

# The Prefrontal Cortex

FIFTH EDITION



Joaquín M. Fuster



# THE PREFRONTAL CORTEX

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"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."

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"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."

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"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.

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FIFTH EDITION

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The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

Fifth edition 2015

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ISBN: 978-0-12-407815-4

#### British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

#### Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress.

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Typeset by MPS Limited, Chennai, India  
[www.adi-mps.com](http://www.adi-mps.com)

Printed and bound in the United Kingdom



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

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# Preface

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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 pre-frontal 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 "biодrives" (hunger, sex, avoidance of pain, and others); these drives ensure internal chemical equilibrium or homeostasis, physical pleasure, defense, survival, and procreation. All biодrives 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 *preadapts* 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

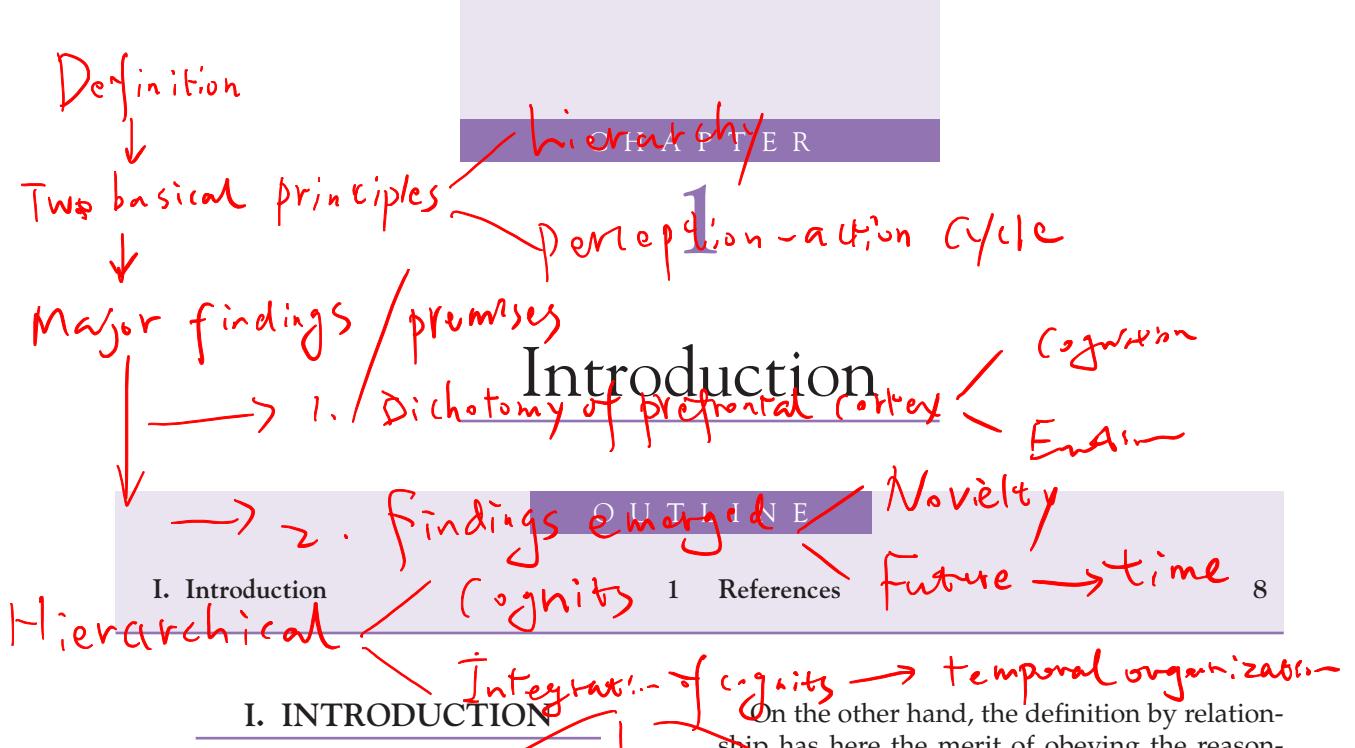
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The prefrontal cortex is the cortex of the anterior pole of the mammalian brain in characterizing the anterior part of the frontal lobe with the adjective *prefrontal*, we make loose, if not improper, use of the prefix *pre* (literally we place that 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

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 preadaptive.

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

The dichotomy of prefrontal cortex  
→ Lateral / medial ; Cognitive / emotional

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," cingulate, 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.

So endogenous attention  
is required.

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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# Anatomy of the Prefrontal Cortex

## OUTLINE

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## I. INTRODUCTION

This chapter is devoted to the anatomy and developmental neurobiology of the prefrontal cortex. It begins with the discussion of issues related to the **phylogenetic development** and comparative anatomy of the neocortex of the frontal lobe. After that, the chapter deals with its **ontogenetic development**. Then, the chapter deals with the anatomy and microscopic architecture of the prefrontal cortex in the adult organism, and with the **morphological changes** it undergoes as a result of aging. Finally, the chapter provides an overview of the **afferent and efferent connections** of the prefrontal cortex in several species. This overview of connectivity of the prefrontal cortex, which is arguably the most richly connected of all cortical regions, opens the way to subsequent chapters, where

connectivity is found to be the key to all its functions.

## II. EVOLUTION AND COMPARATIVE ANATOMY

The prefrontal cortex increases in relative size with phylogenetic development. This can be inferred from the study of existent animals' brains as well as from paleoneurological data (Papez, 1929; Grünthal, 1948; Ariëns Kappers et al., 1960; Poliakov, 1966b; Radinsky, 1969). It is most apparent in the primate order, where the cortical sector named by Brodmann (1909, 1912) the "regio frontalis," which approximately corresponds to what we call the prefrontal cortex, constitutes, by his calculations based on cytoarchitectonics, 29% of the total cortex in

humans, 17% in the chimpanzee, 11.5% in the gibbon and the macaque, and 8.5% in the lemur (Brodmann, 1912). For the dog and the cat, the figures are, respectively, 7% and 3.5%.

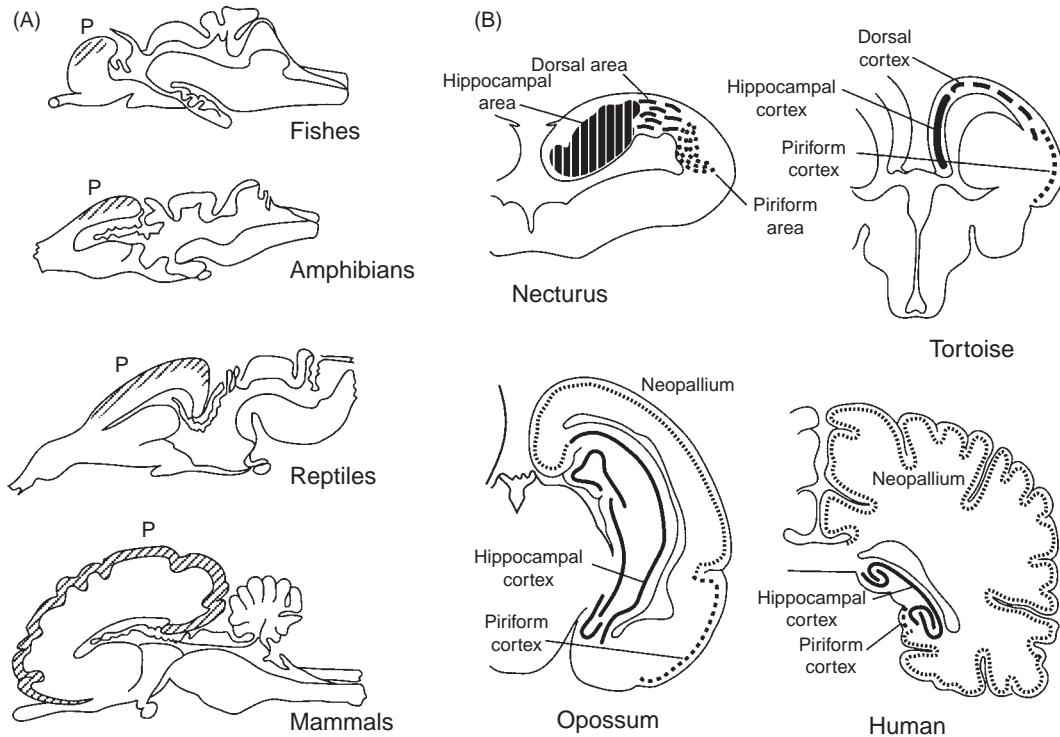
The use of values such as those to estimate differences in evolutionary growth has pitfalls and limitations, however (Passingham, 1973). The old notion that the entirety of the frontal lobe is relatively larger in humans than in other primates has been challenged by the results of brain imaging in several primate species (Semendeferi, 2001). Furthermore, by calculating the volume of the prefrontal cortex and plotting it against the total volume of the brain (in rat, marmoset, macaque, orangutan, and human), some authors have come up with a linear relationship, thus belying the volumetric prefrontal advantage of the human (Uylings and Van Eden, 1990). Others, however, have utilized sound empirical reasons to argue that in the course of evolution the prefrontal region *per se*, strictly defined cytoarchitectonically, grows more than other cortical regions (review by Preuss, 2000). No one has persuasively denied that in the human, as Brodmann showed, the prefrontal cortex attains the greatest magnitude in comparison with those other regions. That greater relative magnitude of the human prefrontal cortex presumably indicates that this cortex is the substrate for cognitive functions of the highest order, which, as a result of phylogenetic differentiation, have become a distinctive part of the evolutionary patrimony of our species. It has even been proposed that certain cortical areas, such as Broca's area – which is arguably prefrontal – have developed by natural selection with the development of language, a distinctly human function (Aboitiz and García, 1997).

It is always difficult to draw evolutionary conclusions from neuroanatomical comparisons between contemporaneous species in the absence of common ancestors (Hodos, 1970; Campbell, 1975). Such comparisons commonly fail to establish the homology of brain structures (Campbell and Hodos, 1970), and this is a

particularly vexing problem when dealing with cortical areas. Ordinarily, for lack of more reliable guidelines, the neuroanatomist uses structural criteria to determine cortical homology. The principal criteria for defining the prefrontal cortex and for establishing its homology across species are topology, topography, architecture, and fiber connections (hodology). The same criteria have been utilized in attempts to elucidate its evolutionary development.

The neocortex of mammals has emerged and developed between two ancient structures that constitute most of the pallium in non-mammalian vertebrates: the hippocampus and the piriform area or lobe (Figure 2.1). The process is part of what has been generally characterized as the evolutionary "neocorticalization" of the brain (Jerison, 1994). What in the brain of the reptile is a sheet of simple cortex-like structure bridging those two structures is replaced and outgrown by the multilayered neocortex of the mammalian brain (Crosby, 1917; Elliott Smith, 1919; Kuhlenbeck, 1927, 1929; Ariëns Kappers et al., 1960; Nauta and Karten, 1970; Aboitiz et al., 2003). Because the growth of the newer cortex takes place in the dorsal aspect of the cerebral hemisphere, the evolutionary process has been characterized as one of "dorsalization" of pallial development. Strictly speaking, however, it is inaccurate to consider the reptile's general cortex as the homologous precursor of the mammalian neocortex (Kruger and Berkowitz, 1960). Moreover, there are other plausible alternate theories of neocortical evolution in addition to the above (Northcutt and Kaas, 1995; Butler and Molnar, 2002). In any case, it appears that the mammalian neocortex is phylogenetically preceded by certain homologous subcortical nuclei in the brains of reptiles and birds.

Studies of cortical architecture in aplacental mammals, such as those by Abbie (1940, 1942), have been helpful to trace neocortical development. They reveal that the neocortex is made of two separate components or moieties, one adjoining the hippocampus and the other the



**FIGURE 2.1** Phylogenetic development of the cortex in several species. (A) Parasagittal brain sections in four vertebrate classes. Abbreviation: P, pallium, generic term for both paleocortex and neocortex. (From Creutzfeldt, 1993, after Eddinger, modified.) (B) Coronal sections of amphibian *Necturus*, tortoise, opossum, and human. (From Herrick, 1956, modified.)

piriform area, that develop in opposite directions around the hemisphere and meet on its lateral aspect. Both undergo progressive differentiation, which consists of cortical thickening, sharpening of lamination, and, ultimately, emergence of granular cells. In higher mammals the two primordial structures, the hippocampus and the piriform lobe, have been outflanked, pushed against each other, and buried in ventromedial locations by the vastly expanded cortex (Sanides, 1964, 1970). Around the rostral pole of the hemisphere, the two phylogenetically differentiated moieties form the prefrontal neopallium.

The external morphology of the frontal region varies so much from species to species

that it is difficult to ascertain the homology of its landmarks. Within a given order of mammals, certain sulci can be identified as homologous and used as a guide for understanding cortical evolution; across orders, however, all comparisons are hazardous. Nevertheless, some general principles of prefrontal evolution seem sustainable. One such principle is that, like the rest of the neopallium, the frontal cortex becomes not only larger but also more complex, more fissured and convoluted, as mammalian species evolve. In primates, the process reaches its culmination with the human brain.

We should note, however, that the phyletic increase in gyration and fissuration can be attributable to mechanical factors and not only

to such factors as functional differentiation. The cortex folds and thus gains surface, keeping up with the three-dimensional expansion of subcortical masses (Bok, 1959). Thus, the overall number of gyri and sulci that form with evolution is largely a function of brain size, as stated by the law of Baillarger-Dareste (Ariëns Kappers et al., 1960). However, where the gyri and the sulci are formed is determined, at least in part, by functional differentiation. Gyri appear to mushroom as functions develop (Welker and Seidenstein, 1959) and, as Clark (1945) first postulated, sulci develop perpendicular to the lines of stress determined by fast area-growth. Not surprisingly, some of the most highly differentiated neuronal functions can be found in the cortex lining sulci (e.g., *principalis*, *central*, *intraparietal*, *lunate*, *superior temporal*). At the same time, and as a consequence of those developments, sulci and fissures generally separate areas of different functional significance. Electrophysiological studies corroborate this finding, although they also reveal several notable exceptions (Welker and Seidenstein, 1959; Woolsey, 1959; Welker and Campos, 1963). It should also be noted that, in the ontogenetic development of the monkey, sulci develop shortly after midgestation, long before functions (Goldman and Galkin, 1978).

With respect to the prefrontal cortex, homologies can be established with confidence only for the furrows that approximately mark its lateral boundary. This boundary is marked in the cat and the dog by the presylvian fissure, a fissure already present in marsupials and one of the most constant in carnivores (Ariëns Kappers et al., 1960). It is homologous to the vertical limb of the arcuate sulcus of monkeys and to the inferior precentral fissure of the larger apes and humans. The large expansion of the presylvian (prearcuate) area is one of the most remarkable developments of mammalian evolution.

Although by hodological and other criteria rodents have been determined to possess a prefrontal cortex (Preuss, 1995), it is difficult

to find in it, or around it, distinctive anatomical landmarks that could be deemed homologous to those found in carnivores or primates. In the anterior pole of the brain of some carnivores, between the presylvian fissure and the midline, there is a short furrow called the proreal or intraproreal fissure. According to Ariëns Kappers et al. (1960), this furrow may be the equivalent of the sulcus rectus of prosimians, more commonly designated the principal sulcus (*sulcus principalis*) in the monkey. In the human and anthropoids, the principal sulcus is represented, rostrally, by the sulcus frontomarginalis of Wernicke. It is uncertain whether, in the human and anthropoids, it is the medial or the inferior frontal fissure that represents the posterior extremity of the sulcus *principalis* (Connolly, 1950; Ariëns Kappers et al., 1960). Cytoarchitecture suggests that it is the inferior frontal fissure (Sanides, 1970).

Sanides (1964, 1970) carried out a remarkable effort to read phylogenetic history into the architecture of the prefrontal cortex. His studies essentially uphold for primates the principle of the dual evolutionary development of the neocortex formerly upheld in lower mammals (Abbie, 1940, 1942). By analysis of frontal architectonic zones, the two primordial trends of cortical differentiation mentioned above can be followed in dorsad progression. Studies of corticocortical connectivity in the adult primate demonstrate, within the prefrontal cortex, two trends of connections: one in ventrolateral and orbital cortex, presumably following the lateral (amygdala-piriform) developmental trend; and the other dorsomedial, presumably following the medial (hippocampal) trend (Yeterian et al., 2012).

A third and later trend seems to have occurred in primates, a trend originating in the more recently differentiated motor cortex and proceeding forward from there. This trend is suggested by the cytoarchitectonic gradations from areas 4 to 6 and from areas 6 to 9 that the Vogts first noted (Vogt and Vogt, 1919). Consequently, as Sanides (1970) points out, the

prefrontal cortex of the primate seems to have resulted from the growth and convergence of three differentiating fields over the polar region: the two primordial fields from cingular (parahippocampal) and insular (parapiriform) areas and the third, more recent field, from the motor cortex. Maximal differentiation can be observed in the frontier zones of the three developing fields. These zones show at its best the granularization of layer IV that is characteristic of the prefrontal cortex of humans and other primates.

As a result of these developments, the granular prefrontal cortex of the mature primate is bordered by a fringe of transitional paralimbic mesocortex, at least in its medial and ventral aspects (Reep, 1984). The cortex of those regions is distinctly agranular, thus phylogenetically more primitive than the granular dorsolateral cortex of the primate. It is on the basis of such differences that [Passingham and Wise \(2012\)](#) conclude that, in the primate brain, the medial and ventral cortex is the remnant of the limbic frontal regions of earlier species, whereas the dorsolateral prefrontal cortex represents the truly new prefrontal cortex of primates.

In any case, Pandya and his colleagues adopted Sanides' concept of developmental architectonic trends and, as noted above, complemented it with evidence of the corticocortical connectivity underlying those trends ([Barbas and Pandya, 1989; Pandya and Yeterian, 1990a; Yeterian et al., 2012](#)). Those connective trends clearly follow gradients from paralimbic, agranular, to granular prefrontal cortex.

The robust anatomical relationship between the prefrontal cortex and the mediodorsal thalamic nucleus has been known since the late nineteenth century ([Monakow, 1895](#)). Many studies demonstrate that the fiber connections between those two structures are organized according to a definite topological order ([Walker, 1940b; Rose and Woolsey, 1948; Pribram et al., 1953; Akert, 1964; Narkiewicz](#)

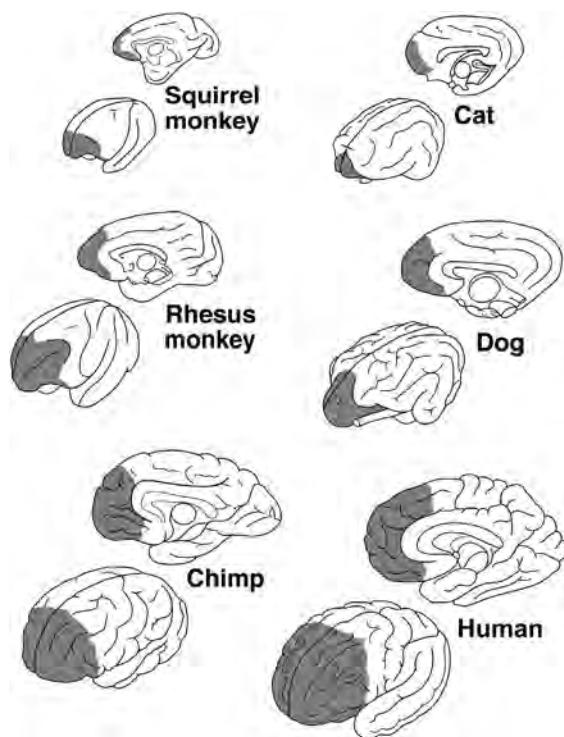
[and Brutkowski, 1967; Tanaka, 1976, 1977; Kievit and Kuypers, 1977](#)). In the light of this fact, some parallels can be expected in the phylogenetic development of the two structures. There is some evidence that, like the prefrontal cortex, its projection nucleus (medialis dorsalis) becomes larger in relation to phylogeny; this evidence, however, is far from indisputable, since, once again, problems of homology remain unresolved and too few species have been studied to reconstruct development ([Clark, 1930, 1932; Ariëns Kappers et al., 1960](#)). Furthermore, the apparent asynchronies in the parallel growth of the mediodorsal nucleus and the prefrontal cortex prevent us from concluding that the two structures develop strictly *pari passu*. One such asynchrony may be observed in the transition to the human and larger apes, where the enormous growth of the prefrontal cortex apparently outstrips that of its thalamic projection nucleus. Could that difference in growth be attributable to the greater functional importance that corticocortical projections acquire in higher species?

A related peculiarity of phyletic development may have considerable functional significance. There is a disparity in the growth of different sectors of the prefrontal cortex and a corresponding disparity in the growth of the different portions of the mediodorsal nucleus to which they are connected. Thus, both the parvocellular portion of the nucleus and the cortex of the lateral prefrontal convexity to which it projects undergo phylogenetically more enlargement, up the primate scale, than do the magnocellular portion and the corresponding (orbital) projection area ([Pines, 1927; Clark, 1930; Khokhryakova, 1979](#)). It is tempting to speculate that the greater growth of the parvocellular nuclear component and of the lateral prefrontal cortex reflects the increasing importance, in the high species, of the cognitive functions that they support. However, too little is still known about the comparative aspects of behavior and of dorsomedial thalamic function

to substantiate this speculation (Warren, 1972). Nonetheless, correlations have been noted between phylogenetic development and degree of proficiency in the performance of certain behavioral tasks – delayed response and alternation – for which the prefrontal cortex has been shown to be essential (Harlow et al., 1932; Maslow and Harlow, 1932; Tinklepaugh, 1932; Rumbaugh, 1968; Masterton and Skeen, 1972).

However imprecise the developmental parallels may be between the mediiodorsal nucleus and the prefrontal cortex, and however uncertain the physiological role of their anatomical relationships, those relationships have become a criterion for homologizing and defining the prefrontal region (Rose and Woolsey, 1948; Akert, 1964; Uylings and Van Eden, 1990). By the use of this criterion, a prefrontal cortex can be identified even in the relatively undifferentiated brain of marsupial mammals (Bodian, 1942). Connectivity is, by and large, a more universally applicable criterion than is cytoarchitecture and than is the topology or the topography of the region. The ultimate corroboration of its value would be the demonstration that structural homologies thus determined are the foundation of functional homologies. In any case, as we will see below, corticocortical connectivity has been lately growing in functional importance with the increasing recognition that cortical neuronal networks are the essence of cognition. Some have, in fact, noted that the large, almost “explosive” development of corticocortical connectivity is a distinctive trait of primate evolution (Adrianov, 1978). In any case, a better anatomical definition of the prefrontal cortex is one that includes not only the criterion of thalamocortical projection but also morphology and corticocortical connectivity (Pandya and Yeterian, 1996).

Figure 2.2 illustrates the prefrontal cortex in some brains widely used for neurophysiological and neuropsychological study. The display is not intended to represent a phyletic scale in the proper sense. For the purpose of delineating the



**FIGURE 2.2** The prefrontal cortex (shaded) in six mammalian species.

prefrontal region, the author has been primarily guided by descriptions of thalamocortical projections, especially those by Walker (1938, 1939, 1940b), Rose and Woolsey (1948), Pribram et al. (1953), Hassler (1959), Akert (1964), and Narkiewicz and Brutkowski (1967). Where there is still uncertainty about thalamic projection, corticoarchitectonic descriptions are used. This is feasible and appropriate at least in primate brains, where the cytoarchitectonically defined frontal granular cortex coincides, at least roughly, with that defined by mediiodorsal projection.

Historically, it has been fashionable to associate the exceptional cognitive abilities of the human in language, temporal integration, technical skill, and other areas with the disproportionate volumetric increase in the prefrontal cortex in the human. In support of that

association is the finding that the increase is more pronounced in the left than in the right hemisphere (Smaers et al., 2011); this observation agrees with the supremacy of the human in cognitive functions such as language and reasoning, which are heavily lateralized in the left hemisphere. It is somewhat simplistic, however, to attribute the cognitive advantage of the human simply to increased volume or increased cortical folding (Toro et al., 2008), which implies a larger surface of gray matter. Despite the reality of these changes, whether we adopt a cytoarchitectonic or hodological definition of the prefrontal cortex, that cognitive advantage may rest more on evolutionary changes in other structural variables that have been revealed in the past few years: relative prefrontal increases in the width of cortical layers (Semendeferi et al., 2001), neurochemical factors such as dopaminergic afferents (Raghanti et al., 2008), neuron packing density (Roth and Dicke, 2012), and dendritic arborization (Teffer and Semendeferi, 2012).

