the past.

Teleology or "teleonomy" (Monod, 1971), thus understood, is at the basis of *planning* and the temporal organizing cognitive functions of the prefrontal cortex. In the human, as arguably in the large ape (Osvath and Osvath, 2008), the prefrontal cortex can create new plans of behavior. This implies a degree of reasoning and experience. New plans are new configurations of old memory for novel short- or long-term adaptive needs. By definition, a plan has a temporal dimension and a goal. That plan may be represented in a schema of action (a new prefrontal cognit) with its goal. The incipient plan or schema of action may be represented with varying degree of detail, but its implementation requires a temporal organization, the orderly activation of its component networks, some of which may extend into posterior (perceptual) cortex. That implementation requires top–down executive attention (see below).

Teleology also lies at the foundation of *decision-making*, another executive function of the prefrontal cortex. Decision-making is usually prompted by a new set of environmental circumstances, external or internal. It is essentially a choice between alternatives of action (including non-action), and thus bears heavily on the issues of individual freedom and responsibility (Fuster, 2013). It is multifactorial, as it is subject to the influences and appraisal, much of it unconscious, of a large variety of biological and "historical events," such as the individual's memory, culture, ethical principles, and experience from similar circumstances in the past. Because it is frequently based on many factors, some of which are imponderable and updatable, a decision is usually to some extent Bayesian, which means based on incompletely or imperfectly educated probability (Jaynes, 1986).

A third major prefrontal function is executive attention, which in many respects, as we will see, is indispensable to the first two, planning and decision-making. Executive top–down attention has three critical components, all three direct participants in the *temporal organization of action*: (1) working memory; (2) preparatory set; and (3) inhibitory control. All three have somewhat different, though partly overlapping, frontal topographies and a different cohort of neural structures with which the prefrontal cortex cooperates to implement them. Strictly speaking, none is localized in this cortex, but all three need their prefrontal base to operate. Furthermore, the prefrontal cortex performs its executive control of temporal organization by orchestrating activity in other neural structures that participate in executive attention. Executive attention, like all forms of attention, implies the optimal use of limited available resources for a given function, wherever they may be in the nervous system.

Working memory is active memory that the animal needs for the performance of acts in the short term. This is why it is often called also "short-term memory." It is not to be confused, however, with short-term memory as the precursor stage of long-term memory. According to the "dualistic" concept of memory, before memories become established they pass through a short-term store. In any case, that concept, which is based on the assumption of separate neural substrates for the two forms of memory, is being replaced by a better supported unitary view of memory with a common cortical substrate. In accord with this view, working memory is the temporary activation of *updated* long-term memory networks *for* organizing actions in the near term. That prospective aspect is essential to the definition of working memory.

The content of working memory may be sensory, motor, or mixed; it may consist of a reactivated perceptual memory or the motor memory of the act to be performed, or both. It may also consist of the representation of the cognitive or behavioral goal of the act. Inasmuch as the content is selective and appropriate for current action, working memory is practically inextricable from attention. In fact, working memory is essentially sustained attention focused on an internal representation. In primates, working memory, depending on its content, engages a portion of lateral prefrontal cortex and, in addition, related areas of posterior (i.e., postcentral, postrolandic) cortex.

The selective activation of posterior cortical areas by the prefrontal cortex, in the process of internal attention that we call working memory, is a major aspect of the neural basis of what has been called "cognitive control" (Miller and Cohen, 2001).

Preparatory set is the readying or priming of sensory and motor neural structures for the performance of an act contingent on a prior event, and thus on the content of the working memory of that event. Set may be rightfully viewed as "motor attention." In the primate, preparatory set also engages a portion of lateral prefrontal cortex – depending on the act – and, in addition, structures below the prefrontal cortex in the hierarchy of motor structures (e.g., premotor cortex and basal ganglia). The modulation of those lower neural structures in the preparation for action is also part of the so-called cognitive control exerted by the prefrontal cortex.