Because of the importance of cortical connectivity for cognitive functions, considerable emphasis has been placed by some (e.g., Schoeneman et al., 2005) on the relative increase in prefrontal white matter in the human brain. The magnitude of that increase, however, has been questioned by others (Sherwood et al., 2005) who nonetheless emphasize, in the human, the probable cognitive role of prefrontal increases in the complexity of internal architecture and connectivity. Nonetheless, the fact remains that, among all cortical regions, the prefrontal cortex of the human is the most heavily interconnected with other cerebral structures. A study of evolutionary white-matter development clearly demonstrates the advantage of the human over the chimpanzee in cortical myelination (Miller et al., 2012). To conclude, in very general terms, the evolutionary increases in the complexity of the cytoarchitecture and connectivity of the prefrontal cortex are, in all probability, related to the richness of human cognition.

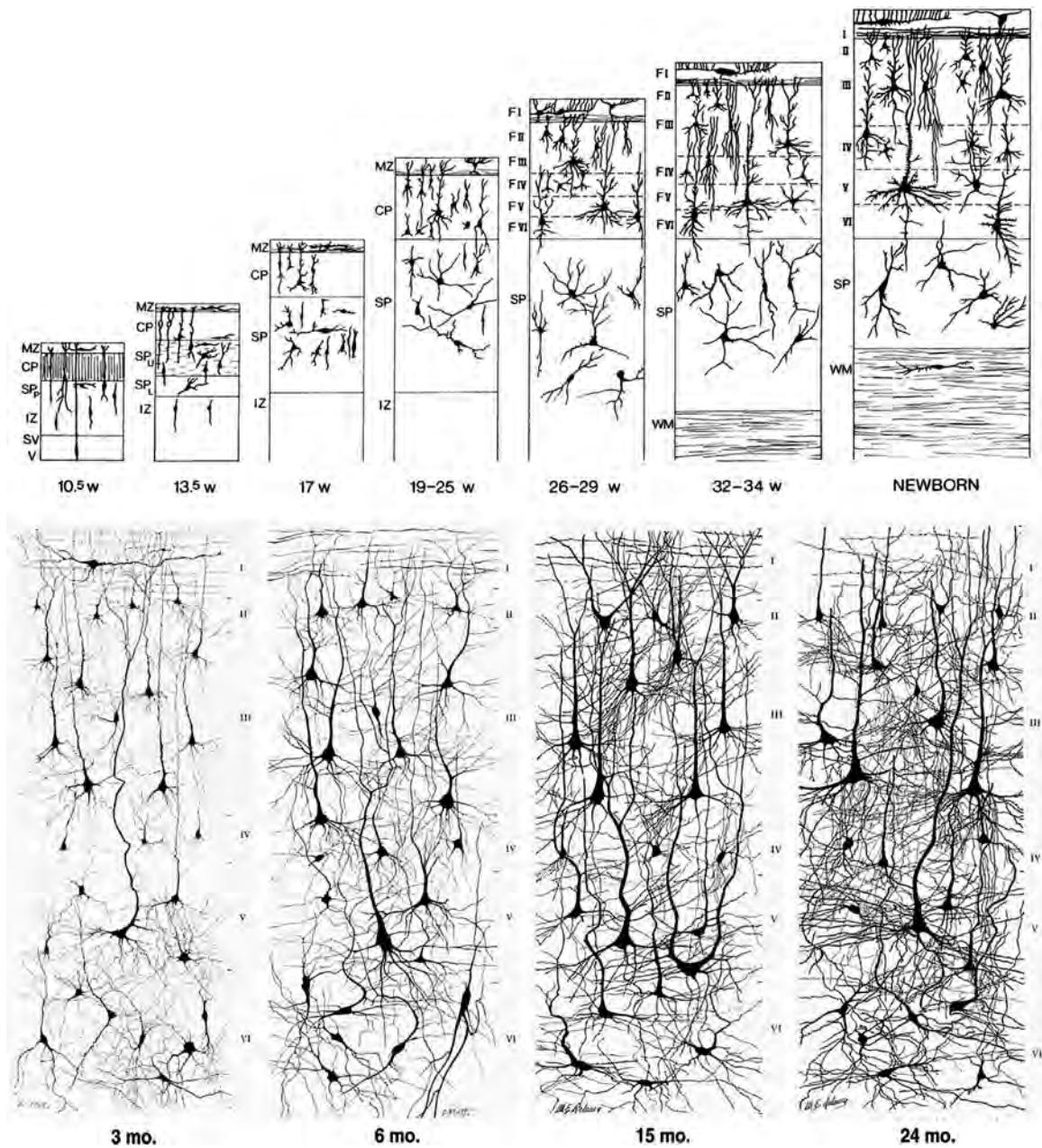
### III. DEVELOPMENT

The genetic development of the prefrontal cortex is still unclear. Presumably, a fibroblast growth factor (FGF) regulates the graded expression of this cortex as, in general, it regulates all rostral telencephalic development (Cholfin and Rubenstein, 2007). It is not known, however, how precisely that FGF or other genetic factors regulate the development and ultimate maturation of the various prefrontal areas.

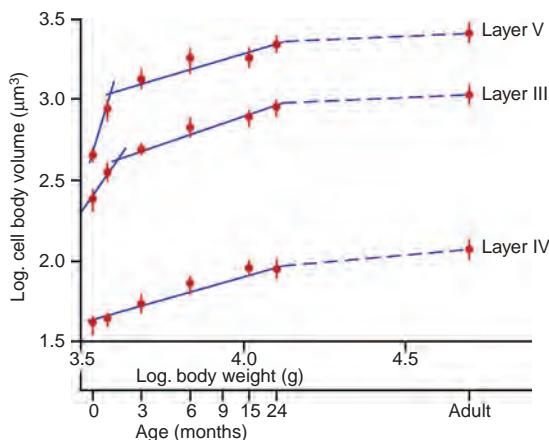
In all mammalian species, the histogenesis and maturation of the prefrontal cortex, like those of the rest of the neocortex, follow characteristic trends of expansion, attrition, cell migration, and lamination (Figure 2.3). Those trends, which are genetically programmed, have been the subject of numerous studies and reviews (Poliakov, 1966a; Angevine, 1970; Sidman and Rakic, 1973; Sidman, 1974; Rakic, 1978; Wolff, 1978; Mrzljak et al., 1988; Uylings et al., 1990; Uylings, 2001).

There is evidence that cortical cell migration and area differentiation occur concomitantly with the arrival of thalamocortical fibers (Marín-Padilla, 1970; Sidman and Rakic, 1973) but not necessarily as a consequence of it (Seil et al., 1974; Rakic, 1976). Glial fibers seem to guide the cells in their migration from the germinal zones, which are adjacent to the ventricle, to their destination in their respective layers (Rakic, 1978).

In rodents, the laminar architecture of the prefrontal cortex does not reach completion until after birth (Van Eden, 1985). In the human, however, the adult configuration of this cortex is already present by the seventh month of uterine life and is virtually complete at birth (Conel, 1939–1963; Larroche, 1966; Mrzljak et al., 1990). At the molecular level, certain prefrontal areas, such as Broca's area, the cortex of areas 44 and 45, of well-demonstrated importance for the spoken language, have been reported to develop under the control of certain special morphogenic genes (Grove and Fukuchi-Shimogori, 2003).



**FIGURE 2.3** Development of neuronal architecture in human prefrontal cortex. *Top:* Prenatal period from 10.5 weeks to birth. (From Mrzljak *et al.*, 1990, with permission.) *Bottom:* 3, 6, 15, and 24 months after birth. (From Cone, 1939–1963, with permission.)



**FIGURE 2.4** Development of cell body volume in human prefrontal cortex. (From Schadé and Van Groenigen, 1961, with permission.)

After reaching their corresponding layers, cortical nerve cells grow their dendrites (Juraska and Fikova, 1979; Mrzljak et al., 1990). In general, the apical dendrites appear and undergo arborization before the basilar ones. In the human prefrontal cortex, at birth, the dendritic arbors are relatively rudimentary and, accordingly, cell volumes are relatively small compared with adult volumes (Schadé and Van Groenigen, 1961). Dendritic density and branching continue to increase relatively rapidly until 24 months of age and at a slower rate beyond that (Figure 2.4). In the rat, there is evidence that the postnatal development of prefrontal dendrites is promoted by, and may even necessitate, environmental experience (Globus et al., 1973; Feria-Velasco et al., 2002; Bock et al., 2005).

At 6 months after birth, in the human, dendritic length is between five and 10 times greater than at birth. In the lateral prefrontal cortex of the human infant, maximum dendritic growth appears to occur between 7 and 12 months, thereafter reaching an asymptote (Koenderink et al., 1994). Neuronal density is maximal at birth and declines thereafter by almost 50% to the adult level, which is already

nearly attained between 7 and 10 years of age (Huttenlocher, 1990).

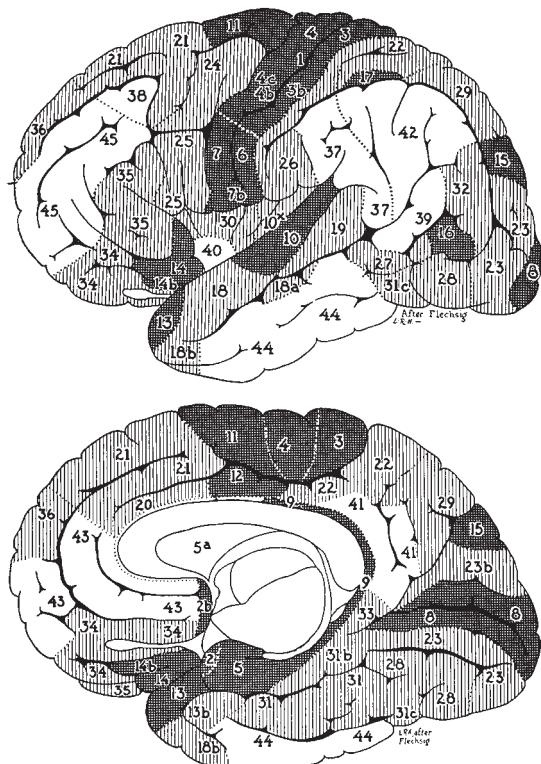
Whereas the basic cytoarchitecture in the human prefrontal cortex is pre-established at birth, its fine development continues for many years. In this cortical region, the fine modeling and differentiation of pyramidal neurons in layer III continues until puberty (Mrzljak et al., 1990). This fact may have momentous implications for cognitive development, since layer III is the origin and termination of profuse corticocortical connections of critical importance for the formation of memory by association (Fuster, 1995, 2003). Such an inference appears all the more plausible by considering that the late maturation of layer III neurons is closely correlated with the development of cholinergic innervation in the same layer (Johnston et al., 1985). Generally speaking, deeper layers – IV, V, and VI – develop earlier and at a faster pace than the more superficial ones – II and III (Poljakov, 1961).

In primates, synaptogenesis has been shown to occur at the same time in all neocortical regions, including the prefrontal cortex. It develops roughly at the same rate throughout the cortex (Rakic et al., 1986, 1994; Bourgeois et al., 1994). In the prefrontal cortex, as elsewhere, synaptic density increases rapidly before birth and, after some perinatal overproduction, descends gradually to the adult level. Some studies in the human (Huttenlocher, 1979; Huttenlocher and de Courten, 1987; Huttenlocher and Dabholkar, 1997) report that prefrontal synaptogenesis appears to lag behind that of other areas (e.g., striate cortex), while also pointing out that synaptic density, after reaching a maximum, undergoes attrition; cell death appears to trim an initial overproduction of neuronal elements and synapses in a long process of stabilization toward adult levels which, according to these studies, is not complete until age 16. The discrepancy between the results of the two sets of studies just mentioned with regard to a prefrontal synaptogenic lag has been interpreted by Rakic and colleagues

(1994) as probably based on methodological differences. Even if there is no prefrontal synaptogenic lag, however, fixed numbers of synapses, whenever they have been formed, do not preclude the enormous potential of the prefrontal cortex for connective plasticity, and thus for learning and memory. There is presumably ample room for the electrochemical facilitation of existing synapses and for thus far imponderable changes in their structure and function.

A well-known, although sometimes also disputed, manifestation of the immaturity of the prefrontal cortex at birth is the absence of stainable myelin sheaths around its intrinsic and extrinsic nerve fibers. From his extensive investigations, Flechsig long ago established that the myelination of cortical areas in the perinatal period follows a definite chronological sequence (Flechsig, 1901, 1920) (Figure 2.5). The last to myelinate are the association areas, the prefrontal among them, where the process not only starts late but also continues for years (Kaes, 1907; Yakovlev and Lecours, 1967). In both the human (Conel, 1939–1963; Brody et al., 1987) and the monkey (Gibson, 1991), myelin develops last in layers II and III. The chronology of myelination has important implications for the development of cognitive functions.

With the discovery of myelogenetic stages, Flechsig launched a much-debated theory: the development of function follows the same sequence as myelination, and is partly dependent on it. A corollary to that theory is that tardily myelinating areas engage in complex functions highly related to the experience of the organism. Flechsig's concepts drew sharp criticism from the most prominent neuroscientists of his day – including Wernicke, Monakow, Nissl, and Vogt – with the notable exception of Cajal (1904, 1955), who praised and defended them. The main difficulties with those concepts can be summarized as follows: (1) staining methods have limitations, and myeloarchitecture is harder to determine reliably than cyto-architecture; and (2) some fibers conduct



**FIGURE 2.5** The order of myelination of cortical areas, according to Flechsig. (From Bonin, 1950, with permission.)

impulses before and without myelination; (3) a temporal correlation between myelination and behavioral development does not necessarily imply a causal link between the two; and (4) an evolutionary trend conflicts with the ontogenetic trend of myelin formation inasmuch as some unmyelinated fiber systems are phylogenetically older than myelinated ones (Bishop, 1965). In that respect and on the basis of behavioral and electrophysiological experiments, it has been argued that some of the association cortices – although not necessarily the prefrontal cortex – are phylogenetically older than the primary sensory cortex (Diamond and Hall, 1969). Nevertheless, none of the stated objections invalidates the orderly pattern of

cortical myelination; nor do they invalidate the myelogenetic principle of functional development, which has obtained considerable support from a number of studies (Langworthy, 1933; Windle et al., 1934; Yakovlev and Lecours, 1967; Lecours, 1975; see more recent review by Guillery, 2005).

Modern neuroimaging (magnetic resonance imaging) studies (Jernigan et al., 1999; Sowell et al., 1999a, 1999b; Bartzokis et al., 2001; Li and Noseworthy, 2002; Toga et al., 2006) provide persuasive evidence that the development of frontal, especially prefrontal, cortex does not reach its completion before the third decade of life or later. According to these studies, that development is characterized by a volumetric reduction of gray matter – presumably accompanied by functional cell selection (Edelman, 1987) – and an increase in white matter (myelination). This neurobiological evidence is in line with the evidence that the higher cognitive functions for which the prefrontal cortex is essential, that is, language, intelligence, and reasoning, which heavily rely on intracortical and corticocortical connectivity (Fuster, 2003), do not reach full maturity until that age. More specifically, neuroimaging provides evidence that (1) in adolescence, together with the maturation of cognitive functions, white matter undergoes enormous growth (Gogtay et al., 2004; Giedd et al., 2013); and (2) the corticocortical axons that develop most between childhood and adulthood are those that run from prefrontal cortex to posterior association cortex. Those axons are part of the top-down frontal efferent pathways critically involved in attentive processes of cognitive control (Bitan et al., 2006; Hwang and Luna, 2013).

In closing this discussion it is worth re-emphasizing the late myelination of layers II and III, another point to ponder with regard to the presumed and already noted importance of neurons in these layers for cognitive function.

Research on the cytoarchitecture and myeloarchitecture of the developing prefrontal cortex

in primates suggests that, as in evolution, its orbital areas mature earlier than do the areas of the lateral prefrontal convexity (Orzhekhovskaia, 1975, 1977). Caviness et al. (1995) provide evidence that neurons in orbital (paralimbic) regions complete their development cycle earlier than those in lateral regions. Insofar as ontogeny and phylogeny are dependent from each other, evidence of this kind is in good harmony with the concepts of phylogeny discussed above (Sanides, 1964, 1970). This evidence, also, has cognitive and behavioral implications that will be discussed in Chapter 4.

The morphological development of the prefrontal cortex is accompanied by the development of its chemical neurotransmission substrate. As is the case for the structure of neurons and synapses, chemical development is also subject to periods of expansion and attrition, although these periods are somewhat longer than for morphological changes. The development of monoamines has been explored in considerable detail in the monkey (Goldman-Rakic and Brown, 1982; Lidow and Rakic, 1992; Rosenberg and Lewis, 1995).

In the human newborn, norepinephrine (noradrenaline) and dopamine are higher in prefrontal cortex than in posterior association cortex, although the reverse is true for serotonin. After birth, cortical monoamines increase gradually to reach their maxima at about age 3 years, and decline thereafter, also gradually, to stabilize at adult levels. Dopamine concentrates more in layer III than in other layers. Again, this is noteworthy in view of the importance of this layer as the source and termination of corticocortical connections, and thus in the formation and maintenance of cognitive networks.

By injecting radioactive amino acids in the fetal prefrontal cortex of the monkey, Goldman-Rakic (1981a, 1981b) succeeded in tracing the prenatal development of corticocortical and corticocaudate projections of this cortex. She concluded that, 2 weeks before birth, both kinds of efferent axons have already reached

their adult targets and distribution. Thus, they do so considerably earlier than other fiber systems (e.g., geniculostriate system). The prefrontal efferents to the caudate at first innervate their targets diffusely, and later in a segregated manner; thus, corticocaudate axons eventually terminate in hollow plexuses surrounding islands of densely packed cells in the mass of the caudate nucleus. The callosal connections between the two prefrontal cortices, right and left, as well as their neurons of origin, also undergo their full development prenatally (Schwartz and Goldman-Rakic, 1991). These findings suggest that the newborn essentially possesses a large fraction of the connective apparatus that the prefrontal cortex will need to interact with other cortical areas and with its principal outlet structures for motor control.

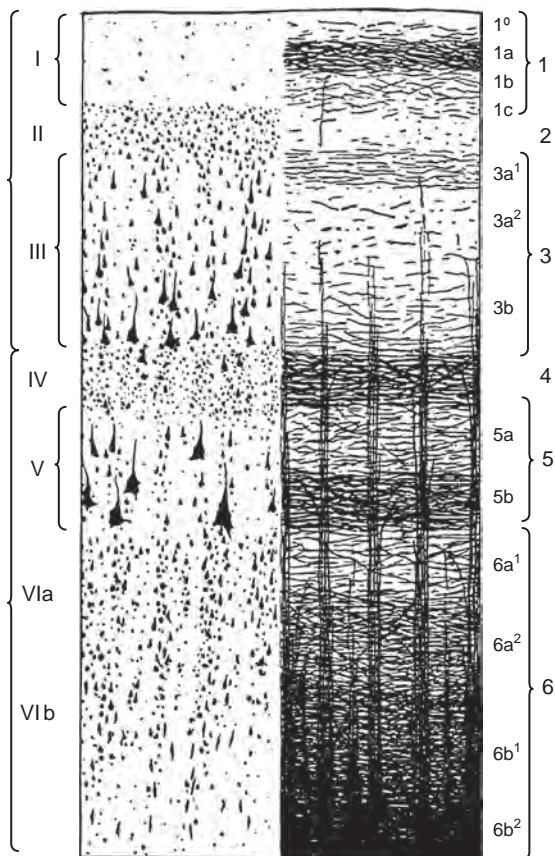
To summarize, the prefrontal cortex develops its structure – cells, synapses, fiber connections, and chemical receptors and transmitters – under the influence of genetic factors and according to a timetable that varies widely from species to species. At every stage of that ontogenetic development, the structural phenotype of the cortex is subject not only to those genetic factors but also to a variety of internal and external influences. Critical among those influences are those that derive from the interactions of the organism with its environment. As a result of those interactions, efferent, afferent, and associative connections are formed and enhanced. It is through those processes that the cognitive networks of the individual are structured in the neocortex at large; through these same processes, executive networks grow in the prefrontal cortex and acquire their controlling properties over behavioral and cognitive neural substrates. Those processes are essentially selective: they select neurons and circuits among those that have been overproduced in earlier stages of development, while other neurons and terminals undergo regression and disappearance. This is what is commonly understood by “selective stabilization.” It is the

result of the competition for inputs on the part of neurons and terminals throughout the nervous system, much as what occurs in the course of evolution at the foundation of natural selection (Edelman, 1987).

## IV. MICROSCOPIC ARCHITECTURE

The architectural order of cells and fibers in the prefrontal cortex basically conforms to the structural plan prevailing throughout the neocortical regions, typified in primates by the microscopic morphology of the so-called isocortex (Vogt and Vogt, 1919; Bailey and Bonin, 1951; Crosby et al., 1962). That plan, as revealed by time-honored histological methods, is hereby illustrated in a classic picture (Figure 2.6). As we see below, certain areas of the prefrontal cortex, notably in its medial and ventral aspects, deviate somewhat from that picture. The structural differences between cortical areas, however, should not obscure their basic similarities. The general features of architecture that are common to all cortical areas, such as the stratified order of cells and plexuses and the regularities in connective patterns, are in all probability of major functional relevance. Furthermore, modern studies increasingly tend to emphasize that, from the functional point of view, cytoarchitectonic differences between cortical areas may not be as important as are the patterns of distribution of afferent fibers, internal connectivity, and the destination of efferent fibers.

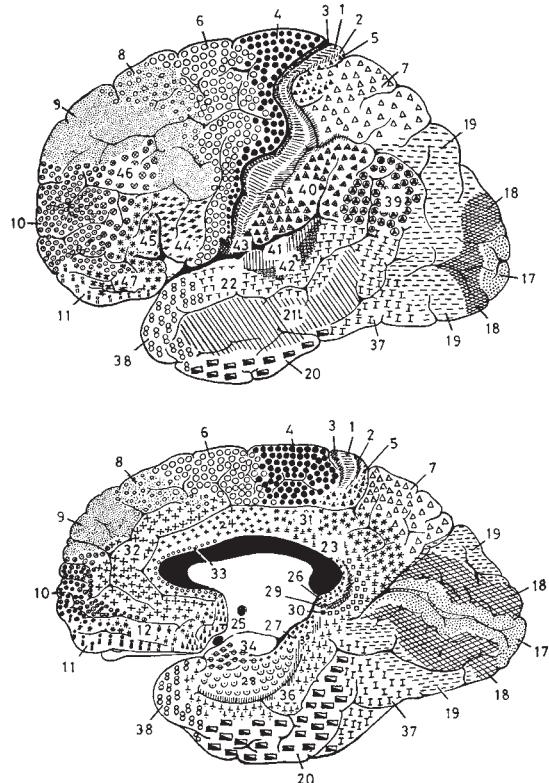
The investigations of cortical architecture, initiated by the Viennese psychiatrist Meynert (1868), culminated at the beginning of the twentieth century with the publication of numerous maps of the cerebral cortex. The most famous maps from that time are those by Campbell (1905), Vogt (1906), Elliott Smith (1907), and Brodmann (1909). Although the main efforts were devoted to mapping the cortex of the human, attempts were also made to



**FIGURE 2.6** The cellular and myelin structure of the cortex, according to Brodmann and Vogt.

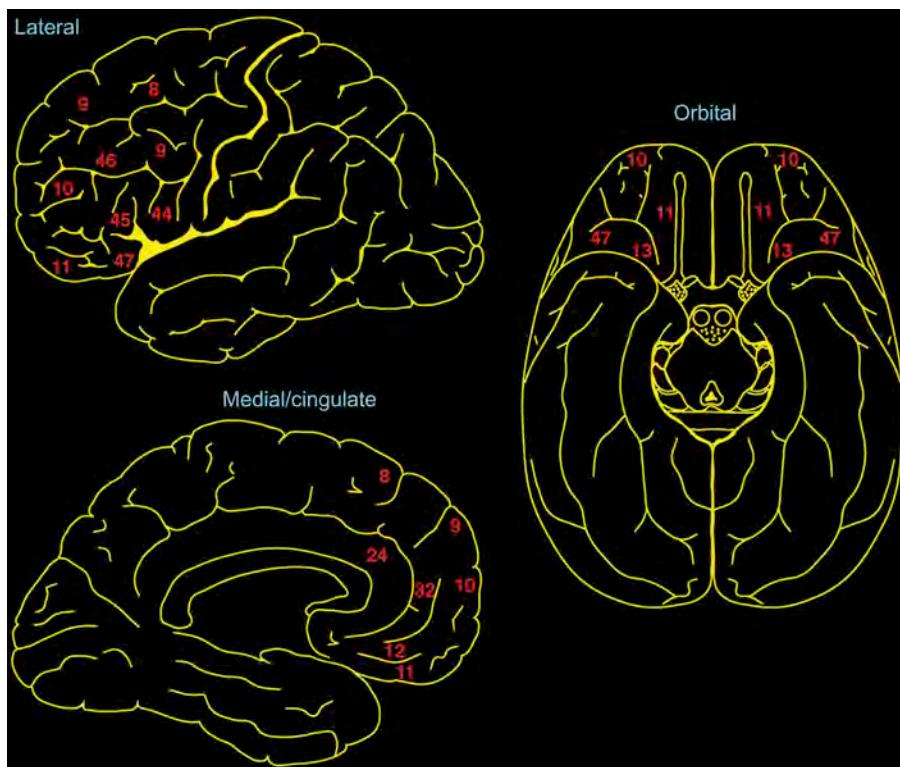
homologize cortical areas in numerous species (Brodmann, 1909). Largely because of differences of architectonic definition, the delimitation of the prefrontal region varies considerably in the better known maps.

The origin of the “prefrontal” designation is uncertain. It is also unimportant, for it seems that from the time it first appeared in the literature, the term meant different things to different writers. It had been used without much precision by neuropathologists and experimentalists before the cortical cartographers used it, but those early writers failed to agree on a definition. Campbell (1905) defined the “prefrontal



**FIGURE 2.7** Brodmann's cytoarchitectonic map of the human cortex. (From Pandya and Yeterian, 1990b, with permission.)

area” as a cap of cortex covering the tip of the frontal lobe and separated from the frontal cortex proper, including much of the granular cortex, by obscure cytoarchitectonic boundaries. For Brodmann (1909), the “area praefrontalis” was an even smaller ventromedially situated area, area 11, within the large “regio frontalis,” which comprises his areas 8, 9, 10, 11, 12, 13, 44, 45, 46, and 47 (Figure 2.7). That region, as a whole, is nearly coextensive with what is now called the prefrontal cortex. Figure 2.8 illustrates schematically the approximate location of prefrontal areas on the three aspects of the human frontal lobe: lateral, orbital, and medial. Petrides and Pandya (1994) published



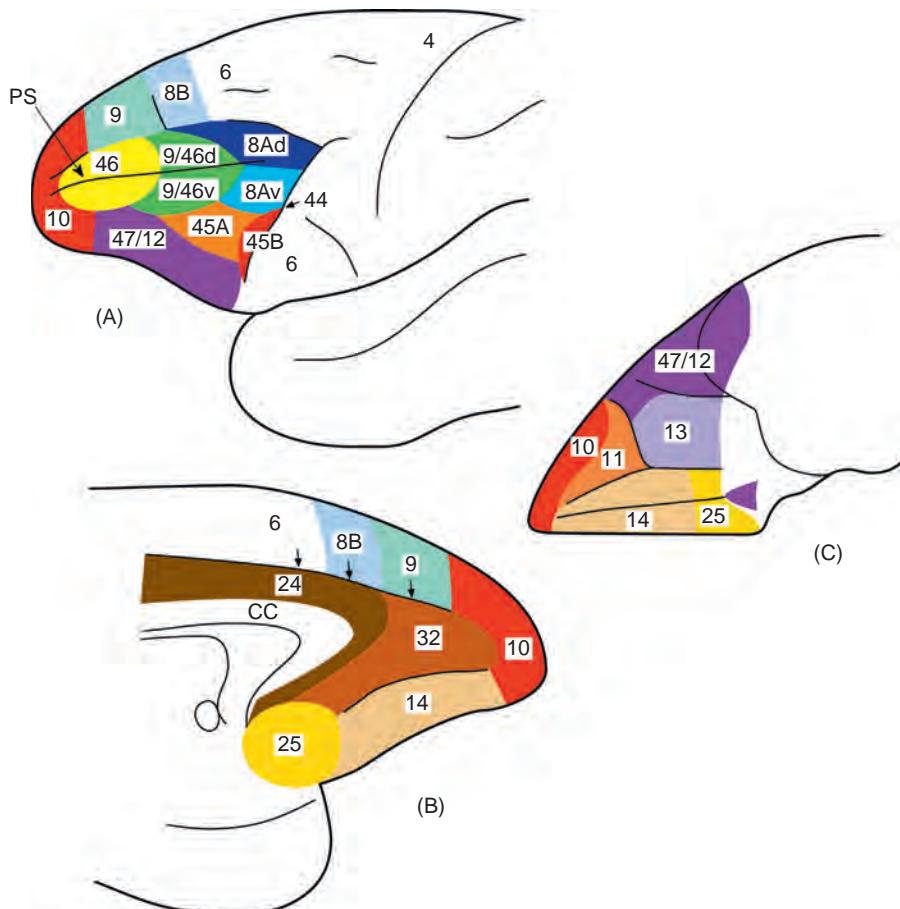
**FIGURE 2.8** Schematic distribution of prefrontal areas on the lateral, orbital, and medial surfaces of the human frontal lobe.

a detailed study of cytoarchitectonic comparisons between the monkey's and the human's prefrontal cortex. [Figure 2.9](#), from that study, shows the monkey's map of cytoarchitectonic areas. More recent work by the same investigators, with the assistance of imaging methods, has refined somewhat the comparative mapping of prefrontal areas in the human and the monkey ([Petrides et al., 2012](#)).

It is not possible, nonetheless, to use microarchitecture as the sole criterion for defining and delineating the prefrontal cortex. One of the principal obstacles is the marked cytoarchitectonic variability from species to species and between individuals of the same species (e.g., the human: [Rajkowska and Goldman-Rakic, 1995](#)), a factor that has made the comparative

cartography of the frontal lobe especially confusing. A more sensible criterion of definition of the prefrontal cortex is the distribution of thalamic fibers. This connective (hodological) criterion is used here for reasons mentioned in Chapter 1, although further research may, in the future, dictate a better – perhaps also connective – criterion. What follows is a brief morphological description of the hodologically defined prefrontal cortex – that is, of the cortical projection area of the mediodorsal nucleus.

In the rat ([Zilles et al., 1989](#)), the prefrontal cortex consists of two major frontal areas of projection of the mediodorsal nucleus: (1) a medial area in the upper edge and medial surface of the hemisphere; and (2) an inferolateral area in the lower and lateral aspect

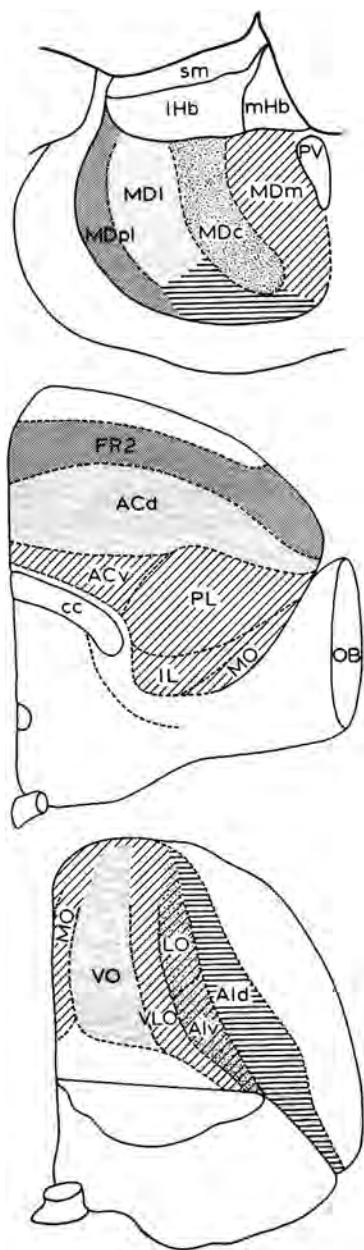


**FIGURE 2.9** Cytoarchitectonic map of the monkey's frontal cortex according to Petrides and Pandya. (A) Lateral view; (B) medial view; (C) inferior (orbital) view. Abbreviations: CC, corpus callosum; PS, principal sulcus. (From Petrides and Pandya, 1994, with permission.)

of the hemisphere, right above the rhinal sulcus; both areas join each other inferomedially (Figure 2.10). In this volume, these two areas of the rodent's prefrontal cortex are designated "medial" or "dorsal" (1) and "sulcal" (2), respectively. The first collects projections from the lateral portion of the mediiodorsal nucleus, the second from its medial portion. Neither of the two areas contains a clear granular layer IV. This fact, among others, has been used to dispute the commonly assumed homology

between the rat's medial (dorsal) prefrontal cortex and the monkey's lateral prefrontal cortex (Preuss, 1995). For an excellent comparative anatomical study of rat and primate prefrontal cortices, the reader is referred to Uylings and Van Eden (1990).

The prefrontal cortex of carnivores is the cortex of the gyrus proreus, which, like the prow (in Latin, *prora*) on a ship, marks the rostral margin of the telencephalon. In the cat, the prefrontal area is almost confined to that gyrus,



**FIGURE 2.10** *Top:* Cross-section of the mediodorsal nucleus of the rat. *Middle:* Medial view of frontal cortex showing areas of projection from the mediodorsal nucleus. *Bottom:* Inferior view of frontal cortex (tip of temporal lobe resected) showing mediodorsal projection. Different parts of the nucleus, shaded differently, project to correspondingly shaded cortical areas. Abbreviations: A Cd, dorsal anterior cingulate cortex; A Cv, ventral anterior cingulate cortex; A Id, dorsal agranular insular cortex; A lv, ventral agranular insular cortex; cc, corpus callosum; FR2, frontal area 2; IL, infralimbic cortex; IHb, lateral habenula; LO, lateral orbital cortex; MDc, mediodorsal nucleus, central part; MDl, mediodorsal nucleus, lateral part; MDm, mediodorsal nucleus, medial part; MDpl, mediodorsal nucleus, paralamellar part; mHb, medial habenula; MO, medial orbital cortex; OB, olfactory bulb; PL, prelimbic cortex; PV, paraventricular nucleus; sm, stria medularis; VLO, ventrolateral orbital cortex; VO, ventral orbital cortex. (From Uylings and Van Eden, 1990, with permission.)

but in the larger brain of the dog it extends ventrally into the gyrus subproreus, laterally into the gyrus orbitalis, and medially into the gyrus pregenualis (Kreiner's nomenclature, 1961);

these three gyri are rudimentary in the cat. The so-called orbital gyrus of the cat is not homologous to that of the dog, for in the cat it lies behind the presylvian fissure and, strictly

speaking (by hodological criteria), is not part of the prefrontal cortex. In both cat and dog the prefrontal region is covered with a six-layer isocortex, but the distinctness of its layers is generally low. Wherever noticeable, layer IV appears as a thin band with low cell density and practically devoid of granule cells (Rose and Woolsey, 1948; Adrianov and Mering, 1959; Kreiner, 1961, 1971; Warren et al., 1962; Akert, 1964). Between the prefrontal and motor areas, in the presylvian sulcus, a transitional zone can be discerned with a faint layer IV and large pyramids in layers III and V. This zone apparently constitutes the frontal eye field (Akert, 1964; Scollo-Lavizzari, 1964), so designated for its physiological properties.

In monkeys, the prefrontal cortex – hodologically defined – is limited by the arcuate sulcus in the lateral surface and by the anterior part of the cingulate sulcus in the medial surface. Both the arcuate and cingulate sulci are small and variable in the relatively lissencephalic brain of the squirrel monkey (*Saimiri*) but are well developed in the macaque. The sulcus principalis is the most significant morphological feature within the lateral area, although that sulcus is also inconstant and difficult to identify in *Saimiri*. In the ventral surface, the prefrontal cortex shows a variable orbital sulcus or sulcal complex that, in the macaque, is commonly constituted by two sagittally oriented and connected sulci forming an H or a Y. In humans and anthropoids, the complexity and variability of the sulcal pattern are such that morphological landmarks cannot be reliably used to determine the posterior boundary of the prefrontal cortex in the lateral and ventral aspects of the hemisphere.

The primate's lateral prefrontal cortex – area FD in the cytoarchitectural maps of Bailey and Bonin (Bonin and Bailey, 1947; Bailey et al., 1950; Bailey and Bonin, 1951), areas 8, 9, 10, 45, 46, and 47 of Petrides and Pandya (1994) – is homotypical isocortex, clearly laminated, with a well-developed internal granular layer (IV) that

differentiates it from the rest of the frontal cortex (Economy, 1929; Walker, 1940a; Bonin and Bailey, 1947; Bailey et al., 1950; Bailey and Bonin, 1951; Akert, 1964; Rosabal, 1967). This layer becomes thicker and more distinct on approaching the frontal pole, although the cortex as a whole becomes thinner. Layer IV contains small pyramids but is primarily constituted by granule cells, small Golgi type II cells that exhibit considerable polymorphism (Cajal, 1904, 1955). The most common are stellate cells, characterized by short dendrites that branch out in the vicinity of the soma and extend in all directions, forming a spherical dendritic field. Their axons, also short, remain within the cortex and form nets around neighboring pyramids. The axonal plexus of layer IV, mostly made of terminal afferent fibers, constitutes the outer strip of Baillarger. The pyramids of layers III and V are larger the closer they lie to layer IV. Another gradient of pyramid size can be observed in the anteroposterior direction, as pyramids become gradually larger toward the posterior prefrontal boundary. There, a transitional zone, area 8 of Brodmann, with large pyramidal cells and a well-developed layer IV, can be differentiated. As in carnivores, that transitional zone appears to represent the frontal eye field (Akert, 1964). In the macaque, this field lies in the concavity marked by the arcuate sulcus.

The cortex of the medial and orbital prefrontal regions is composed of numerous cytoarchitectonically diverse areas that are smaller than those identified by Brodmann, and thus constitute subdivisions of them (Carmichael and Price, 1994). These regions, with the exception of the most anterior orbital region, do not conform to the six-layered – “eulaminated,” granular – architecture of the lateral frontal convexity (Barbas and Rempel-Clower, 1997; Semendeferi et al., 2001). Their architecture is so-called agranular or dysgranular, with prominent and dense deep layers (V and VI) and practically absent layer IV. The immunohistochemical staining of cell-molecular structure

confirms those architectural differences (Condé et al., 1994; Dombrowski et al., 2001). This staining method basically determines the concentration of calcium binding proteins, such as parvalbumin and calbindin, that have differential affinity for different types of neurons and the cortical layers they constitute (see review by DeFelipe, 1997).

The prefrontal cortex of the human extends into the third (inferior) frontal convolution. In the left (dominant) hemisphere, the most posterior part of this convolution, Brodmann's areas 44 and 45, is the seat of Broca's speech area. Architectonically, this area also has a transitional character and does not conform to the granular pattern as well as do more anterior areas (Riegele, 1931; Bailey and Bonin, 1951; Amunts et al., 1999, 2003). The dendritic arborization of its neurons has been reported to be greater than that of neurons in the homologous area of the right (non-dominant) hemisphere (Scheibel et al., 1985). With the assistance of imaging methods, Uylings and collaborators have refined the cytoarchitectonic parcellation of the orbitofrontal cortex (Uylings et al., 2010).

Several studies of cortical function have directed attention to the vertical aggregates of neural elements observable in the neocortex. Although the anatomical substrate of the functionally defined columns (Mountcastle, 1957; Hubel and Wiesel, 1968; Asanuma, 1975) is still uncertain, the revelation of their existence rekindled morphologists' interest in all vertical arrays within the cortical structure. Some such arrays have long been known and can be readily observed in Nissl and Weigert preparations (Figure 2.6); they are present in the prefrontal cortex, although not as conspicuously as elsewhere (Bonin and Bailey, 1947; Bonin and Mehler, 1971). Other vertical formations are the plexuses of terminal thalamic afferents (Lorente de Nó, 1949; Scheibel and Scheibel, 1970), the axons of local chandelier neurons (Lewis and Lund, 1990), and the bundles of apical dendrites traversing the upper cortical layers

(Fleischauer, 1978). In the prefrontal cortex, such bundled dendrites have been shown to be part of pyramidal cells with somas situated as deeply as in layer VI (Sakai, 1985).

By axon labeling methods, it has been demonstrated that corticocortical callosal fibers of prefrontal origin terminate also in the form of vertically oriented and regularly spaced plexuses that traverse the entire width of the prefrontal cortex (Goldman and Nauta, 1977b; Goldman-Rakic and Schwartz, 1982; Schwartz and Goldman-Rakic, 1984). It is worth noting, however, that the axon terminals and collaterals of some prefrontal pyramidal neurons extend several millimeters horizontally beyond the boundaries of the mentioned vertical arrays (Levitt et al., 1993). These fibers seem to form an intrinsic system of lateral connectivity suitable for intra-prefrontal association and other interactions, including lateral inhibition. The organization of vertical terminal plexuses in the prefrontal cortex is discussed further below.

## V. AGING

After adolescence and throughout adult life, the cytoarchitecture of the human cortex appears to be relatively stable (Cragg, 1975; Huttenlocher, 1979) until senescence. Nonetheless, whereas early reports of gradual loss of cortical cells as a function of age (Brody, 1955) were disputed on methodological and empirical grounds (Cragg, 1975), some degree of age-related cell degeneration and loss seems to occur, particularly in frontal and temporal areas (Haug et al., 1981; Terry et al., 1987; Lemaitre et al., 2005). The prefrontal cortex is among the brain regions most likely to show these changes, which at the macroscopic level manifest themselves in the form of thinning (Salat et al., 2004), decreased volume (Raz et al., 1997; Van Petten et al., 2004), and density (Tisserand et al., 2002, 2004) of prefrontal gray matter. Age-related cell loss has also

been reported in the prefrontal cortex of the rat (Stein and Firl, 1976) and the monkey (Brizzee et al., 1980; Peters et al., 1994). In the monkey, the most conspicuous changes occur in lateral prefrontal cortex, where research has also demonstrated age-related reductions in microcolumnar structure (Cruz et al., 2004), in synapses and dendritic spines (Peters et al., 1998; Duan et al., 2003), and in myelination of fibers (Peters and Sethares, 2002).

In the human, white matter volume, which in at least one study (Bartzokis et al., 2001), has been shown to increase until age 45 and begins to diminish thereafter (below). These changes are undoubtedly detrimental to the connectivity of associative prefrontal cortex, which is of fundamental importance for such cognitive functions as working memory, decision-making, and the perception-action cycle.

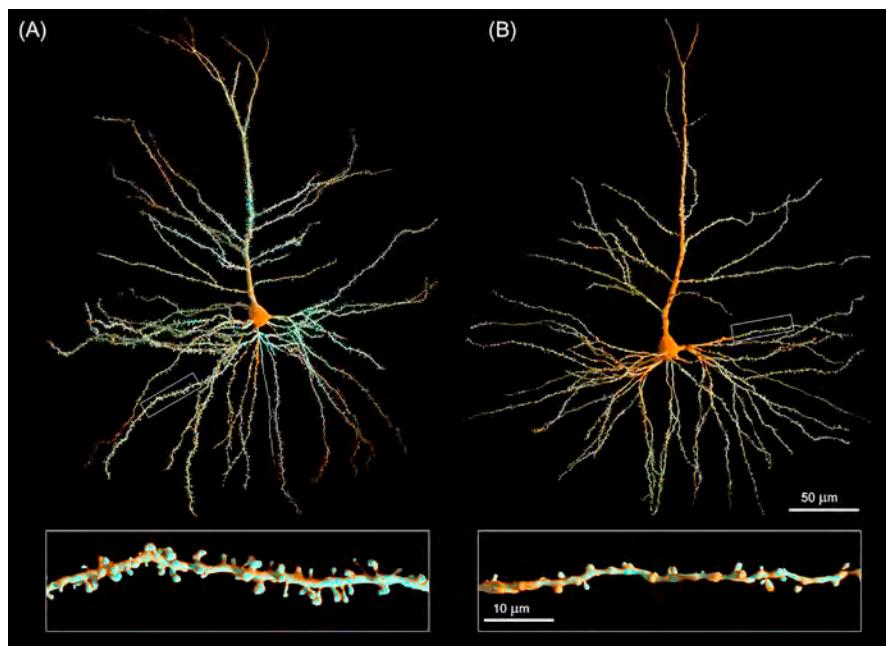
In the seventh or eighth decade of the life of the human, several manifestations of involution are consistently found in the prefrontal cortex (Uemura and Hartmann, 1978; Huttenlocher, 1979; Haug et al., 1981, 1983; Terry et al., 1987; Liu et al., 1996; de Brabander et al., 1998; Uylings and de Brabander, 2002). The size, volume, and density of cells are generally decreased, probably in part as a result of defective protein metabolism, as suggested by diminished RNA levels and deficits in gene transcription and expression; the revelation of these deficits has led to the characterization of a “molecular profile” of the aging human prefrontal cortex (Erraji-Benckroun et al., 2005).

Much of the decrement in neuronal size is attributable to shrinkage and disappearance of dendrites (Scheibel et al., 1975; de Brabander et al., 1998; Uylings and de Brabander, 2002). That age-dependent attrition of dendrites, which has been substantiated also in the monkey (Cupp and Uemura, 1980; Peters et al., 1994, 1998; Duan et al., 2003; Morrison and Baxter, 2012), is consequently accompanied by a decrease in synaptic density (Uemura, 1980; Huttenlocher, 1979; Peters et al., 1998);

all dendrites, basal as well as apical, seem to lose synaptic spines in the aging prefrontal cortex. The axons of some prefrontal neurons, especially pyramidal cells of layer III, exhibit a spindle-shaped enlargement of their proximal segment (Braak et al., 1980). Morphological changes of prefrontal neurons, such as the last one mentioned, are commonly precursors of the intracellular deposit of substances (e.g., lipofuscin,  $\beta$ -amyloid peptides) associated with nerve cell degeneration (Hartig et al., 1997).

Several studies have shown, in humans and monkey, correlations between cognitive decline and some of the noted age-related microscopic changes in the prefrontal cortex (Cruz et al., 2004; Tisserand et al., 2002, 2004; Morrison and Baxter, 2012). Because of their importance for neuroplasticity and cognitive function, two age-related morphological alterations appear critical: (1) a decrement in synaptic contacts; and (2) a decrement in axonal myelin.