In functional terms, working memory and preparatory set have opposite and symmetrical temporal perspectives, the first toward the recent past and the second toward the near future. The two of them, operating in tandem through their respective neural substrates and under prefrontal control, mediate *cross-temporal contingencies*. That means that the two functions together reconcile past with future: they reconcile a sensory cue or a reactivated memory with a subsequent – and consequent – act; they reconcile acts with goals, premises with conclusions, subjects with predicates. Thus, the prefrontal cortex, with its two temporal integrative functions of set and working memory, manages to bridge for the organism whatever temporal distances there may be between mutually contingent elements in the behavioral sequence, the rational discourse, or the construct of speech.

Inhibitory control complements those two temporal integrative functions of the lateral prefrontal cortex (working memory and set). In emotional behavior, it has an impact on the functions of the orbitomedial prefrontal cortex. Throughout the central nervous system, inhibition plays the role of enhancing and providing contrast to excitatory functions. A pervasive role of inhibition is evident in sensory systems (e.g., the retina) as well as motor systems (e.g., the motility of the knee). Inhibition is a critical component of attention; selective attention is accompanied by the suppression, by the inhibition, of whatever cognitive or emotional contents or expressions may interfere with the focused attention. In the prefrontal cortex, inhibition is the mechanism by which, during the temporal organization of actions in the pursuit of goals, sensory inputs and motor or instinctual impulses that might impede or derail those actions are held in check. In sum, an important aspect of the executive and controlling role of the prefrontal cortex is to suppress whatever internal or external influences may interfere with the sequence currently being enacted. In primates, this function seems to be represented mainly, though not exclusively, in orbitomedial prefrontal cortex and to engage other cortical and subcortical structures. The orbitomedial prefrontal cortex is known to be involved also in reward; it contains important components of neurotransmitter systems (e.g., dopamine) activated by rewards.

Each of the executive functions of the prefrontal cortex that we consider components of executive attention – working memory, set, and inhibitory control – finds support in a different category of data. For example, the working-memory function is strongly supported by neurophysiological data from single-unit studies, not only in frontal cortex but in other cortices as well. Ever since 1971, when the first demonstration of prefrontal "memory cells" was published, there has been a tendency to identify working memory, by whatever name, as the cardinal executive function of the prefrontal cortex. This ignores the evidence that working memory has an ancillary role, along with the other functions, under the superordinate function of temporal organization. The same can be said of preparatory set and inhibitory control.

The subdivision of prefrontal function into its components is made reasonable not only by the apparent specialization of prefrontal areas in different subfunctions of temporal organization, but also by the specialization of those areas in different forms of action (action domains). That subdivision, however, often results in the conceptual "Balkanization" of the prefrontal cortex into a topographic quilt of areas dedicated to a seemingly endless succession of supposedly independent cognitive or emotional functions, without regard for the two principles that I will try to outline in the subsequent chapters of this book: first that all prefrontal functions and areas are to some degree interdependent; and second that the various functions have areas and networks in common. Without these principles in sight, we are easily led to a sterile compartmentalization of functions. Thus, for example, to attribute only eye-movement control to area 8 and speech to Broca's area ignores that both these functions depend also on other neural structures. It also ignores the evidence that both areas participate in the more general prefrontal function of temporal organization ("syntax of action"), which transcends both ocular movement and the spoken language. Nonetheless, a useful empirical approach is first to use whatever degree of specialization may be discernible in a given prefrontal area to investigate the basic mechanisms that support it, and then to examine that specialization within the superordinate organizing function. This approach respects the basic physiological principles of prefrontal function while also respecting areal or "domain" specificity where there is one. The approach allows for specificity but puts it under the overarching umbrella of temporal organization.

To sum up, this book emphasizes the role of the prefrontal cortex in coordinating cognitive functions and underlying neural structures in the temporal organization of new behavior; that is, in the formation of novel and coherent behavioral sequences toward the attainment of goals. My purpose in making this case is both deductive and inductive, goes often from the general to the particular and *vice versa*. It is my hope that this work will continue to generate new research, which in turn will provide us with a more solid basis of empirical knowledge than we now have of the neural mechanisms underlying that temporal integrative function of the prefrontal cortex.

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