The age-related decrement in synaptic contacts is the subject of a review by Morrison and Baxter (2012). The emphasis of the review is the progressive loss of thin dendritic spines observed as a function of age in the pyramidal cells of the prefrontal cortex of aging monkeys. The most remarkable finding is that, whereas the number of neurons and the length of their dendrites are relatively preserved, the thin dendrites show a clear, age-dependent, loss of spines – that is, of synaptic contacts (Figure 2.11). The synaptic changes are most severe in cortical layers II and III (Peters et al., 2008), which are the source and termination of corticocortical axons, extremely important for the formation of cognitive networks or *cognits* (Fuster, 2003). Reportedly, those changes in synaptic connectivity are accompanied by some attrition of microarchitectural minicolumns. Arnsten and her colleagues (Wang et al., 2011), who have studied in depth the age-dependent decline of prefrontal cognitive function, have observed close correlations between deficits in working memory, neuronal activity, and synaptic



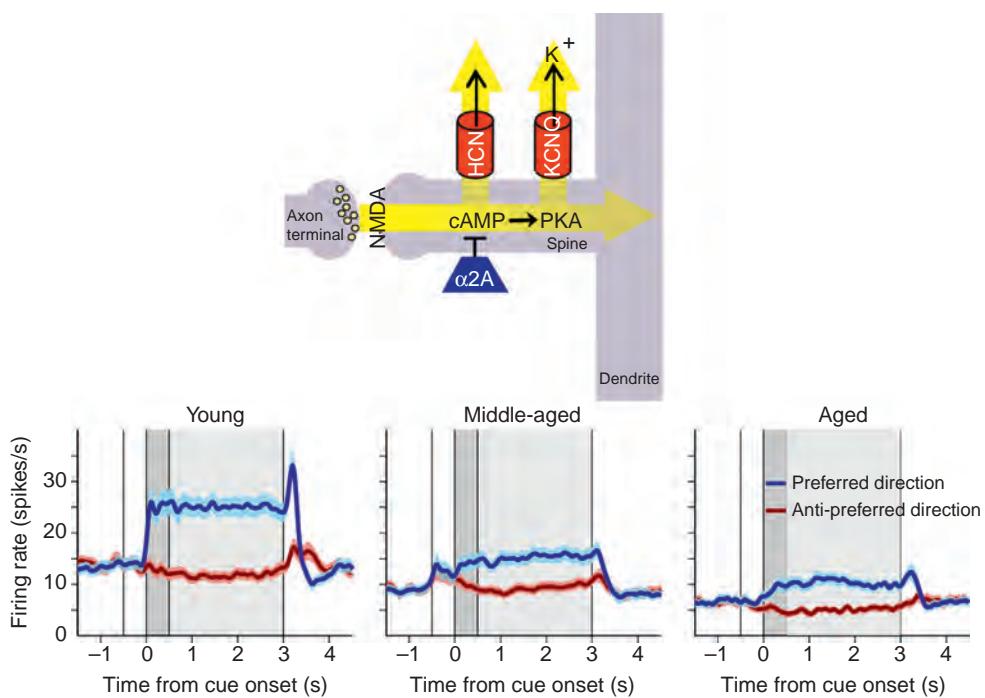
**FIGURE 2.11** Prefrontal neuron synaptic spines in young and aged monkeys, as viewed by laser-scanning microscopy. The rectangles mark segments of basal dendrites. Note the paucity and lesser volume of dendritic spines in the old (A) compared to the young (B) animal. (*From Morrison and Baxter, 2012*, with permission.)

function in the prefrontal cortex of aging monkeys (Figure 2.12). It is hypothesized that age-related decreases in synaptic connectivity lead to failure of intraspine cyclic adenosine monophosphate to mediate the sustained activation of prefrontal neurons during the memory period of delay tasks.

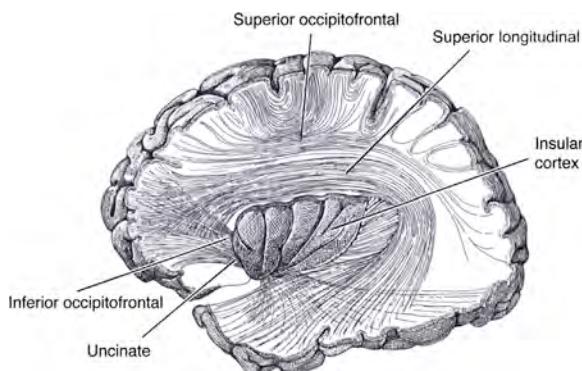
The age-dependent decrement in axonal myelin takes place mainly in long axons that are part of the longitudinal fasciculi and connect frontal with posterior cortex (Figure 2.13). These axons are part of re-entrant circuits that engage the two major sectors of associative cortex, of critical importance for working memory, top-down cognitive control, and the perception-action cycle. Beginning in normal individuals at age about 45, there is a gradual breakdown of myelin in those axons (Figure 2.14), which can be best demonstrated by

structural anatomy (Marner et al., 2003) and imaging, including diffusion tensor imaging (Bartzokis et al., 2001, 2012; Bartzokis, 2004; Lu et al., 2011, 2013).

As may be expected, the relationship between prefrontal morphological change and cognitive deficit is especially apparent in patients with dementia of the Alzheimer or the Pick (frontotemporal) type (Gutzmann, 1984; Liu et al., 1996; Salat et al., 1999, 2001; Uylings and de Brabander, 2002; Bussiere et al., 2003; Bubber et al., 2005). At the molecular level, cells in the prefrontal cortex of Alzheimer's patients are reported to contain messenger RNA that encodes  $\beta$ -amyloid protein, an abnormal protein related to the development of neurofibrillary tangles, which is one of the characteristic degenerative signs of the disease (Bahmanyar et al., 1987; Hartig et al., 1997). Prefrontal pyramids, especially in layers III and V,



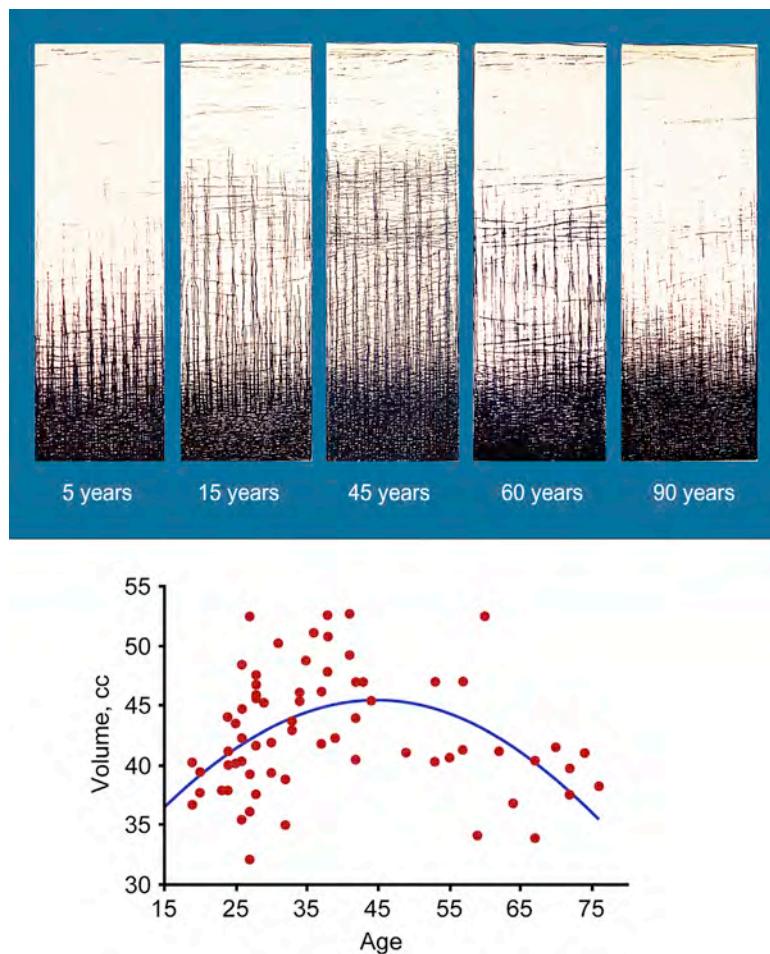
**FIGURE 2.12** Top: Regulation of network firing strength by cyclic adenosine monophosphate (cAMP). Schematic of one of the dendritic spines that are supposed to play an essential role in working memory. The synaptic strength, and thus postsynaptic cell discharge, is modulated by cAMP–protein kinase (PKA) signaling, which regulates nucleotide-gated channels (HCN and KCNQ). Abbreviations:  $\alpha$ 2A, adrenoreceptor; NMDA, *N*-methyl-D-aspartate receptor (glutamate receptor). Bottom: Age-dependent changes in average firing of prefrontal neurons in working memory, as recorded in young, middle-aged, and aged monkeys. The dark gray time period coincides with the presence of the cue or memorandum, light gray with the memory period. Note that the increased firing of the cells during the memory period – after the cell-preferred cue – diminishes as a function of age. (From Wang et al., 2011, modified, with permission.)



**FIGURE 2.13** The four major white-matter fasciculi, bundles of myelinated fibers that link cortical areas within each cortical hemisphere.

seem exceptionally liable to the degenerative changes of Alzheimer's disease (Hof et al., 1990; Bussiere et al., 2003).

It is hazardous to draw general conclusions about the development and involution of neural structures, especially when those conclusions are deemed to apply to more than one animal species. Yet, on the basis of the neuro-anatomical and neuropathological findings noted in this section, it is plausible to infer that those parts of the neocortex that evolve last, including the prefrontal cortex, are the first to undergo involution and also the most vulnerable to geriatric disorder.



**FIGURE 2.14** Myelination and demyelination in the prefrontal cortex of the normal human as a function of age. *Top:* Postmortem myelin stains of anterior frontal cortex from subjects of different age (by Kaes, 1907). *Bottom:* *In vivo* magnetic resonance imaging data (Bartzokis et al., 2001) using inversion recovery images, which are especially sensitive to the high cholesterol levels in myelin. (From Bartzokis, 2011, modified, with permission.)

## VI. CONNECTIONS

At the beginning of the twentieth century, Monakow (1904) used the evidence of retrograde degeneration in the thalamus after a frontal lesion as an argument against the association theory espoused by Flechsig (1901, 1920): if the prefrontal cortex received such copious afferent fibers from a thalamic nucleus, it could

hardly be alleged that its role is simply one of associating neural events occurring in other cortical areas. At that time the cortical connections of the prefrontal cortex were far from clear in any case. As we shall see, the evidence we now have on those connections, although not sufficient to fully vindicate Flechsig or to substantiate his most gratuitous functional assertions, goes a long way toward endorsing

the associative character and functions of the prefrontal cortex. Recent investigations have revealed a great profusion of connections, especially in primates, between the prefrontal region and other cortical areas implicated in sensory and motor processing.

By the early 1960s, the development of new silver-staining methods provided a major thrust to the research into those connections, especially in the rhesus monkey. Perhaps not entirely by coincidence, that research occurred at about the time that Norman [Geschwind \(1965\)](#), in a remarkable synthesis of clinical and experimental data, postulated the disruption of various cortical interconnections as the pathogenetic foundation of neurological syndromes involving the higher integrative functions, including speech. Since then, by the application of autoradiography, axon transport methods, fluorescent dyes, and immunohistochemistry to the tracing of neural connections, we have obtained a detailed, although not yet complete, picture of the connectivity of the frontal lobes, especially in non-human primates. Our knowledge of corticocortical connectivity in the human, however, is still lagging behind. Given the cytoarchitectonic homologies between human and monkey, it seems legitimate, as some have done (e.g., [Mesulam, 1998](#)), to extrapolate to the human the corticocortical connectivity that has been so far substantiated in the monkey. But the ever more pressing evidence from brain imaging studies, which demonstrates the widely distributed and variable character of cortical networks, makes it imperative to further scrutinize corticocortical connectivity in the human in order to better understand the complexities of cognition.

Nonetheless, in recent years it has become increasingly evident that the prefrontal cortex is very much involved in emotional and social behavior. Certain portions of this cortex, notably its medial and orbital regions, which form in early development and which are closely tied to limbic structures, are implicated in the

control of emotions and of the autonomic nervous system. A complex system that includes the posterior medial and orbital prefrontal areas ("paralimbic" prefrontal cortex), as well as the hypothalamus, the anterior thalamus, and the amygdala, appears essential for the evaluation of the emotional significance of environmental events and for decision-making. This evidence has shown the functional significance of the connections between those prefrontal areas and those subcortical centers, connections that in previous editions of this book were generally treated in a descriptive manner and without substantially elaborating on their functional importance. In this edition, that connectivity is emphasized and its functional implications are updated.

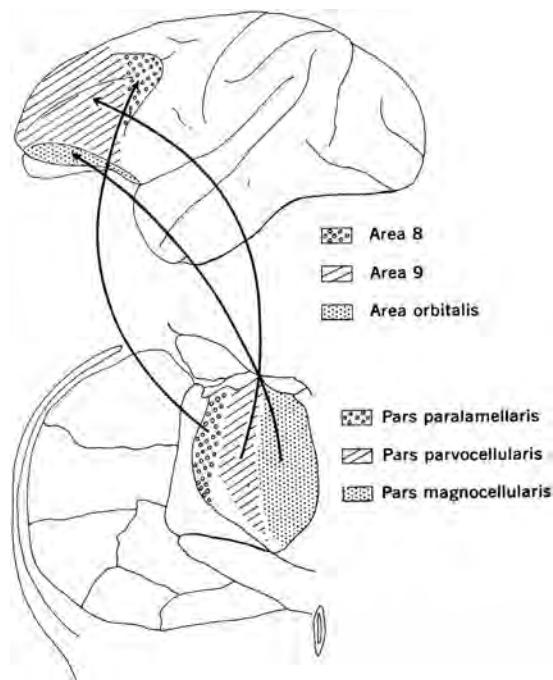
## A. Afferents

The most prominent subcortical afferents come to the prefrontal cortex from the mediodorsal nucleus. Such afferents have been well documented in the rat ([Leonard, 1969](#); [Jones and Leavitt, 1974](#); [Krettek and Price, 1977](#); [Divac et al., 1978a, 1978b, 1993](#); [Condé et al., 1990](#); [Uylings and Van Eden, 1990](#)), the mouse ([Guldin et al., 1981](#)), the rabbit ([Rose and Woolsey, 1948](#)), the cat ([Rose and Woolsey, 1948](#); [Warren et al., 1962](#); [Akert, 1964](#); [Leonard, 1972](#); [Markowitsch et al., 1978](#); [Martínez-Moreno et al., 1987](#); [González and Avendaño, 1989](#); [Musil and Olson, 1991](#); [Tanibuchi, 1992](#)), the dog ([Akert, 1964](#); [Narkiewicz and Brutkowski, 1967](#); [Sychowa et al., 1968](#); [Kosmal, 1981](#)), non-human primates ([Walker, 1936, 1938](#); [Mettler, 1947a](#); [Chow and Hutt, 1953](#); [Pribram et al., 1953](#); [Akert, 1964](#); [Tanaka, 1976](#); [Kievit and Kuypers, 1977](#); [Goldman-Rakic and Porrino, 1985](#); [Barbas et al., 1991](#); [Ray and Price, 1993](#)), and the human ([Meyer et al., 1947](#); [Freeman and Watts, 1948](#); [McLardy, 1950](#); [Hassler, 1959](#); [Van Buren and Borke, 1972](#); [Klein et al., 2010](#)). The projections of the mediodorsal nucleus reach the prefrontal cortex as part of the

anterior thalamic radiations and the inferior thalamic peduncle (Crosby et al., 1962). These projections appear to be topologically organized in all species, although some details of that organization are still unclear (for a review, see Steriade et al., 1997).

In primates, the mediodorsal nucleus has two major cytoarchitectonically different components: a medial component, called magnocellular because of the large size of its cells, and a lateral one, with mostly small cells, called parvocellular (Clark, 1930; Walker, 1938; Olszewski, 1952). This division of the nucleus is difficult and debatable in mammals other than primates. In phylogenetically ancient primate species, the magnocellular component is better represented than is the parvocellular one, whereas the reverse is true in newer species. The magnocellular portion projects mainly to the orbital and medial prefrontal cortex (of early phylogenetic and ontogenetic development), and the parvocellular portion projects mainly to the (newer) cortex of the lateral prefrontal convexity (Walker, 1938, 1940b; Pribram et al., 1953; Akert, 1964; Tanaka, 1976; Goldman-Rakic and Porrino, 1985; Barbas et al., 1991) (Figure 2.15). A lateral segment of the nucleus, the pars paralamellaris, situated between the parvocellular subdivision and the internal lamina, projects to Brodmann's area 8, the frontal eye field (Pribram et al., 1953; Scollon-Lavizzari and Akert, 1963; Akert, 1964; Barbas and Mesulam, 1981). Despite the noted preferences of projections, however, it should be noted that any component of the nucleus mediodorsalis projects to some degree to more than one prefrontal region (Pandya and Yeterian, 1996). In addition to afferents from the mediodorsal nucleus, area 8 receives afferents from the pulvinar (Trojanowski and Jacobson, 1974, 1976; Bos and Benevento, 1975).

Contrary to previous suppositions, it appears that all areas of the primate's prefrontal cortex, as traditionally defined by cytoarchitecture and morphology, receive afferents



**FIGURE 2.15** Projections to the prefrontal cortex from different portions of the mediodorsal nucleus of the thalamus in the monkey.

from one portion or another of the mediodorsal nucleus. In the monkey, medial areas formerly presumed to be athalamic were found to receive some projections from the caudal and dorsal portions of the nucleus (Tobias, 1975; Tanaka, 1976; Barbas et al., 1991). In general, and on the basis of early work (Meyer et al., 1947; Freeman and Watts, 1948; McLardy, 1950; Hassler, 1959; Van Buren and Borke, 1972), the distribution of fibers from the mediodorsal nucleus in the human prefrontal cortex appears to conform to the distribution observed in other primates. In the light of the monkey evidence mentioned above, that distribution can be reasonably assumed to include the cortex of the anterior cingulate sulcus and gyrus (areas 24 and 32). This is an important consideration to keep in mind in view of the neuropsychological interest that this cortex has attracted.

As recognized by early investigators (Nauta, 1964, 1971, 1972; Leonard, 1972), the mediodorsal nucleus undoubtedly relays to the prefrontal cortex neural influences from many other subcortical structures. Anatomical studies have shown that its medial component, the pars magnocellularis, collects afferents from the mesencephalic reticular formation (Guillery, 1959; Velayos and Reinoso-Suárez, 1982) and from structures of the temporal lobe, namely, the amygdala (Nauta, 1972; Krettek and Price, 1974, 1977; Porrino et al., 1981; Ray and Price, 1993), the prepiriform cortex (Powell et al., 1965; Ray and Price, 1993), and the inferior temporal cortex (Whitlock and Nauta, 1956; Ray and Price, 1993). By contrast, the lateral (parvocellular) component appears relatively free of afferents from other than the prefrontal cortex itself (Nauta, 1972). However, both components of the mediodorsal nucleus have been shown to receive projections from the substantia nigra, pars reticulata (Ilinsky et al., 1985) and are thus presumed to relay to the prefrontal cortex input related to movement. Also probably related to movement are the inputs from the cerebellum and the globus pallidus that are relayed to lateral prefrontal cortex – in the monkey – by the mediodorsal and ventrolateral nuclei of the thalamus (Middleton and Strick, 1994).

Other thalamic nuclei project to the prefrontal cortex, notably the nucleus ventralis anterior, the rostral intralaminar nuclei (Nauta and Whitlock, 1954; Scheibel and Scheibel, 1967; Carmel, 1970; Martinez-Moreno, 1972; Jones and Leavitt, 1974; Kievit and Kuypers, 1975b, 1977; Krettek and Price, 1977; Goldman-Rakic and Porrino, 1985; Morecraft et al., 1992; Cavada et al., 2000), and the pulvinar (Goldman-Rakic and Porrino, 1985; Barbas et al., 1991; Cavada et al., 2000). Before they were anatomically confirmed, the afferents from the nuclei of the diffuse thalamic projection system had been inferred from electrophysiological findings, which suggested their widespread and non-topological distribution

over the frontal region (Starzl and Whitlock, 1952). However, investigations by Kievit and Kuypers (1977) and by Goldman-Rakic and Porrino (1985) in the monkey not only confirmed the described topological order of prefrontal projections from the mediodorsal nucleus but also demonstrated that the order holds for projections from other thalamic nuclei. According to the first two investigators, the thalamic cells projecting to the prefrontal cortex form a series of roughly vertical and parallel slabs that cut across lamina interna and nuclear borders. They extend from the medial pulvinar in the back through the medialis dorsalis to the ventralis anterior and the intralaminar nuclei in the front. The most medial slab, adjacent to the midplane, projects to the orbitofrontal cortex; the others project to respective transverse sectors or strips of the prefrontal convexity, between the frontal pole and the arcuate sulcus. Thus, progressively more caudal parts of the cortex receive afferents from progressively more lateral thalamic neurons.

This arrangement of connections suggests that the hodological definition of prefrontal cortex would have to be modified to include, in addition to mediodorsal nucleus projections, the projections from those other thalamic nuclei. Such a qualification, however, would not probably change much, if at all, the cortical territory defined. In any event, most of the thalamic neurons projecting to the prefrontal cortex (over 80%) are located in the mediodorsal nucleus (Barbas et al., 1991).

Not all the subcortical and limbic inputs to the prefrontal cortex are relayed by thalamic neurons. Axonal transport studies have demonstrated direct afferents from the brainstem tegmentum (Llamas et al., 1975; Reinoso-Suárez and Llamas, 1975; Divac et al., 1978a, 1978b; Porrino and Goldman-Rakic, 1982), the pons (Arnsten and Goldman-Rakic, 1984), the hypothalamus (Kievit and Kuypers, 1975a, 1975b; Jacobson et al., 1978; Rempel-Clower and Barbas, 1998), and the amygdala (Krettek and

Price, 1974; Jacobson and Trojanowski, 1975; Llamas et al., 1977, 1989; Divac et al., 1978b; Porrino et al., 1981; Barbas and De Olmos, 1990; Granato et al., 1991; McDonald, 1991; Morecraft et al., 1992; Cavada et al., 2000; Barbas et al., 2002, 2011). The amygdalar projections, as do many other limbic inputs, terminate mainly in medial and orbital areas of the prefrontal cortex (Porrino et al., 1981; Amaral and Price, 1984; Llamas et al., 1989; Barbas and De Olmos, 1990; McDonald, 1991; Morecraft et al., 1992; Barbas et al., 2011). In the rat, cat, and monkey, the prefrontal cortex has also been reported to receive afferent fibers from the hippocampus, the cingulate cortex, and other areas of the limbic cortex (Pandya and Kuypers, 1969; Jones and Powell, 1970; Beritoff, 1971; Pandya et al., 1971; Jacobson and Trojanowski, 1977a; Rosene and Van Hoesen, 1977; Goldman-Rakic et al., 1984; Ferino et al., 1987; Jay and Witter, 1991; Morecraft et al., 1992; review by Barbas et al., 2002; Ishikawa and Nakamura, 2006; Barbas et al., 2011; Yeterian et al., 2012). The hippocampus seems to project mainly if not exclusively to orbitomedial prefrontal cortex (Cavada et al., 2000), although the lateral prefrontal cortex indirectly receives hippocampal inputs through the thalamus and the orbital cortex. In general, afferents from limbic regions seem to have a less topical, more diffuse distribution than do those, discussed below, from neocortical areas.

The lateral prefrontal cortex, especially area 46, receives connections from the cerebellum. Some such afferents originate in cerebellar cortex (Kelly and Strick, 2003; Glickstein and Doron, 2008). Others originate in the ventral dentate nucleus of the cerebellum (Dum and Strick, 2003). The former constitute the cerebellar–prefrontal component of connective loops made of reciprocal connections between the two structures. Other cerebellar–prefrontal loops course through the basal ganglia and the lateral thalamus (Kelly and Strick, 2004). Undoubtedly, those loops play an important role in the temporal organization of motor actions.

Of special interest, because of their regulatory role over wide expanses of cortex, are the afferents to the prefrontal cortex from the basal forebrain, the locus coeruleus, the ventral tegmental area, and the raphe nuclei. These are the origin of essential neurotransmitter systems (acetylcholine, norepinephrine, dopamine, and serotonin) with global effects on neocortical function. All of them innervate, to one degree or another, the lateral, the medial, and the orbital prefrontal areas (for reviews, see Lewis et al., 1986; Mesulam, 1995; Steriade, 1996; Arnsten, 1997; see also Chapter 3).

In summary, the prefrontal cortex receives, directly or through the thalamus, inputs from the hypothalamus, the subthalamus, the mesencephalon, the limbic system, and the cerebellum. The precise nature of some of these inputs is unknown, but can be tentatively inferred from what is known about the functions of the structures of origin. Influences from the hippocampus, in particular, may be crucial for motor learning and memory, whereas the inputs from the substantia nigra and some of the lower brain structures are probably related to the execution of movement. Inputs from the mesencephalon, the hypothalamus, and the amygdala are related to the internal state, drives, and motives of the organism. Inputs from the cerebellum are most likely involved in the coordination of motor actions. Inasmuch as some of the structures sending afferents to the prefrontal cortex receive inputs from sensory areas, they probably pass on to it information about the motivational significance of external stimuli. Next, we shall see that the prefrontal cortex also receives sensory information directly through neocortical pathways; that information may deal not so much with affective and motivational aspects of the environment as with its cognitive aspects, more specifically, with perception and memory.

The prefrontal cortex is extensively interconnected with other cortical regions. For several decades, studies of fiber degeneration,

neuronography, and evoked potentials provided evidence of corticocortical fiber connections. It is only in more recent years that, thanks to the newer histological methods, it has been possible to uncover the richness and detail of that connectivity. Most recently, imaging methods, notably diffusion tensor imaging, have also contributed to this body of knowledge.

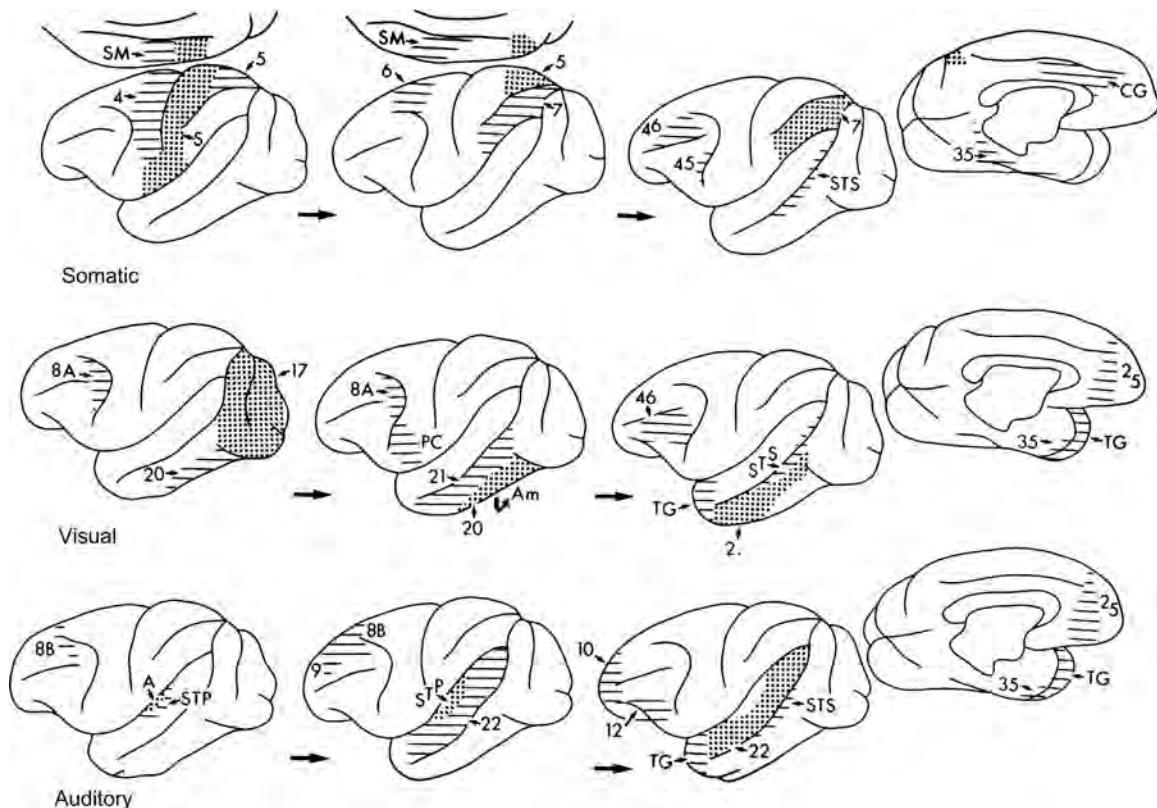
The cortical afferents to the prefrontal cortex originate, for the most part, in areas that have not been physiologically characterized as primary sensory or motor. The evidence of these afferents is clearer and more impressive in primates than in other species, probably because of differences, presumably phylogenetic, in the degree of development of both the corticocortical connectivity and the prefrontal cortex. In the brain of the rhesus monkey, the non-primary areas that project to the prefrontal cortex are components of a vast system of interconnected areas that appear to constitute the cortical system for sensory and perceptual processing.

Jones and Powell (1970), summarizing their own findings and those of others (Kuypers et al., 1965; Jones, 1969; Jones and Powell, 1969), outlined the organization of the system as it pertains to the cortex of the lateral convexity of the hemisphere and to the cortical pathways for sensory processing of the three major modalities: somesthesia, vision, and audition (Figure 2.16). The primary sensory area for each of those three modalities projects, first, to an adjacent associative area of parietal, occipital, or temporal cortex. That is the beginning of a sequential order of cortical areas that make up a cortical pathway for that sensory modality. Each area in the sequence projects not only to the next in line but, by way of long association fibers, to a discrete area of the frontal cortex, which in turn reciprocates by sending fibers back to the projecting area. The fields that constitute the third link in each of the three pathways – namely, parietal area 7 (somatic), temporal area 22 (auditory), and inferotemporal area 21 (visual) – project to the cortex in the

depths of the superior temporal sulcus and, in addition, to the prefrontal cortex.

Results of other primate studies (Myers, 1967; Pandya and Kuypers, 1969; Pandya et al., 1969; Benevento and Fallon, 1975; Chavis and Pandya, 1976; Jacobson and Trojanowski, 1977a, 1977b; Andersen et al., 1985; Barbas and Mesulam, 1985; Ungerleider et al., 1989; Barbas et al., 2013; Yeterian et al., 2012), although differing in details, have supported the basic scheme proposed by Jones and Powell with regard to cortical sensory processing. Some have emphasized additional features, such as projections from the cortex in the depths of the superior temporal sulcus to the cortex of the sulcus principalis area (Jacobson and Trojanowski, 1977a; Seltzer and Pandya, 1989; de Lima et al., 1990) or the commissural prefrontal connections (Pandya et al., 1971; Goldman and Nauta, 1977b; Jacobson and Trojanowski, 1977b). Also, the prefrontal fields of afferent distribution have been better defined (Chavis and Pandya, 1976; Jacobson and Trojanowski, 1977a; Barbas and Mesulam, 1981, 1985; Goldman-Rakic and Schwartz, 1982; Petrides and Pandya, 1984, 2002). Figure 2.17 illustrates the major cortical afferent fiber bundles or fascicles to prefrontal cortex, according to Petrides and Pandya (2002).

Within a given fascicule, remarkable topological correspondence has been observed between separate posterior areas and prefrontal areas, for example, between the subdivisions of area 7, and the different parcels of prefrontal cortex to which they project (Cavada and Goldman-Rakic, 1989a, 1989b). Similar segregation of corresponding cortical fields has been observed between inferotemporal and prefrontal cortex (Pandya and Yeterian, 1985; Webster et al., 1994). The connectivity within and between parietal and temporal regions has also been further clarified; on the basis of connective patterns, the superior temporal sulcus appears to be a region of polymodal sensory convergence in the posterior brain (Mesulam, 1981;

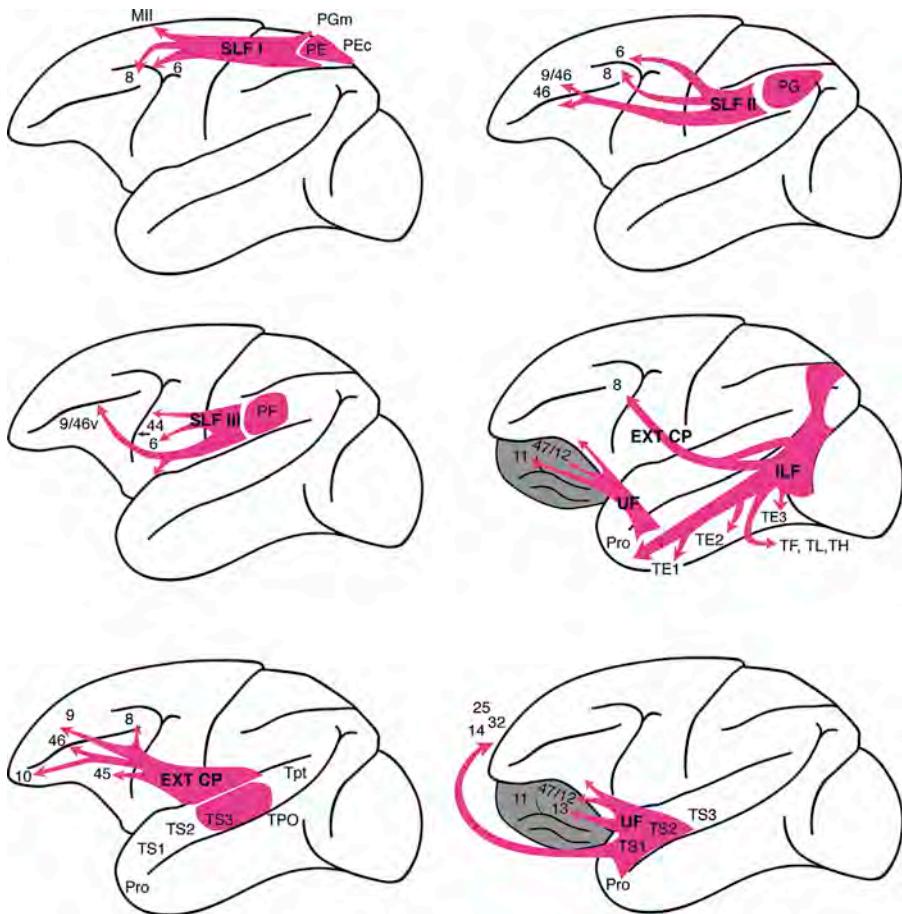


**FIGURE 2.16** Stepwise projection of connections originating in the somatic, visual, and auditory areas of the monkey's cortex. Each step is shown by a dotted pattern, and the succeeding regions of termination by a pattern of horizontal lines. Note that most areas project to others nearby and to the prefrontal cortex. Abbreviations: A, auditory cortex; CG, cingulate gyrus; S, somatosensory cortex; SM, supplementary motor cortex; STP, superior temporal plane; STS, superior temporal sulcus; TG, temporal polar cortex. (Adapted by Amaral, 1987, from Jones and Powell, 1970, with permission.)

Pandya and Seltzer, 1982; Seltzer and Pandya, 1984; Pandya and Yeterian, 1985), much as the prefrontal cortex is in anterior brain.

As is the case for other sensory inputs, olfactory and gustatory inputs also reach the prefrontal cortex. Both arrive in caudal orbital cortex (area 13), the first through fibers from the primary olfactory cortex in the prepiriform paralimbic area (Barbas, 1993; Carmichael et al., 1994), and the second from the primary gustatory cortex – also paralimbic – of the frontal operculum and insula (Rolls, 1989). The orbitofrontal cortex also receives projections from the

association cortex of the other sensory modalities, that is, vision, audition, and somesthesia (Cavada et al., 2000; Barbas et al., 2011), including the visual polar region of the temporal lobe (Barbas et al., 2002). The medial prefrontal cortex receives only scanty projections from visual and somatic areas, but more substantial ones from auditory areas (Barbas, 1988; Barbas et al., 1999). Furthermore, medial prefrontal areas (24, 25, and 32) receive profuse projections from the hippocampus (Barbas and Blatt, 1995; Cavada et al., 2000) and from areas of the medial temporal lobe (28, 35, and 36) that have been implicated



**FIGURE 2.17** Major bundles (fasciculi) of fiber projections from sensory association areas of posterior cortex to frontal cortex (orbitofrontal in gray): superior longitudinal fasciculus I (SLF I), superior longitudinal fasciculus II (SLF II), superior longitudinal fasciculus III (SLF III), inferior longitudinal fasciculus (ILF), extreme capsule (EXT CP) fasciculus, and uncinate fasciculus (UF). All projections are reciprocated by frontal efferents running in the opposite direction. Area notations in frontal cortex according to Brodmann (1912) and in posterior cortex according to Bonin and Bailey (1947), and Pandya. (From Petrides and Pandya, 2002, slightly modified, with permission.)

in the formation of long-term memory (Vogt and Pandya, 1987; Carmichael and Price, 1995; Bachevalier et al., 1997; Barbas et al., 2002).

In a review that portrays some of their own work, Barbas et al. (2011) point out the discrete prefrontal distribution of fibers from visual, auditory, and somatosensory systems. They emphasize in particular the afferents of those systems on orbitofrontal cortex, where they

meet afferents from the amygdala. Thus, the authors remark on the capacity of that cortex to integrate sensory and emotional inputs, as required in social behavior.

To sum up, the principle has been upheld and firmly established that, in the monkey, the prefrontal cortex is a region for convergence of corticocortical pathways that originate in primary somatic, auditory, visual, olfactory, and

gustatory areas. The number of synaptic steps in each pathway is somewhat uncertain; a matter for disagreement and speculation is the function of each cortical step, which undoubtedly is much more than simply a relay station and most probably serves as a stage in a hierarchy of processing stages for one or several aspects of sensory information. Nevertheless, the finding that cortical sensory pathways are relatively independent of one another until they reach the prefrontal cortex could not fail to suggest the importance of this cortex, in the aggregate, as an area of cross-modal association.

However, the cortical afferents to the prefrontal cortex do not all converge on identical locations but, as emphasized by some of the studies mentioned above, show a degree of differential distribution. On arrival at the prefrontal region, each pathway seems to preserve some individuality. In any case, the fact remains that five cortical fiber paths of separate sensory origin terminate in contiguous or nearly contiguous, if not identical, parcels of the prefrontal cortex. Furthermore, some bimodal and even trimodal overlap of projections is suggested by histological data in the area of the sulcus principalis, as well as in the ventral and medial aspects of the prefrontal cortex (Jones and Powell, 1970; Chavis and Pandya, 1976; Jacobson and Trojanowski, 1977a). In addition, an analysis of the local circuitry by the same methods that have revealed distant projections provides evidence of convergence beyond their point of arrival, inasmuch as different terminal sites are seen to project, in turn, to common sites within the prefrontal region itself (Jones and Powell, 1970; Pandya et al., 1971; Jacobson and Trojanowski, 1977a).

Aside from the noted qualifications on the associative character of the prefrontal cortex, as can be gleaned from its afferent sensory connections, it seems important to emphasize that those connections can be divided into two major groups, each with a different prefrontal target region. The lateral prefrontal cortex is

the target of visual, auditory, and somatic afferents, whereas the orbitomedial prefrontal cortex is the target of olfactory and gustatory, in addition to auditory and – to a lesser extent – visual and somatic afferents (Carmichael and Price, 1995; Barbas et al., 2002, 2011). It is highly probable that the two sets of sensory afferents serve the integration of sensory information toward the execution of two broad categories of actions of the organism. The lateral prefrontal cortex would collect sensory information for the organization and execution of goal-directed sequences of actions, which, as we will see, are major functions of that cortex. The orbitomedial prefrontal cortex, on the other hand, would collect sensory information for emotional behavior. Here, the reciprocal relations between that cortex and the amygdala would seem crucial, inasmuch as this limbic structure is essential for the evaluation of the motivational significance of sensory information. It remains to be mentioned, because of their emotional implications, that the orbitofrontal cortex also receives copious visceral inputs (Öngür and Price, 2000), which arrive to it via some of the cortical and subcortical afferents noted above. They include afferents from the cingulate cortex (Öngür and Price, 2000), amygdala (Amaral and Price, 1984), hypothalamus (Rempel-Clower and Barbas, 1998), and periaqueductal gray (Rempel-Clower and Barbas, 1998).

Area 8 (frontal eye field) is paradigmatic of a prefrontal area of the lateral convexity that is dedicated to the integration of sensory information in the service of the integration of goal-directed sequential activity (eye movements). It receives afferents from distant areas of occipital, parietal, and temporal cortex (Pandya and Kuypers, 1969; Jones and Powell, 1970; Benevento and Fallon, 1975; Jacobson and Trojanowski, 1977a; Barbas and Mesulam, 1981; Petrides and Pandya, 1984; Huerta et al., 1987; Webster et al., 1994). In addition, it receives afferents from adjacent and contralateral areas of the prefrontal cortex (Pandya and Kuypers,

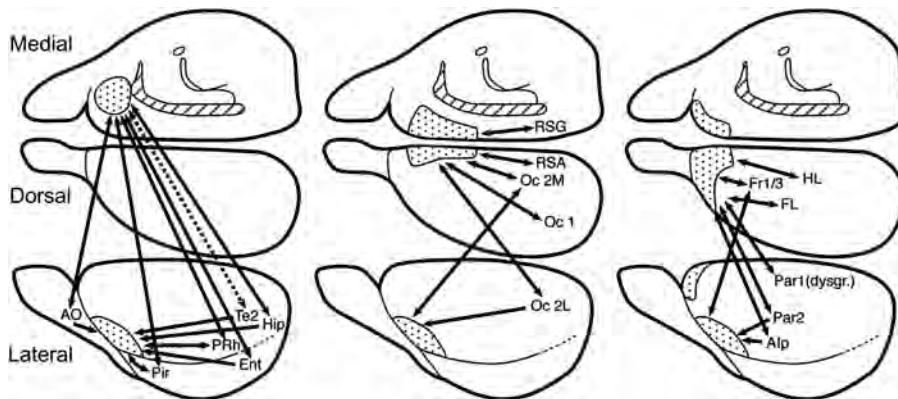
1969; Jacobson and Trojanowski, 1977a, 1977b; Watanabe-Sawaguchi et al., 1991). Partly on the basis of its connections, area 8 has been considered an important component of the cortical apparatus for visual attention (Mesulam, 1981).

The gyrus proreus of the cat has been shown to receive afferents from the homotopical cortex of the opposite side (Ebner and Myers, 1965; Voneida and Trevarthen, 1969; Luttenberg, 1974a; Cavada and Reinoso-Suárez, 1981), as well as from the nearby cortex of the sigmoid and orbital gyri (Kawamura and Otani, 1970; Beritoff, 1971). As in the monkey, the cat's prefrontal cortex also receives afferents from limbic cortex (Cavada and Reinoso-Suárez, 1985). The discovery of the organization of cortical sensory pathways in the monkey, as presented by Jones and Powell (1970), encouraged the exploration of general cortical connectivity in the cat. Heath and Jones (1971) found in this animal an arrangement of pathways in many ways similar to that found in the monkey. Different fields of the suprasylvian cortex were identified as component steps in three connective chains of somatic, visual, and auditory origin. Here again, the three chains are interlocked with the frontal cortex, for each step sends projections to a frontal field. However, these frontal projections spare the prefrontal cortex itself (see also Markowitsch et al., 1980) and reach only as far as area 6, in the precruciate cortex of the anterior sigmoid gyrus, where there is considerable overlap. Thus, it appeared from that work that in the cat the transcortical sensory projections converge at an earlier stage than they do in the monkey. Furthermore, reciprocal projections from the frontal cortex to the preceding cortical steps seemed fewer. Later investigations, however, have demonstrated direct afferents to the prefrontal cortex not only from other frontal regions but also from parietal, temporal, and limbic regions (Cavada and Reinoso-Suárez, 1985). An electrophysiological study (Criado et al., 1992) has substantiated the parietal afferent connections. Thus, judging from these later

studies, the general pattern of corticocortical connectivity in the cat may not differ much from that in the monkey. At any rate, whether or not the cat's prefrontal region is entered, as it is in the monkey, by segregated sensory pathways, there is some evidence that the precruciate area, where the pathways converge, projects to the prefrontal–proreal region that lies directly in front (Kawamura and Otani, 1970; Beritoff, 1971; Heath and Jones, 1971; Luttenberg, 1980), although that evidence has been disputed (Cavada and Reinoso-Suárez, 1985).

The prefrontal cortex of the rat, like that of the cat and the monkey, receives corticocortical projections from sensory areas, as well as motor and limbic areas (Uylings and Van Eden, 1990; Van Eden et al., 1992; Uylings et al., 2003). Most of these projections are reciprocated by efferents to those areas (Figure 2.18). However, because of the difficulties that the rodent's cortex poses to the establishment of homologies with the cortices of those other two species, the equivalence of corticocortical connectivity across species that include the rat is not evident. In any case, it is clear that the rat's prefrontal cortex is suitably connected to other cortices to be capable of integrating multimodal sensory information, as well as gating or in some manner controlling sensory inputs at cortical level.

Histochemical labeling procedures have led to a better understanding of the patterns of origin and termination of corticocortical projection fibers to and from the prefrontal cortex. In general, these cortical associative connections, like the more extensively investigated corticocortical connections that involve sensory cortex (Jones et al., 1979; Jones, 1981; Van Essen and Maunsell, 1983), largely originate and terminate in supragranular layers of the cortex, especially layer III (Jacobson and Trojanowski, 1977a; Luttenberg, 1974b; Kosmal et al., 1983; Schwartz and Goldman-Rakic, 1984; Andersen et al., 1985; Barbas et al., 2002). For example, the cells of the posterior parietal cortex (area 7) that project to the lateral prefrontal cortex are



**FIGURE 2.18** Corticocortical connections of the prefrontal cortex of the rat. Abbreviations: AO, anterior olfactory nucleus; Alp, posterior agranular insular cortex; Ent, entorhinal area; FL, forelimb area; Fr1/3, frontal cortical areas 1 and 3; Hip, hippocampus; HL, hindlimb area; Oc 1, primary occipital (visual) cortex; Oc 2L, lateral part of occipital cortex area 2; Oc 2M, medial part of occipital cortex area 2; Par1 (dysgr.), dysgranular part of parietal cortex area 1; Par2, parietal cortex area 2 (supplementary somatosensory cortex); Pir, (pre)piriform cortex; PRh, perirhinal cortical area; RSA, agranular retrosplenial cortex; RSG, granular retrosplenial cortex; Te2, area 2 of temporal cortex. (From Uylings et al., 2003, with permission.)

much more common in layer III than in any other layer (Andersen et al., 1985). On the other hand, within the prefrontal cortex itself, cells in layers II and III of granular, well-laminated, cortex tend to terminate in lower layers (V and VI) of agranular or dysgranular paralimbic areas of orbital and medial cortex (Barbas et al., 2002). In the cortex of the sulcus principalis, the terminals from posterior parietal cells have been noted to form transverse columns that span the entire thickness of the cortex and are interspersed, in alternating fashion, with similar terminal columns from cells in contralateral prefrontal areas (Goldman-Rakic and Schwartz, 1982) (Figure 2.19). This pattern of interdigitation of terminals from distant and separate cortical regions is another indication of the fundamentally associational character of the prefrontal cortex.

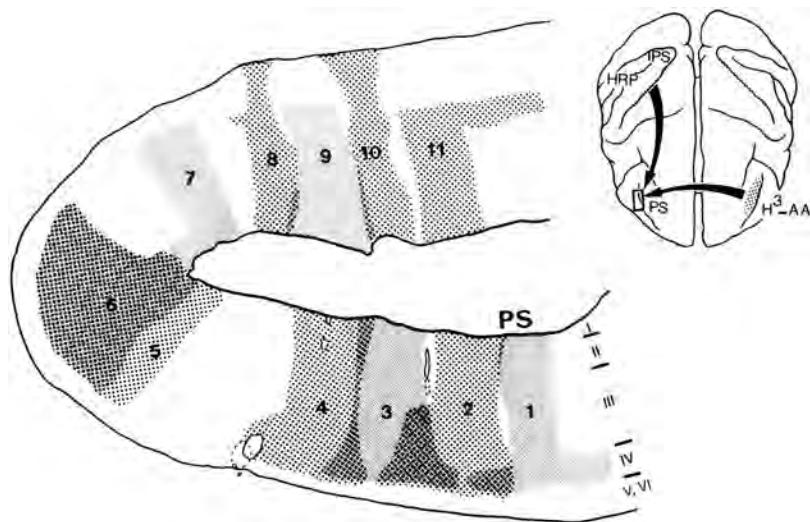
## B. Efferents

In accord with an almost universal law of cortical connectivity, the prefrontal cortex sends fibers to practically every structure from which

it receives them. Furthermore, the distribution of efferents generally conforms to the topographical order of afferents, and a remarkable degree of mutual correspondence can be observed, at least in primates, between different prefrontal fields and the structures with which they are connected. There are, however, exceptions to the rule of reciprocity. For example, the prefrontal cortex emits efferents to an important group of subcortical structures, the basal ganglia, from which it does not seem to receive direct afferents.

Because of the rule of reciprocal connections, and because of the clear cross-species homologies of most subcortical structures connected with the prefrontal cortex, the following description of prefrontal efferents, unlike that of afferents, will often omit mention of the species in which a given referenced observation has been made.

Efferent fibers emanating from the prefrontal region have been traced to multiple and diverse subcortical locations. The mediodorsal nucleus is a prime recipient (Clark, 1932; Mettler, 1947b; Meyer, 1949; Krieg, 1954; Auer, 1956; Nauta, 1964;



**FIGURE 2.19** Convergence of projections from parietal and contralateral prefrontal cortices on the cortex of the sulcus principialis (PS), traced by the double-label [horseradish peroxidase (HRP) and  $^3\text{H}$ -arachidonic acid ( $^3\text{H}$ -AA)] axon-transport method. IPS, intraparietal sulcus. Parietal terminal zones (1, 3, 6, 7, and 9) are marked by fine shading, and callosal (contralateral) terminal zones (2, 4, 5, 8, 10, and 11) by coarse shading. (From Goldman-Rakic and Schwartz, 1982, with permission.)

Tanaka, 1977; Goldman, 1979; Schwartz et al., 1991; Siwek and Pandya, 1991; Buchanan et al., 1994; Klein et al., 2010). Projections to the ventral and intralaminar nuclei have also been reported (Auer, 1956; DeVito and Smith, 1964; Nauta, 1964; Johnson et al., 1968; Rinvik, 1968; Buchanan et al., 1994). In general, the topology of prefrontal efferents to the thalamus appears to correspond to that of fibers running in the opposite direction.

Other subcortical targets of prefrontal efferents, mostly but not exclusively arising in the ventral (orbital) cortex, have been identified in the hypothalamus, subthalamus, septum, mesencephalon, and pons (Levin, 1936; Bonin and Green, 1949; Clark and Meyer, 1950; Kanki and Ban, 1952; Auer, 1956; DeVito and Smith, 1964; Nauta, 1964; Johnson et al., 1968; Brodal, 1971; Leichnetz and Astruc, 1976; Tanaka and Goldman, 1976; Leichnetz et al., 1981; van der Kooy et al., 1982; Terreberry and Neafsey, 1983; Buchanan et al., 1994; reviews by Alheid and

Heimer, 1996; Zaborszky et al., 1999; Barbas et al., 2002).

Whereas some of these subcortical structures also receive inputs from other cortical areas, the prefrontal cortex seems to be the only cortical district that sends direct projections to the hypothalamus, septum, and preoptic region. Nauta (1964) remarked that several of the brainstem structures receiving prefrontal output are part of the limbic system by virtue of their location and associations. This applies to the structures of the diencephalon and mesencephalon that are connected with the amygdala, itself also the target of direct prefrontal efferents (Leichnetz and Astruc, 1976, 1977; review by McGaugh et al., 1996; Barbas et al., 2002, 2011). In addition, an important contingent of prefrontal projections to limbic cortex courses through the white matter of the gyrus cinguli and around the corpus callosum, and distributes terminal fibers in the overlying cortex along the way, from the anterior cingulate

region to the hippocampus (Nauta, 1964, 1971, 1972). In the monkey, prefrontal fibers that apparently follow that route have been shown to terminate in cingulate, retrosplenial, entorhinal, and hippocampal cortex (Adey and Meyer, 1952; Johnson et al., 1968; Van Hoesen et al., 1972; Leichnetz and Astruc, 1975a, 1975b, 1976; Goldman and Nauta, 1977b; Goldman-Rakic et al., 1984; Pandya and Yeterian, 1985; Bates and Goldman-Rakic, 1993).

A more direct route from the prefrontal cortex to the hippocampus and entorhinal cortex, through the uncinate fasciculus, has also been described in the monkey (Leichnetz and Astruc, 1975a, 1975b, 1976; Van Hoesen et al., 1975; Goldman-Rakic et al., 1984). However, most, if not all, cortical inputs to the hippocampus seem to be relayed through the entorhinal cortex (Van Hoesen, 1982; Amaral, 1987). Those from the prefrontal cortex are no exception (Goldman-Rakic et al., 1984). In the cat, however, fibers that follow the cingulate route have been reported to join the fornix and to terminate in the caudal cingulate cortex and septal nuclei, but not in the hippocampus or entorhinal cortex (Voneida and Royce, 1974).

Nauta (1964), on the basis of primate data, was one of the first to point out that the orbitofrontal cortex is prominently connected to the amygdala complex and related subcortical structures. The direct reciprocal connections of the prefrontal cortex with the amygdala and the medial cortex of the temporal lobe are most probably involved in the formation of new memory (Amaral, 1987; McGaugh et al., 1996; Barbas et al., 2002) or retrieval of old memory (Cavada et al., 2000). Because of the importance of the prefrontal cortex in executive functions, it is reasonable to suppose that those connections play an essential role in the formation and retrieval of executive memory (Fuster, 1995, 2003). In addition, they probably play an important role in emotional and social behavior.

As a counterpart to the prefrontal efferents that distribute themselves in the limbic cortex

of the medial and basal telencephalon, efferent fibers flow from the prefrontal cortex to neocortical areas of the dorsal and lateral aspects of the hemisphere. Some of those fibers cross over to the contralateral hemisphere and terminate in homotopical and heterotopical prefrontal sites (Ebner and Myers, 1965; Voneida and Trevarthen, 1969; Pandya et al., 1971; Luttenberg, 1974a; Goldman and Nauta, 1977b; Jacobson and Trojanowski, 1977b; Isseroff et al., 1984; McGuire et al., 1991a). Others terminate in the ipsilateral cortex; in cat and dog, prefrontal fibers have been traced to the cortex of the orbital, sigmoid, anterior sylvian, ectosylvian, suprasylvian, and lateral gyri (Mikeladze and Kiknadze, 1966; Kiknadze, 1968; Beritoff, 1971; Heath and Jones, 1971; Luttenberg, 1980; Cavada and Reinoso-Suárez, 1985).

Of special functional interest are the intracortical connections that reciprocally link prefrontal areas with one another. Replicating what had previously been shown in the monkey by histological methods, such connections have been evinced in the human by modern imaging methods (diffusion tractography) (Catani et al., 2012). The abundance of these short U-shaped connections is one more indication of the strongly integrative nature of prefrontal functions.

Area 8, like the rest of the prefrontal cortex, projects to diencephalic, mesencephalic, limbic, neocortical, and striatal structures (Hirazawa and Kato, 1935; Crosby et al., 1962; Brucher, 1964; Kuypers and Lawrence, 1967; Pandya and Kuypers, 1969; Pandya and Vignolo, 1971; Künzle et al., 1976; Künzle and Akert, 1977). Through long reciprocal connections, area 8 maintains close relationships with posterior parietal areas (area 7, lateral intraparietal area) that are involved in visual attention and the control of ocular motility (Mesulam, 1981; Andersen et al., 1985; Huerta et al., 1987; Cavada and Goldman-Rakic, 1989a, 1989b). It, too, is part of motor frontal–subcortical loops (below). Some of the subcortical projections of

this area are also of particular functional significance for ocular motility. Those are the projections to the pulvinar, pretectal region, and the superior colliculus (Kuypers and Lawrence, 1967; Künzle et al., 1976; Künzle and Akert, 1977; Leichnetz et al., 1981; Komatsu and Suzuki, 1985; Huerta et al., 1986). The presence of direct efferents from area 8 to the oculomotor nuclei of the brainstem, however, is not firmly established (Astruc, 1971; Künzle and Akert, 1977; Leichnetz, 1980).

Although the efferent projections of area 8 to the structures mentioned above clearly suggest a role of that area in visual attention and visually guided behavior, it should be noted that area 8 is not the sole prefrontal locus implicated in those functions. Other portions of the lateral and medial prefrontal cortex, reciprocally interconnected with area 8 (Pandya and Kuypers, 1969; Goldman and Nauta, 1977b; Künzle and Akert, 1977), have been reported to project to the pulvinar and superior colliculus (Kuypers and Lawrence, 1967; Goldman and Nauta, 1976; Künzle et al., 1976; Leichnetz and Astruc, 1976; Leichnetz et al., 1981) and may thus also be involved in those visual functions.

In the monkey, the organization of corticocortical prefrontal efferents is more apparent than in the dog, the cat, or the rat. As a general principle it has been firmly established that prefrontal areas reciprocate with efferent projections to all those areas of posterior cortex from which they receive afferents. Of special interest in this respect is the cortex in and around the sulcus principalis. Some studies show that, in addition to sending efferent fibers to the limbic cortex, the principalis cortex sends projections to temporal and parietal areas that have been identified as components of associative sensory pathways. Thus, the cortex ventrolateral to the sulcus principalis, at the receiving end of the visual neocortical path, projects back to the preceding link in that path, that is, the inferotemporal cortex of area 21 and the lower bank of the superior temporal sulcus (Pandya and Kuypers, 1969; Jones

and Powell, 1970; Pandya et al., 1971; Künzle, 1978; Pandya and Yeterian, 1985). Conversely, the cortex above the sulcus principalis projects to auditory area 22 and the upper bank of the superior temporal sulcus (Pandya and Kuypers, 1969; Pandya et al., 1971; Pandya and Yeterian, 1985). It is worth noting that some of the prefrontal projections to those posterior cortices are inhibitory (Medalla et al., 2007).

The projections from the sulcus principalis to the superior temporal sulcus – which like most frontotemporal connections constitute a part of the uncinate fasciculus – have also been found arranged in topological order along the two sulci (Pandya et al., 1971; Ban et al., 1991). Projections to somatic parietal areas 5 and 7 arise in both banks of the sulcus principalis and in the anterior bank of the arcuate sulcus (Pandya et al., 1971; Mesulam et al., 1977). Some of those projections extend to secondary somatic cortex (SII) in the insular region (Preuss and Goldman-Rakic, 1989). The terminal distribution of some projections from the prefrontal cortex to other contralateral (through the corpus callosum) or ipsilateral cortical areas has been noted to adopt the columnar pattern (Bugbee and Goldman-Rakic, 1983; Isseroff et al., 1984).

Probably no efferents from the prefrontal cortex are more closely related to its executive and motor functions than those that flow from it to other areas of the frontal lobe and to the basal ganglia. The analysis of corticocortical connections within the frontal lobe reveals that the prefrontal cortex is the origin of a cascade of connective links that flow down from it to premotor and supplementary motor areas (SMAs) (area 6), and from there to primary motor cortex (area 4). This cascade of motor links, which are reciprocal and to some degree topologically organized, has been best substantiated in primate brains (Matelli et al., 1986; Barbas and Pandya, 1987; Arikuni et al., 1988; Watanabe-Sawaguchi et al., 1991; Bates and Goldman-Rakic, 1993; Luppino et al., 1993; Morecraft and Van Hoesen, 1993; Lu et al., 1994).

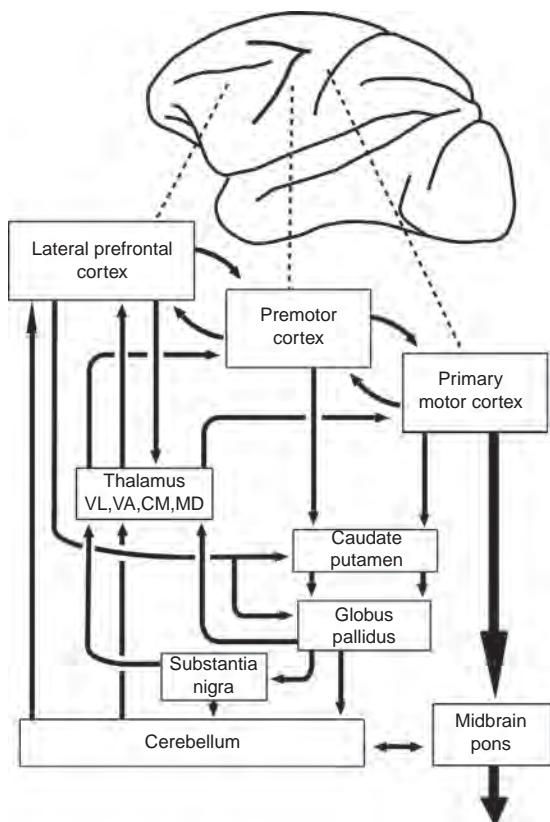
Basically, the connective and areal organization of the frontal lobe, as a whole, constitutes a hierarchy of interconnected motor structures, with the prefrontal cortex on top, the premotor cortex (including cingulate and supplementary motor areas) under it, and the motor cortex at the bottom. It is a frontal motor hierarchy symmetrical to the perceptual hierarchies of posterior, postrolandic, cortex. In perceptual hierarchies, the connectivity flows from primary sensory cortices to cortex of association, whereas in the frontal motor hierarchy it flows from cortex of association (prefrontal) to primary motor cortex. At every level, the sensory and motor hierarchies are reciprocally inter-linked, and the aggregate of connections within and between hierarchies constitutes the cortical connective architecture of the perception–action cycle, to be discussed in later chapters.

Like other cortical regions, the prefrontal cortex sends profuse efferents to the basal ganglia. The caudate nucleus and the putamen are known to receive such efferents in the rat (Leonard, 1969; Kitai et al., 1976), the cat (Webster, 1965; Beritoff, 1971), the dog (Beritoff, 1971), the monkey (Wall et al., 1951; DeVito and Smith, 1964; Nauta, 1964; Johnson et al., 1968; Kemp and Powell, 1970, 1971; Leichnetz and Astruc, 1975a, 1976; Cavada et al., 2000), and the human (Kanki and Ban, 1952; Leh et al., 2007). Prefrontal–caudate connections terminate mainly, if not exclusively, in the head of the nucleus, with a degree of topological organization (Webster, 1965; Johnson et al., 1968; Kemp and Powell, 1970; McGuire et al., 1991b; Yeterian and Pandya, 1991). Contrary to previous notions, the entire caudate nucleus, including the tail, receives prefrontal projections (Goldman and Nauta, 1977a; Jacobson et al., 1978; Selemon and Goldman-Rakic, 1985). One study (Selemon and Goldman-Rakic, 1985) notes that the projections from the lateral prefrontal cortex terminate all along a central strip of the caudate, from head to tail; another longitudinal strip, ventral and medial to that

one, receives fibers from the orbital prefrontal cortex, the anterior cingulate cortex, and the superior temporal cortex. The same study demonstrates a degree of interdigitation of terminals from different cortical areas within the mass of the nucleus. Another study (Arikuni and Kubota, 1986) indicates that the prefrontal–caudate connections consist mainly of the axons of relatively large pyramidal or round cells in cortical layers III–Va.

Efferents from the prefrontal cortex have also been traced to the globus pallidus (Kanki and Ban, 1952; DeVito and Smith, 1964; Johnson et al., 1968; Beritoff, 1971; Leichnetz and Astruc, 1977; Haber et al., 1995), claustrum (De Vito and Smith, 1964; Narkiewicz, 1972; Leichnetz and Astruc, 1975a), substantia nigra (DeVito and Smith, 1964; Beritoff, 1971; Leichnetz and Astruc, 1976, 1977; Haber et al., 1995), and nucleus accumbens (Haber et al., 1995; Taber and Fibiger, 1995; Yang et al., 1996). Through the pontine nuclei, the prefrontal cortex sends efferents to the cerebellum. Figure 2.20 illustrates schematically the main connections of the prefrontal cortex with other neural structures implicated in motor function.

The involvement of the prefrontal cortex and the basal ganglia in motor function has been further clarified as more knowledge has been obtained of the input connections from subcortical structures on to the major sectors of frontal cortex: prefrontal, premotor, and motor. These three cortical sectors receive separate projection pathways from subcortical structures. Each pathway appears to contribute a different kind of feedback to the cortex for control of motor behavior. One connective loop including such feedback is formed by connections from the prefrontal cortex to the caudate nucleus and anterior putamen, from these structures to the substantia nigra (Parent et al., 1984), and from there back to the prefrontal cortex, either directly or through the ventral anterior and mediodorsal nuclei of the thalamus (Porrino and Goldman-Rakic, 1982; Ilinsky et al., 1985).



**FIGURE 2.20** Connectivity of the prefrontal cortex with structures involved in motor function. The three lateral frontal regions of the motor hierarchy (prefrontal, premotor, and motor cortices) are interconnected with the thalamus, basal ganglia, and cerebellum by recurrent axonal loops that are essential to motor control. Abbreviations: CM, central median nucleus; MD, mediodorsal nucleus; VA, anteroventral nucleus; VL, ventrolateral nucleus.

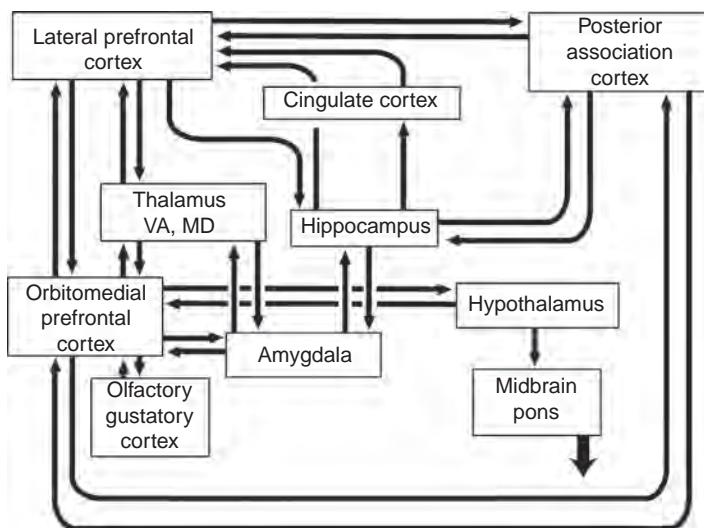
A second pathway would collect influences from several cortical areas, including premotor cortex (Künzle, 1978), and lead them – processed and transformed – through the posterior putamen, the globus pallidus (Parent et al., 1984), and the ventrolateral thalamus to the premotor areas of the arcuate and medial frontal regions (Schell and Strick, 1984).

The medial premotor cortex is the so-called supplementary motor area (SMA) of Woolsey

et al. (1952). In both premotor areas, arcuate and SMA, there is a degree of somatotopical organization, that is, differential representation of the body (Woolsey et al., 1952; Muakkassa and Strick, 1979). The primary motor cortex, where somatotopy is even more marked, receives not only topologically organized afferent inputs from premotor areas (Muakkassa and Strick, 1979) but also, through the ventral lateral thalamus, inputs from the cerebellum (Asanuma et al., 1983). With the improved knowledge of cortical–subcortical connections, DeLong and his colleagues (DeLong and Georgopoulos, 1981; Alexander and Crutcher, 1990) offer a broad view of the substrate for motor control consisting of a series of re-entrant corticosubcortical connective loops that course through the basal ganglia and the lateral thalamus (Figure 2.20, circuitry depicted by clockwise connections).

Thus, the three frontal cortices, with their respective subcortical connections, appear to constitute the substrate for three hierarchical processing stages devoted to the organization of action. At the highest level, the prefrontal cortex would participate in the organization of the more global, abstract, and schematic aspects of behavioral action. At a lower level, the motor cortex would engage in the more immediate and minute aspects of movement, the “microgenesis of action” (Brown, 1977).

That vast system of structures and connections dominated by the lateral frontal cortex and the aforementioned subcortical loops, which is largely devoted to the organization of skeletal motility, parallels and interacts with another system, this one dominated by orbitomedial prefrontal cortex and involving limbic structures, that is largely devoted to emotional behavior. The connectivity of this second system (first in evolutionary terms), which is critical for the regulation of instinct and social interactions, can be deduced from the analysis of the connections of the orbitomedial prefrontal cortex, especially in the non-human primate.



**FIGURE 2.21** Connectivity of the prefrontal cortex with structures involved in emotion. Abbreviations: VA, anteroven-tral nucleus; MD, mediodorsal nucleus.

Figure 2.21 depicts, again schematically, this emotional-social system, of which the orbitomedial prefrontal cortex is a vital component.

## VII. SUMMARY

The prefrontal cortex is the cortex of the anterior pole of the brain; it lies in front of motor cortex on the lateral surface of the hemisphere and of limbic cortex on its orbital and medial surfaces. It can be defined, anatomically, as the part of the cerebral cortex that receives projection fibers from the mediodorsal nucleus of the thalamus – although it also receives them from many other subcortical structures. Certain segments of its boundary are marked by gross morphological features: in carnivores by the presylvian fissure, in primates by the homologs of that fissure (arcuate sulcus, inferior precentral fissure) and by the anterior curvature of the cingulate sulcus.

In the course of evolution, the prefrontal cortex undergoes more expansion than does the

rest of the cortex. Its relative size (with respect to brain size or body weight) reaches a maximum in the human, where it constitutes nearly one-third of the entire neocortex. The phylogenetic development of its component areas can be traced by the microscopic study of its architecture. Such study indicates that the lateral areas undergo later development and further differentiation than do the medial and inferior (orbital) areas.

The ontogenetic development of the prefrontal cortex reflects its phylogeny. Orbitomedial areas mature earlier than lateral ones. In early life, neurons in the prefrontal cortex proliferate, migrate to their ultimate cortical destination, and experience growth according to the timetable that prevails throughout the neocortex. At birth, the prefrontal cortex of the primate is completely configured in terms of cellular architecture and basic structure of cellular elements. A perinatal overproduction of neurons gives way to a reduction in neuronal numbers and density that continues until adulthood. Dendrites grow speedily in the newborn and

then gradually to an asymptote in the young adult. Neurons in deeper layers develop earlier and more rapidly than those in upper layers. Synapses undergo perinatal overproduction and, after birth, gradual reduction to adult levels. Prefrontal myelin and white matter develop late. In the human, they reach full development in the twenties, apparently coinciding with maturation of the cognitive functions of the prefrontal cortex.

In primates, including the human, the cortex of the lateral prefrontal convexity is typical six-layered ("eulaminated") neocortex (also called "isocortex" because of its structural uniformity). It is characterized by a well-marked internal granular layer (layer IV), and for this reason is also called "frontal granular cortex." The cortex of some of the medial and orbital prefrontal regions, on the other hand, is so-called dysgranular or agranular, with a scanty or non-existent granular layer and prominent deeper layers (V and VI). The prefrontal cortex of the posterior lateral and orbital regions bordering motor and limbic areas is of transitional type, incorporating features of the adjacent motor or limbic cortex. In general, cortical layers are better defined in the prefrontal cortex of the primate than in the cortices of rodents and carnivores.

In the prefrontal cortex of the normal human subject, involutional signs usually appear in the seventh or eighth decade of life. They include volume loss (of gray matter, as well as individual neurons), atrophy of dendrites, and loss of synaptic spines. They also include a gradual breakdown of the myelin that covers the long axons that connect prefrontal with posterior association cortex. The prefrontal cortex leads most cortical areas in morphological aging. It is also one of the most vulnerable to the neurodegenerative changes that take place in dementias.

The prefrontal cortex receives afferent fibers from numerous structures of the diencephalon, the mesencephalon, and the limbic system. In addition to the nucleus medialis dorsalis,

other thalamic nuclei project to that cortex. Some of those thalamic projections convey to the prefrontal cortex influences from lower levels of the brainstem, from the cerebellum, and from limbic structures. The prefrontal cortex also receives direct afferents from the hypothalamus, the midbrain, the amygdala, and the limbic cortex. In addition, fibers from various neocortical areas implicated in sensory functions converge on both the lateral and orbitomedial aspects of the prefrontal cortex. This pattern of multimodal convergence can be clearly discerned in the monkey. Practically all the prefrontal connections are reciprocal: structures sending fibers to the prefrontal cortex are also the recipients of fibers from it. Exceptional in that regard are the basal ganglia and pontine nuclei, to which the prefrontal cortex sends some unreciprocated direct projections.

Different regions of the prefrontal cortex have different sets of reciprocal connections. Thus, a different topological pattern of connectivity can be recognized, particularly in primates, for orbitomedial and lateral areas, which are heavily interconnected. The orbital and medial prefrontal cortex is primarily connected with the medial thalamus, the hypothalamus, the amygdala, and limbic and medial temporal cortex, including the hippocampus. This complex interconnected system, composed of phylogenetically old, early developing structures, is the anatomical substrate for emotional, instinctive, and affect-modulated behavior.

The lateral prefrontal cortex, on the other hand, is primarily connected with the lateral thalamus, the dorsal caudate nucleus, and the neocortex. This newer system of interconnected structures constitutes the substrate for executive cognitive functions and behavior. A hierarchy of interconnected areas of motor function, with lateral prefrontal cortex at the summit, can be discerned in the convexity of the frontal lobe of the primate. All stages of this frontal motor hierarchy (prefrontal, premotor, and primary motor) are connected with posterior neocortical

areas of sensory and mnemonic functions. They are also connected with the basal ganglia by re-entrant connective loops that course through the lateral thalamus and the cerebellum. The three stages of that frontal hierarchy constitute the upper stages of the perception-action cycle, which is the circular flow of information processing that links the organism with its environment in the course of goal-directed behavior.

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# Chemical Neurotransmission

## OUTLINE

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## I. INTRODUCTION

Information concerning the environment, internal states, motives, and behavioral acts is transmitted within the brain by spatiotemporal patterns of neuronal discharge. Communication between neurons takes place by electrochemical transactions mostly at synaptic junctions. Typically, these junctions are between the axon terminals of the presynaptic neuron and the dendrites of the cell body of the postsynaptic neuron, although other forms of synaptic contact (e.g., axoaxonic) are also present in certain brain regions. Moreover, electrochemical communication between cells may take place through certain forms of interface other than

synapses (e.g., ephapses). In any case, the transmission is basically effected across nerve cell membranes by interdependent chemical and electrical changes. Cells produce certain chemical substances called neurotransmitters and neuromodulators that, through specific receptors embedded in presynaptic and postsynaptic membranes, modify the electrical activity of other nerve cells.

In the most typical intercellular transaction, the arrival of an action potential in the axon terminal of a given neuron results in the opening of calcium ( $\text{Ca}^{2+}$ ) channels in the cell's terminal presynaptic membrane, whereby the cation flows into the terminal. The accumulation of intracellular  $\text{Ca}^{2+}$  promotes the

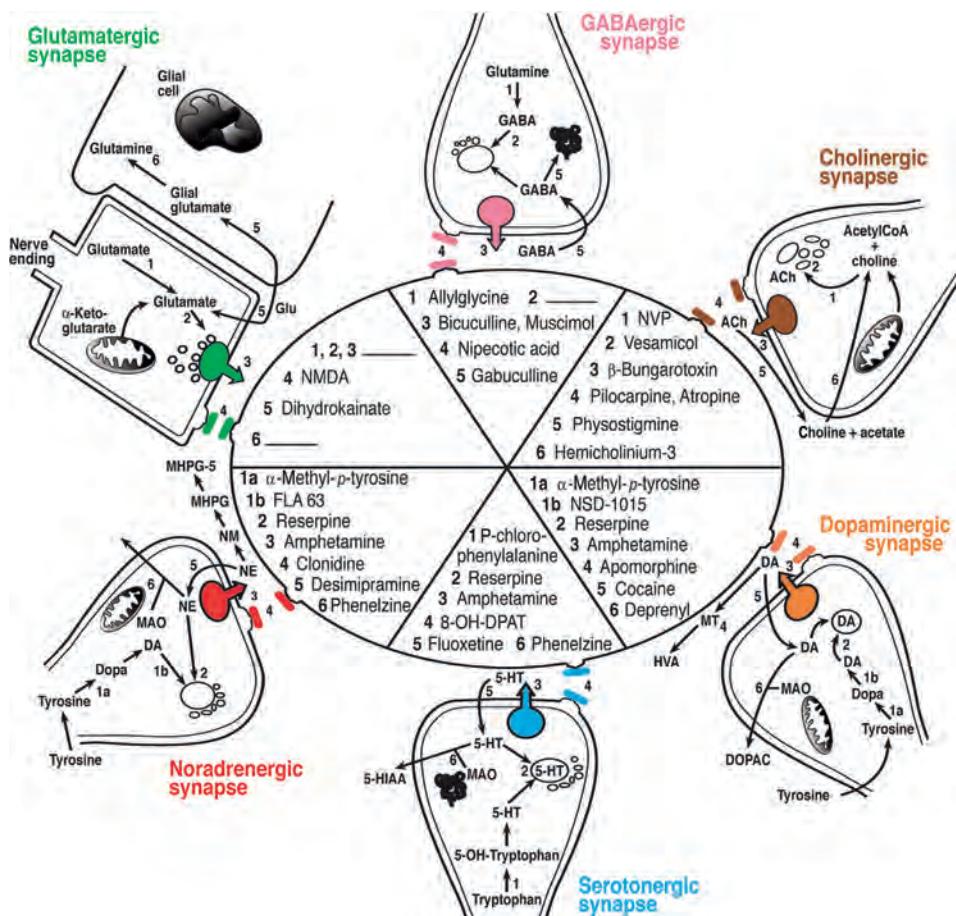
release (exocytosis) of a neurotransmitter substance from the synaptic vesicles of the pre-synaptic membrane into the extraneuronal synaptic space. Thereupon, specific receptors, which are made of proteins in the postsynaptic membrane, recognize and incorporate the transmitter or ligand into their structure. This alters membrane ion permeability, membrane potential, and metabolism in the postsynaptic neuron, frequently through the intervention of second messengers such as cyclic adenosine monophosphate (cAMP). The cumulative effect of such changes (from repeated presynaptic action potentials) is to modify the firing rate of the postsynaptic neuron. By virtue of enzymatic reactions and servomechanisms, including chemical feedback to the presynaptic membrane and its specialized receptors (e.g., autoreceptors), the neurotransmitter remaining in the extraneuronal space is inactivated or taken up by the presynaptic terminal, and both the production and the transsynaptic effects of the neurotransmitter are momentarily arrested. The entire process unleashed by a single action potential is extremely rapid, sometimes on the sub-millisecond time-scale.

Although the designation “neurotransmitter” is used in this chapter generically for all chemical transmitter substances, in recent years and especially in the context of prefrontal physiology, the distinction has been made between neurotransmitters proper and neuromodulators. Glutamate and  $\gamma$ -aminobutyric acid (GABA) are included among the first, which are characterized by rapid effects on the ion channels that mediate transmission. For example, glutaminergic pyramidal cells of the prefrontal cortex engage in rapid, persistent activity during working memory, while GABAergic neurons help to tune the network’s firing by inhibiting responses to irrelevant stimuli and memories (Rao et al., 2000). Neuromodulators, on the other hand, include most other transmitters (monoamines, acetylcholine, etc., and sometimes also glutamate and GABA when they act

on certain receptors). They are relatively slow acting and often involved in changes of general state (e.g., between sleep and wakefulness) or reward value.

Neurotransmitters are produced within the body of the nerve cell and transported along the axon to its terminal synaptic vesicles, which in some cases are considerably remote from the soma; for example, catecholamine transmitters generated in certain cells of the lower brainstem are conveyed all the way to the cortex by the axons of those cells. The rate of neurotransmitter synthesis within a given cell is subject to a variety of metabolic factors, but the level of the substance at the terminals is kept relatively constant. Numerous chemical substances, however, can modify that level and, more generally, modify synaptic transmission by acting on one or more of the six successive steps that any given neurotransmitter undergoes. These steps are the following: (1) biosynthesis in the presynaptic neuron; (2) storage in synaptic vesicles; (3) release into the synaptic cleft; (4) binding and recognition by target receptors; (5) reuptake; and (6) metabolic inactivation. Figure 3.1 schematically illustrates the process for the more common – “classical” – neurotransmitters, as well as the sites or steps of the action of some drugs on their respective synapses.

There are two basic kinds of neurotransmitter receptors. The first are called “ionotropic,” as their protein structure forms ion channels through the membrane that mediate rapid electrochemical transmission. Receptors of the second kind are called “metabotropic”; they are made of polypeptides that, upon binding a transmitter, undergo certain intracellular changes that make them capable of binding and activating so-called G-proteins. G-protein activation initiates a cascade of intracellular chemical events that can have numerous effects on the cell. These can be very rapid (e.g., phosphorylating ion channels to change cell responsiveness) or very slow (e.g., altering transcription to change the makeup of a cell). In either case, they



**FIGURE 3.1** Synaptic processes – depicted in and around synaptic vesicles – for six major neurotransmitters: glutamate (Glu), γ-aminobutyric acid (GABA), norepinephrine (NE), dopamine (DA), serotonin (5-hydroxytryptamine, 5-HT), and acetylcholine (ACh). Each neurotransmitter undergoes six basic successive processing steps (designated by number): (1) synthesis; (2) vesicular uptake; (3) release; (4) receptor binding; (5) reuptake; and (6) inactivation. In the sector of the central circle corresponding to every transmitter, chemical agents are inserted that act at the steps indicated by the numbers that precede them. Abbreviations: CoA, coenzyme A; DOPAC, 3,4-dihydroxyphenylacetic acid; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; MAO, monoamine oxidase; MHPG, 3-methoxy-4-hydroxyphenylglycol; MT, 3-methoxytyramine; NM, normetanephrine; NMDA, N-methyl-D-aspartate; NVP, naphtyl vinyl pyridinium ion; 8-OH-DPAT, 8-hydroxydipropylaminotetralin. FLA-63 and NSD-1015 are pharmaceutical code names. (From Wilcox and Gonzales, 1995, modified, with permission.)

can have the net effect of increasing a receptor's affinity for a transmitter (although, conversely, desensitization is also possible and common). Because of the complexity of the enzymatic reactions of metabotropic receptors, their

responses to transmitter binding are generally slower and of longer duration (from seconds to hours) than those of ionotropic receptors. The majority of the classical transmitters can bind to and activate ionotropic as well as metabotropic

receptors, thereby inducing both fast and slow postsynaptic changes. Some of the transmitters, dopamine (DA) for example, will bind differentially to subclasses ( $D_1$ ,  $D_2$ , ...,  $D_5$ , ...) of one category or the other. Different receptors are coupled to different G-proteins, and thus have different second messenger effects. For example, DA increases cAMP production via  $D_1$  receptors coupled to  $G_s$ , while DA decreases cAMP production via  $D_2$  receptors coupled to  $G_i$ .

Autoreceptors constitute a special group of receptors that are in charge of regulating the presynaptic concentration and postsynaptic effects of neurotransmitters by inhibiting transmitter release and synthesis. The so-called transporters, too, have a regulating function, by taking transmitter back into the cell. In the aggregate, autoreceptors and transporters are capable of binding, inactivating, or taking up the excess amounts of the particular neurotransmitter released into their adjacent synaptic cleft. There are probably as many autoreceptors and transporters as there are neurotransmitters, and their mechanisms of action vary considerably. These mechanisms, which essentially ensure one form or another of negative feedback, have the ultimate important objective of limiting subsequent – and unnecessary or adverse – release of a particular neurotransmitter.

The regional concentration of a given transmitter or class of receptors generally differs for different brain structures, in some cases markedly. This is true in the three animal species – rat, cat, and monkey – most intensively investigated. Certain neural structures and pathways have been grouped and characterized as forming separate functional systems because they share a prevalent neurotransmitter. Accordingly, there is a tendency to ascribe a given function (cognitive, affective, behavioral, or other) to a given neurotransmitter, yet given the present state of our knowledge there is little justification to do so with any of the many neurotransmitters so far identified. In any event, none of them can have more functional specificity than the system

of interconnected brain structures in which it operates. To pretend otherwise is tantamount to confusing the message with the messenger, an all-too-common reductionist error in neuroscience. In any event, any assumption of functional specificity for any particular neurotransmitter has to contend with the increasing evidence that many cells, notably in the cortex, colocalize several neurotransmitters. Furthermore, most regions of the primate's cortex receive monoaminergic and cholinergic input from the brainstem and basal forebrain.

Nevertheless, the differentiation and analysis of neurotransmitter systems have gained enormous importance in the quest for understanding higher integrative functions and their disorders. Neurotransmitter studies are especially relevant to the functions and pathology of the frontal lobes. On the one hand, there is the mounting evidence that the modulation of synaptic transmission in the most plastic brain regions, such as the association areas of the cortex (e.g., the prefrontal cortex), is at the foundation of learning and memory. On the other, there is the evidence that certain pathological conditions of neurotransmitter systems are at the foundation of neuropsychiatric disorders. For example, a clear relationship exists between the degeneration of a dopaminergic system in the basal ganglia and Parkinson's disease; and schizophrenia is associated with abnormalities of another dopaminergic system also involving the basal ganglia and the prefrontal cortex.

The following are the most important classes of neurotransmitters thus far identified in the cerebral cortex: (1) amino acids (i.e., glutamate, aspartate, GABA); (2) the monoamines, including two catecholamines, dopamine (DA) and norepinephrine (NE, or noradrenaline), and an indoleamine, 5-hydroxytryptamine (5-HT) or serotonin; (3) acetylcholine (ACh); and (4) neuropeptides (e.g., enkephalins, substance P, somatostatin, neurotensin). The most widely used methods of neurotransmitter study are the following: high-pressure liquid

chromatography, autoradiography, immunohistochemistry (including radioimmunoassay), electron microscopy, local application of selective neurotoxins [e.g., 6-hydroxydopamine (6-OHDA) and kainic acid], turnover analysis, molecular protein analysis, and administration of neurotransmitter agonists and antagonists.

## II. DEVELOPMENT AND AGING

Considerable progress has been made since the 1980s on the genetic and molecular biology of neurotransmitter systems. Genes and gene families have been identified that participate in the development of the classical neurotransmitters and receptors (see reviews by [Deutsch and Roth, 1999](#); [Waxham, 1999](#)). For example, the gene has been identified that leads to the expression of tyrosine hydroxylase (TH), the enzyme that critically intervenes in the metabolism of tyrosine toward the formation of the two catecholamines, DA and NE. Also identified have been the ancestral genes for glutamate and cholinergic receptor families. The events associated with the opening of one acetylcholine receptor (nAChR) have been revealed almost at the atomic level.

The genetic expression and molecular structure of various kinds of DA receptors have also been clarified; some of these receptors, which play a major role in the prefrontal cortex of the primate, are implicated in the pathogenesis of schizophrenia. At the same time, the development of DA in the child's prefrontal cortex is dependent on some aspects of gene expression that may be impaired in certain genetic disorders, leading to cognitive deficits; phenylketonuria (PKU), a genetic disorder that impairs the formation of tyrosine, leads to low levels of DA in the prefrontal cortex, with consequent cognitive abnormalities ([Diamond, 1996, 2007](#)). On the other hand, the presence of a certain gene responsible for the formation of catechol-O-methyltransferase (COMT) slows

the breakdown of DA in the prefrontal cortex, resulting in improved cognitive performance ([Diamond et al., 2004](#)). However, COMT, possibly because of a pathological phenotypical interference with DA metabolism, has been associated with increased risk for schizophrenia ([Weinberger et al., 2001](#); [Tan et al., 2007](#); [Williams et al., 2007](#)).

The development of monoamine systems and metabolism has been the object of considerable scrutiny. It was largely as a result of developmental studies in the rat that the three monoaminergic systems (NE, DA, and 5-HT) were characterized as functionally independent ([Coyle and Axelrod, 1972](#); [Kellogg and Wennerström, 1974](#); [Tassin et al., 1975](#); [Bourgoin et al., 1977](#)). Later studies have clarified various aspects of the development of the monoamine systems of the rat that originate in the brainstem and project to the cerebral cortex. The prefrontal cortex is a major recipient of those projections, which it needs for its development early in life. In the young animal (e.g., the postnatal rat, 16–20 days old), 5-HT has been shown to increase neuronal activity in the prefrontal cortex, thus presumably playing a role in the formation of synapses and prefrontal connectivity ([Beique et al., 2004a, 2004b](#)); DA has also been attributed such a role ([Sugahara and Shiraishi, 1998](#)). In the monkey, early lesions of the mesocorticolimbic DA system (within the first 3 weeks after birth) lead to faulty neuronal development in the prefrontal cortex ([Bertolino et al., 1997](#)).

Neurochemical research in the rhesus monkey led to the original findings on the developmental timetables and regional distributions of monoamines in the neocortex of the primate ([Brown and Goldman, 1977](#); [Goldman-Rakic and Brown, 1982](#)). At birth, the primate's cortex already shows the basic pattern of monoamine distribution of the adult cortex, with NE and DA high in frontal cortex and relatively low in occipital cortex, and 5-HT the opposite. From birth to 3 years of age, NE concentration shows

in all areas a progressive increase toward adult levels, including a characteristic peak in somatosensory cortex. DA has generally reached adult levels by 5 months of age. In the prefrontal cortex, DA has already almost reached the adult level at birth, but it falls temporarily during infancy, and its adult concentration is not reattained until the animal is 2–3 years of age. In general, 5-HT maturation is more rapid than that of the other amines. In the prefrontal cortex, however, it parallels that of DA.

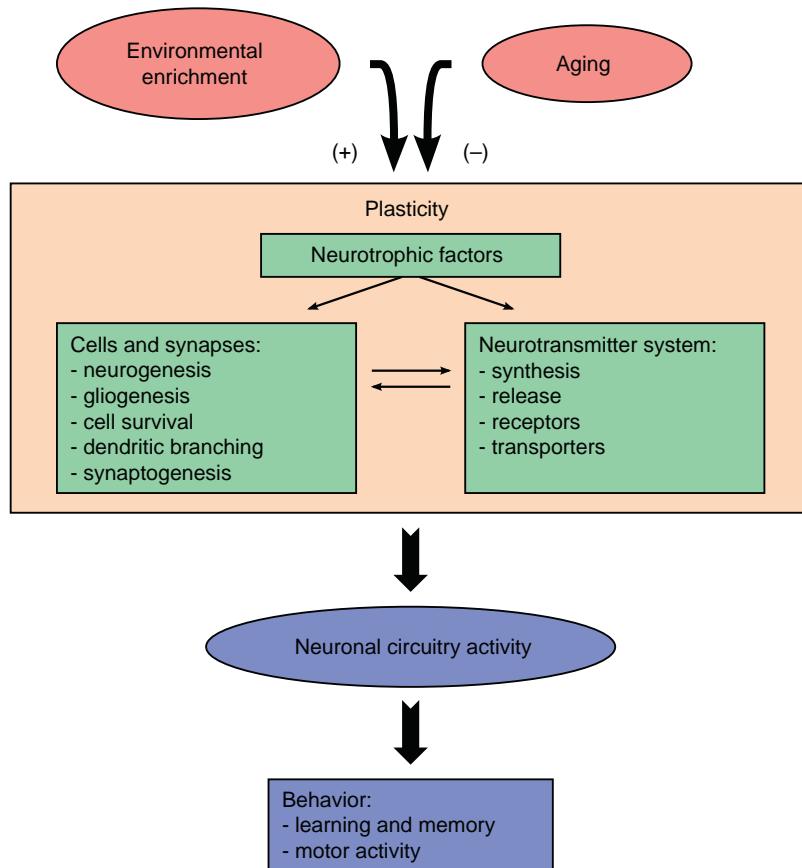
Subsequent studies have shown that most all known cortical neurotransmitters and receptors, not only the monoamines, are present in the cortex at birth and generally develop in synchrony thereafter; this is true also in the prefrontal cortex (Johnston et al., 1985; Van Eden et al., 1987; Lidow and Rakic, 1992; Schwartz and Meinecke, 1992). The development of GABA, the inhibitory neurotransmitter, seems to be an exception to the rule of synchronous development of the classical neurotransmitters; developmental studies of GABA markers in the monkey's prefrontal cortex indicate that different types of GABA terminals and receptors have different postnatal timetables of morphogeny and/or habilitation (Erickson and Lewis, 2002; Cruz et al., 2003). In the primate, transmitters and receptors, along with synaptogenesis (see Chapter 2), tend to reach a postnatal peak and then undergo gradual descent (attrition from pruning) to adult levels. Early in life, an adequate supply of DA appears essential for the normal development of cortical cells: rats in which the prefrontal cortex has been depleted of DA innervation by postnatal lesion of the VTA show markedly diminished length of the basal dendrites of pyramidal cells in layer V (Kalsbeek et al., 1989). As noted above, lesions of the DA system hamper neuronal development in the prefrontal cortex (Bertolino et al., 1997).

In the course of normal aging, the cerebral cortex undergoes gradual changes in metabolism and in the concentration of certain chemicals. Such changes are related to the

age-dependent changes in morphology noted in Chapter 2 and to the more or less subtle deficits in cognitive function that advanced age ordinarily brings about. In normal aging, as in early development, there are complex interactions between the environment and the nervous system that enhance or depress the plasticity of neural elements for the acquisition and retention of cognitive information. The cerebral cortex is especially sensitive to those interactions. A comprehensive review of the relevant literature by Mora et al. (2007) highlights the opposite effects of “environmental enrichment” and aging on a number of structural and neurochemical variables (Figure 3.2).

As a function of age, all neocortical regions show a tendency toward lower metabolic activity. That decline, according to cerebral glucose metabolism studies in the human (Kuhl et al., 1982; Smith, 1984), is greatest in the frontal region. The reasons behind this drop in cortical metabolism are not clear. It may have something to do with the reduction of cortical circulation that occurs in old age and to which the frontal cortex is particularly liable. In fact, investigations of regional cerebral blood flow have shown an age-dependent decline in cortical blood flow that prominently affects the frontal cortex (Gustafson et al., 1978; Shaw et al., 1984). However, carefully screened, healthy old subjects, free of vascular disease and vascular risk factors, have been reported to have frontal metabolism (Duara et al., 1984) and blood flow (Mamo et al., 1983) comparable to those of young subjects.

A cortical metabolic decline may also be related to the general diminution in the presence and availability of transmitters and modulators, especially catecholamines, that has been shown to result from normal aging in rodents (Finch, 1978; Mora et al., 2007), monkeys (Goldman-Rakic and Brown, 1981), and humans (Carlsson, 1981). The aging of the prefrontal cortex in the monkey is accompanied by a number of morphological and neurochemical



**FIGURE 3.2** Relationship between environmental enrichment and aging. By changing the level of expression of neurotrophic factors, the two have opposite effects on a number of structural and neurochemical variables bearing on synaptic plasticity, cognition, and behavior. (From Mora et al., 2007, with permission.)

changes: loss of dendritic spines, loss of synapses in several layers, “blebbing” of white matter, loss of  $\alpha_2$ -adrenoreceptors, and loss of DA (Moss et al., 1997).

The age-dependent reduction of cortical catecholamines may in part be attributed to a deterioration of the subcortical components of catecholamine systems; in other words, of the brainstem nuclei and of the cells that provide those neurotransmitters to the cortex. In any event, the cortical catecholamine losses occurring with advancing age are very likely to lie at the foundation of concomitant cognitive losses

(Bartus et al., 1978; Luine et al., 1990; Wang et al., 2011; Sambataro et al., 2013). That this is indeed the case is suggested by the evidence that the administration of NE agonists, acting on  $\alpha_2$ -noradrenergic receptors, can reverse the behavioral – for example, delayed response – deficit that occurs presumably as a result of the aging of the prefrontal cortex and its neurochemical substrate (Arnsten and Goldman-Rakic, 1985; Carlson et al., 1992; Rama et al., 1996; Wang et al., 2011).

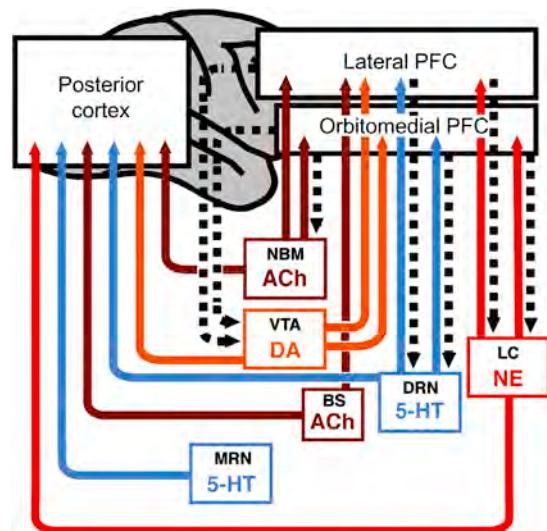
The inference that age-dependent cortical neurotransmitter loss is the basis for at least

some of the cognitive deficits of elderly people is supported by findings from numerous studies in patients with Alzheimer's disease. The dementia that characterizes this disease has often been shown to be accompanied by deficits in neurotransmitters, notably ACh, both at the cortical level and at their subcortical sources (for a review, see [Mann and Yates, 1986](#)). In severe cases, cell death is a major factor. These alterations are particularly conspicuous in frontal and temporal association cortices and the subcortical nuclei that provide them with transmitters ([Adolfsson et al., 1979](#); [Winblad et al., 1982](#)).

To sum up, in Alzheimer's disease, there is accentuation and acceleration of both the cognitive disorders and the loss of the neurotransmitter support of cortical function that characterize the normal aging of the brain. The issue will be further discussed in the section on neurodegenerative disease, later in this chapter. The conclusion seems inescapable that the two deficits, cognitive and neurochemical, are causally related in normal as well as in pathological aging. The prefrontal cortex is particularly affected by the neurochemical deficit, and therefore any age-related cognitive deficit is probably to a large extent a reflection of prefrontal dysfunction.

### **III. TRANSMITTERS IN THE PREFRONTAL CORTEX**

Before entering the discussion of any particular neurotransmitter and its role in the prefrontal cortex, it is appropriate to mention a couple of generalities about the origin and prefrontal termination of the six best known transmitters: glutamate, GABA, NE, DA, 5-HT, and ACh. The most pervasive of them, the amino acid GABA, is the prime inhibitory neurotransmitter in the central nervous system, as prevalent in the prefrontal cortex as it is elsewhere; as we shall see below, it is largely a local transmitter, which serves interneurons and acts for the



**FIGURE 3.3** Schematic diagram of the principal cortical projections of chemically defined monoaminergic [dopamine (DA), norepinephrine (NE), serotonin (5-HT)], and cholinergic (ACh) systems of the brainstem. Dashed lines designate backprojections from the prefrontal cortex (PFC). Abbreviations: BS, brainstem cholinergic cell groups; DRN, dorsal raphe nuclei; LC, locus coeruleus; MRN, medial raphe nuclei; NBM, nucleus basalis of Meynert; VTA, ventral tegmental area. (From [Arnsten and Robbins, 2003](#), modified, with permission.)

most part upon neighboring cells. The other four neurotransmitters originate in nuclear formations of the brainstem and project to both orbitomedial and lateral prefrontal cortex. The origin and prefrontal projections of those neurotransmitter systems are schematically depicted in [Figure 3.3](#). Note that the subcortical nuclei of neurotransmitter origin receive back-projections from the prefrontal regions to which they project.

#### **A. Glutamate**

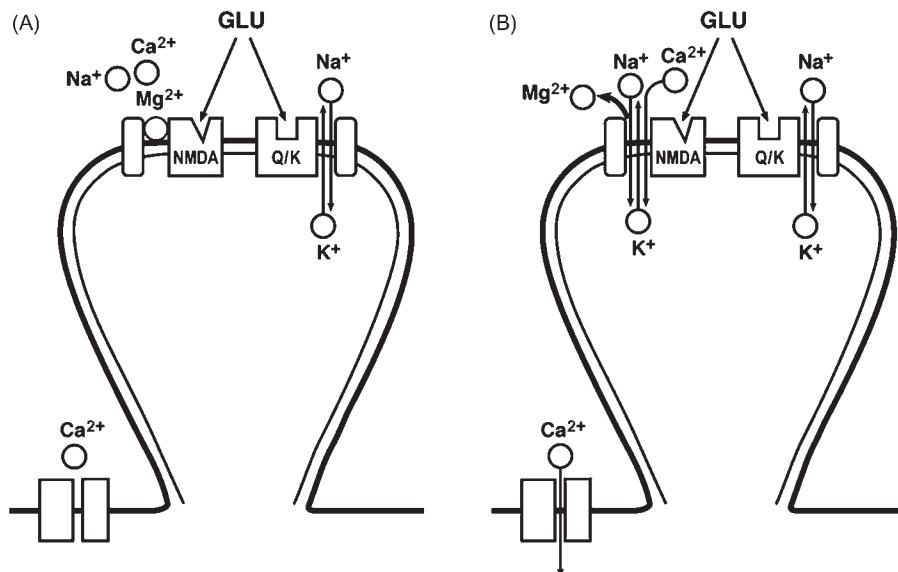
Glutamic acid is the major excitatory neurotransmitter in the nervous system. It is found in large quantities in all of the nervous system, and there is hardly a neural structure in which it has

not been found. It shares its excitatory function with aspartic acid, another amino acid, although the latter is less ubiquitous and less understood. Both excitatory amino acids are part of intermediary glucose metabolism, glutamate deriving from the Krebs cycle. For this reason, their identity as neurotransmitters is difficult to disambiguate from their metabolic role. Also difficult to disambiguate are glutamate- from aspartate-containing neurons. Neither transmitter crosses the blood-brain barrier. Glutamate derives directly from glucose by transamination of  $\alpha$ -ketoglutarate or from glutamine, which is synthesized by glial cells. Thus, transactions between excitatory neurons and glia play an important role in the availability and regulation of glutamate. Upon depolarization of the nerve terminal that contains it, glutamate is released in the synaptic cleft in a calcium-dependent manner. The release is regulated by a metabotropic autoreceptor. Inactivation is metabolic, largely by reversion of glutamate into glutamine and partial reincorporation into glia cells.

Glutamate is the prime excitatory transmitter of pyramidal cells; they are glutamate-containing neurons, although they may colocalize other transmitters in addition to glutamate. In essence, nonetheless, these cells are the excitatory counterpart to the inhibitory GABA neurons. They are projection neurons. Because of the numerical and volumetric pre-eminence of pyramidal cells, glutamate, and to a lesser degree aspartate, are the excitatory neurotransmitters at maximal concentrations in the cerebral cortex. Region by region, glutamate is found in large concentrations throughout (Kim et al., 1977; Fonnum et al., 1981; Westbrook and Jahr, 1989), notably in the prefrontal region (Peinado et al., 1984; Sanz et al., 1993). Both, glutamate and aspartate have been reported in corticostriatal and corticothalamic axons (Bromberg et al., 1981), especially of prefrontal origin (Fonnum et al., 1981). Glutamate probably plays an important role in the reciprocal connectivity between the hippocampus and the prefrontal cortex.

There are four categories of glutamate receptors, the first three ionotropic and the fourth metabotropic: (1) N-methyl-D-aspartate (NMDA, agonist NMDA); (2) kainate (agonist kainate); (3) amino-methyl-isoxazole-propionate (AMPA, agonist AMPA); and (4) metabotropic glutamate receptor (agonists L-AP4, ACPD, L-QA). The first three depolarize the postsynaptic membrane by opening ion channels (Figure 3.4). NMDA receptors have received considerable interest as they are presumed to be critically involved in learning and memory (Dingledine, 1983; Cotman and Iversen, 1987). Because they are voltage dependent and because of the long course of the current changes they induce, they are eminently suitable for the temporal integration of information, as required for the establishment of associative memory (Fuster, 1995). Furthermore, they have been found at the foundation of the phenomenon of long-term potentiation (LTP), which is a model mechanism for synaptic plasticity in memory formation. NMDA plays a key role in this mechanism, which is regulated by GABA, although nitric oxide (Böhme et al., 1983) and AMPA (Maren et al., 1993) are suspected to play coadjuvant roles.

LTP was first demonstrated in the hippocampus (see Nicoll et al., 1988, for a review). Although it is a plausible mechanism of long-term plastic synaptic change in memory formation, it has not yet been conclusively demonstrated as such. Moreover, whereas NMDA receptors are exceedingly common in the cerebral cortex (Cotman et al., 1987), their role in cortical plasticity is also yet to be established. However, because NMDA receptors are most common in layers II and III (Cotman et al., 1987), which are the origin and termination of most corticocortical connections (see Chapter 2), it is possible that glutamate-NMDA synaptic transactions are at the root of cortical plasticity in the formation of associative memory, perhaps under the critical influx of concomitant hippocampal inputs.



**FIGURE 3.4** Electrochemical transactions across the membrane of cells with glutamate (Glu) receptors. (A) Normal synaptic transmission,  $\text{Na}^+$  and  $\text{K}^+$  flowing through quisquulate/kainate (Q/K) channels, not *N*-methyl-D-aspartate (NMDA) channels. (B) In high-frequency depolarization, NMDA channels are unblocked, allowing  $\text{Ca}^{2+}$  to flow through them. At the bottom of the figure are voltage-dependent calcium channels. (From Nicoll et al., 1988, slightly modified, with permission.)

Jay et al. (2004), reviewing their own research and that of others, emphasize the critical role of the hippocampus for the appearance of LTP in the prefrontal cortex. By investigating the effects of ventral tegmental area (VTA) stimulation and cortical DA depletion, they show that DA (through specifically  $\text{D}_1$  receptors) is essential for LTP at hippocampal–prefrontal junctions. Conceivably, these interactions between neurotransmitters (DA, glutamate) and receptors ( $\text{D}_1$ , NMDA) may constitute the physiological basis for the acquisition of executive memory in the associative networks (*cognits*: Fuster, 2003) of the prefrontal cortex.

By microdialysis in the dorsolateral prefrontal cortex of monkeys, glutamate has been shown to facilitate a sensory-guided task (Kodama et al., 2002), but not a working-memory task (unlike DA, which does facilitate the latter). Also, glutamate has been reported to be elevated by stress in the medial prefrontal

cortex of the rat (Moghaddam, 1993). Stress has also been shown to inhibit hippocampal–prefrontal LTP (Jay et al., 2004), which is presumably paradigmatic of the formation of cortical memory. Although the mechanisms behind these phenomena are not entirely clear, it is possible that, in all of them, prefrontal glutamate projections to brainstem nuclei play a role by activating positive-feedback loops in catecholamine systems that, while increasing anxiety, may be deleterious to cognition.

## B. $\gamma$ -Aminobutyric Acid

About one-quarter of all the neurons in the cerebral cortex – and the prefrontal cortex is no exception – utilize GABA, the prime inhibitory synaptic transmitter and the most abundant of all neurotransmitters thus far identified in the central nervous system. It was discovered by Eugene Roberts in 1950 (Roberts and Frankel,

1950). The brain content of GABA is between 200 and 1000 times greater than that of any of the transmitters reviewed so far. Unlike them, however, it is mainly an intrinsic neurotransmitter. It mediates mostly transactions between neighboring cells, in local circuitry where inhibition plays a role. It is presumed to serve all inhibitory interneurons, which are found practically everywhere in the nervous system. GABA is the mediator of the inhibitory action that Purkinje cells have upon other neurons in the cerebellum.

GABA, unlike the monoaminergic and cholinergic transmitters, is embedded in the metabolism of glucose, the “foodstuff of the brain,” and this may be one of the reasons for its pervasiveness. Its metabolic precursor is the amino acid glutamate. Glutamate is converted into GABA under the action of glutamic acid decarboxylase (GAD), the synthesizing enzyme, which is practically as pervasive as GABA itself and a useful marker of GABA. There are two principal types of GABA receptors: GABA<sub>A</sub> and GABA<sub>B</sub>. GABA<sub>A</sub> is the main postsynaptic receptor, molecularly akin to the ACh receptor family, with which it probably shares a common ancestral gene (Waxham, 1999); GABA<sub>B</sub>, however, has been identified as mainly an autoreceptor involved in the self-regulation of GABA. The reuptake of GABA takes place into both neurons and glia. It shares this demise with the other amino acid transmitter, glutamate, perhaps because the two are metabolic intermediaries in addition to being neurotransmitters.

Although GABA- and GAD-immunoreactive neurons are ubiquitous throughout the cortex, they are most common in layers II–IV (Hirsch and Robins, 1962; Hendry et al., 1987; Gabbott and Bacon, 1996), where GABA is released during inhibition (Iversen et al., 1971; Kolachana et al., 1997). GABA is mainly detectable in non-pyramidal cells, such as granules and stellate cells (Houser et al., 1983). Because of its uniform distribution and its high concentration in intrinsic cells, it is reasonable to suppose that

in the prefrontal cortex (Emson and Lindvall, 1979), as elsewhere (Krnjevic, 1974; Dykes et al., 1984), GABA supports local inhibitory functions – possibly lateral inhibition – that enhance the saliency and contrast of the excitatory patterns of prefrontal neurons in the exercise of their main functions. GABA’s inhibitory role has been physiologically substantiated in several frontal areas, including the prefrontal cortex (Brailowsky et al., 1986; Oishi and Kubota, 1990; Matsumura et al., 1992). Prefrontal GABA depletion in the monkey induces a deficit in delay-task performance (Sawaguchi et al., 1988a). On the basis of iontophoretic, immunological, and behavioral observations, it has been postulated that GABA interneurons exert modulating influences upon the cell bodies or initial axon segments of pyramidal memory cells, so as to regulate the sustained activity of those cells during the maintenance of working memory (Sawaguchi, 2001; Lewis et al., 2002). Recurrent inhibition through GABA<sub>A</sub> and NMDA receptors is at the basis of one of the most cogent computational models (see Chapter 6) of prefrontal working memory (Brunel and Wang, 2001).

For a long time, GABA neurons have been widely considered to be mainly inhibitory interneurons, as noted above, enmeshed in local cortical circuitry and performing local functions. This view has changed in recent years, however, largely as a result of research on GABA in the prefrontal cortex. With the advent of new neuroanatomical and immunological methods, and the discovery of antibodies against GABA and GAD, it is becoming apparent that numerous GABA neurons with long axons project to the prefrontal cortex, and *vice versa*, that many such neurons with soma in the prefrontal cortex project to distant structures under prefrontal control. Especially noteworthy in this respect are the discoveries of neurons in brainstem nuclei that project to the prefrontal cortex axons with GABA, along with other neurotransmitters. Thus, remarkably, GABA-containing

neurons with projections to the prefrontal cortex have been identified in the VTA (Carr and Sesack, 2000); this area, therefore, provides the prefrontal cortex with DA and GABA. Similar findings have been made in the basal forebrain region, projecting to prefrontal cortex both ACh and GABA (Sarter and Bruno, 2002), and in the raphe nuclei, projecting both 5-HT and GABA (Puig et al., 2005). Curiously, in the latter case, it appears that the nuclei of the raphe modulate prefrontal pyramids by dual and opposite influences: 5-HT-mediated excitation, on the one hand, and GABA- and 5-HT-mediated inhibition, on the other.

Goldman-Rakic and her colleagues (Rao et al., 1999, 2000) conducted pioneering investigations in the monkey on the role of GABA in the microcircuitry of the prefrontal cortex. They discovered that GABA plays a critical role in the inhibition of prefrontal cell responses to non-preferred or irrelevant stimuli in working memory. Insofar as working memory is a form of attention – directed to an internal representation (see Chapters 5 and 6) – those authors substantiate in the microcolumnar organization of the lateral prefrontal cortex an important aspect of the physiology of the exclusionary (inhibitory) component of attention.

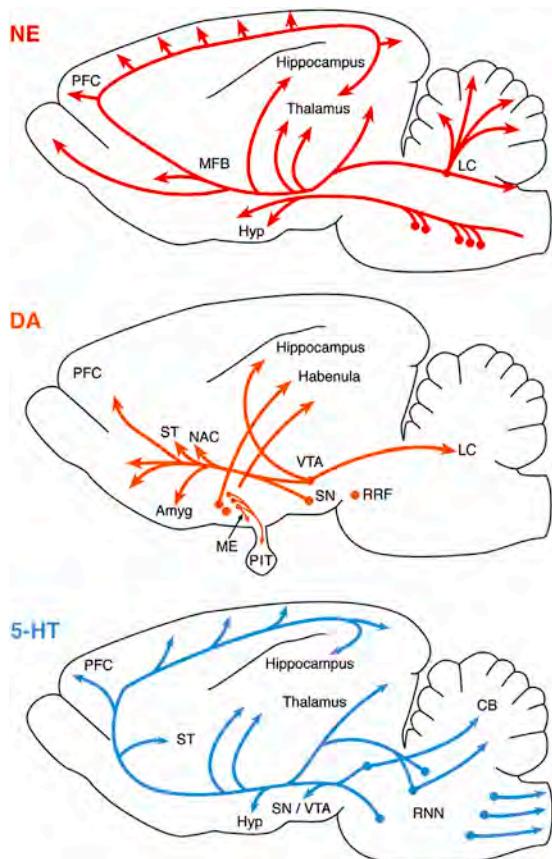
Hashimoto et al. (2004) summarize their thinking on the types of GABA neurons in the human prefrontal cortex. In this cortex, they characterize three major types of GABA cells: (1) neurons with inhibitory synapses to initial segments of neighboring pyramidal neurons that they presumably regulate (these GABA cells express the calcium-binding protein parvalbumin); (2) neurons with inhibitory synapses to distal dendrites of pyramidal neurons, where they regulate their excitatory inputs (these GABA cells express calretinin); and (3) neurons with inhibitory synapses to other GABA cells, whereby in effect they disinhibit – downstream – pyramidal cells.

Glycine is another inhibitory amino acid transmitter. It is mainly present and active in

the spinal cord, the medulla, the pons, and the diencephalon. In the cerebral cortex, it is present in only small amounts. In addition to GABA and glycine, there is a special class of substances that are characteristic of certain classes of non-pyramidal interneurons (including some chandelier and basket cells): the calcium-binding proteins, calretinin, parvalbumin, and calbindin. They seem to play a protective role against excessive intracellular calcium levels. All three are present in the prefrontal cortex (Lund and Lewis, 1993; Condé et al., 1994). They, and the cells that contain them, are probably essential for the proper functioning of local prefrontal circuits. At the same time, some of those calcium-binding proteins, notably parvalbumin and calbindin, have been shown to mediate influences from anterior lateral, medial, and orbital prefrontal areas upon interneurons of superior temporal cortex (Barbas et al., 2005). It is reasonable to infer that these influences are at the basis of the inhibitory control that those areas exert upon the posterior cortex. Such inhibitory control, as we shall see, is of critical importance for the prefrontal cortex to play its top-down role in such functions as sensory attention and perception.

## C. Norepinephrine

In the rat, where catecholamine systems were first discovered and described, two major norepinephrine (NE) pathways originate in the brainstem reticular formation (Ungerstedt, 1971). One is a ventral bundle of axons from pontine and medullary reticular formation cells; it innervates several nuclei of the hypothalamus and the upper brainstem (Figure 3.5). The other adrenergic pathway, this one with a major cortical destination, can be best characterized as a system of pathways with a common origin: a densely packed group of cells constituting the locus coeruleus, a nucleus adjacent to the wall of the fourth ventricle, in the lateral medulla. The axons of these cells follow diverging



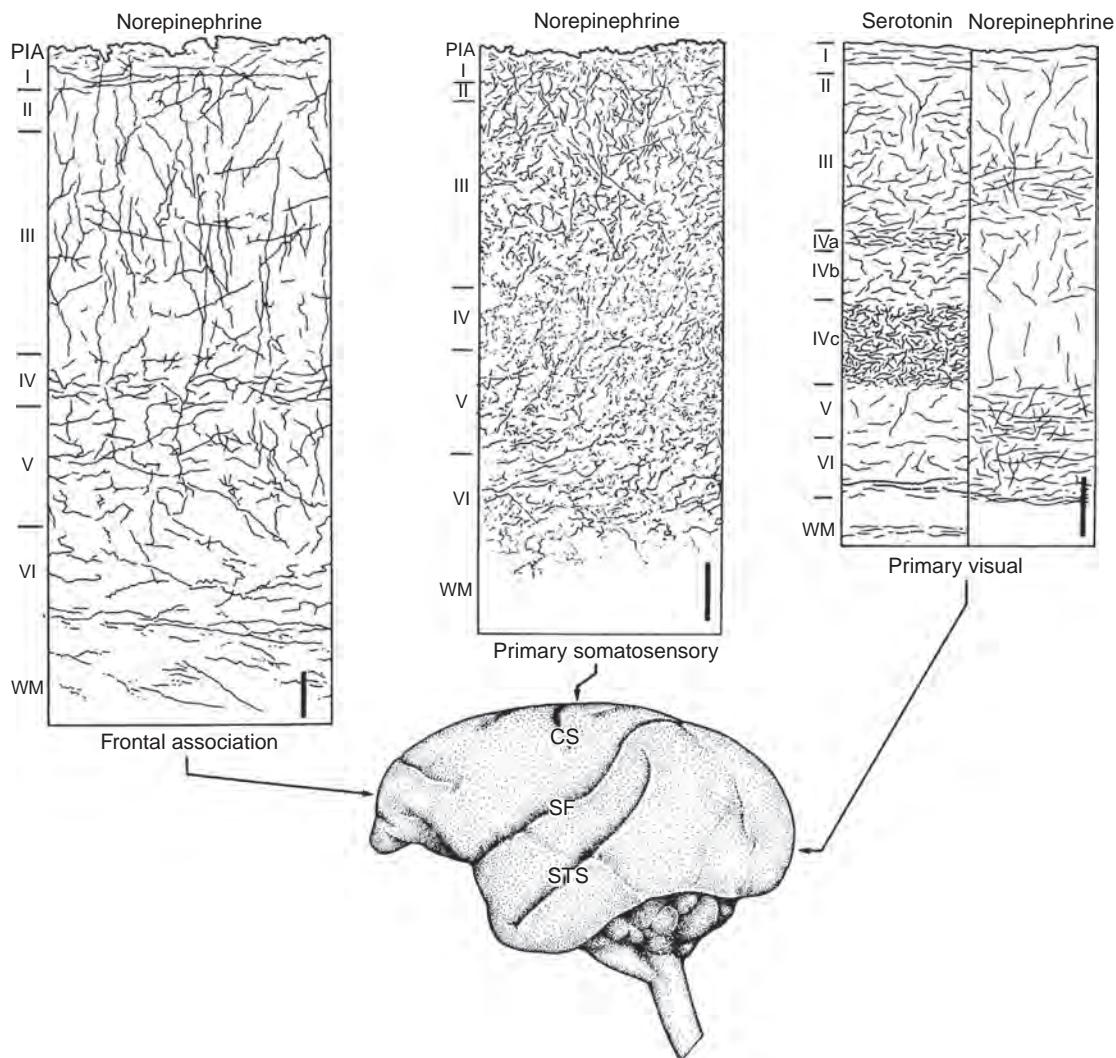
**FIGURE 3.5** Schematic of the major collections of monoaminergic neurons and their projections in the rat brain: noradrenergic (NE), dopamine (DA), and serotonin (5-HT). Abbreviations: Amyg, amygdala; CB, cerebellum; Hyp, hypothalamus; LC, locus coeruleus; ME, median eminence; MFB, medial forebrain bundle; NAC, nucleus accumbens; PFC, prefrontal cortex; PIT, pituitary; RNN, raphe nuclei; RRF, retrotrubral field; SN, substantia nigra; ST, striatum; VTA, ventral tegmental area. (From Deutsch and Roth, 1999, modified, with permission.)

trajectories along the nerve axis, some ascending and some descending. They innervate the spinal cord, the cerebellum, the hippocampus, and the entire cerebral cortex by a direct hypothalamic route. The noradrenergic fibers first enter the cortex of the frontal poles of both hemispheres and then arch

backward, running rostrocaudally within the gray matter and innervating the various cortical areas (Morrison et al., 1979; Morrison and Magistretti, 1983; Fallon and Loughlin, 1987). Within a given area, NE terminal fibers can be seen in all cortical layers, but they appear most dense in layers IV and V. In addition, a mesh of tangential NE fibers, running parallel to the cortical layers, may be observed in layers I and VI. This pattern of organization leads to the logical inference that NE innervation can affect diffusely wide areas of the cortex.

In the monkey, the same basic NE pathways can be found as in the rat (Felten and Sladek, 1983), but their organization and terminal distribution are somewhat different. The cortical distribution of NE and its terminals is more selective and differential in the monkey than in the rat, both regionally and in terms of layers (Brown and Goldman, 1977; Björklund et al., 1978; Brown et al., 1979; Morrison and Magistretti, 1983; Levitt et al., 1984; Lewis et al., 1986a; Lewis, 1992). In the monkey, NE axons and receptors appear especially abundant in intermediate layers, II–V (Lewis and Morrison, 1989; Goldman-Rakic et al., 1990). Catecholamine terminals and receptors are generally more highly concentrated in the anterior than in the posterior portions of the primate cortex; however, the somatosensory cortex of the postcentral gyrus shows a maximum of NE fiber concentration (Morrison and Magistretti, 1983) (Figure 3.6). A high NE concentration in somatosensory cortex has also been found in the dog (Vogt, 1954), the human (Bertler et al., 1958; Gaspar et al., 1989), and the mouse (Lidov et al., 1978).

Despite profuse cortical overlap of the two catecholamines, DA and NE, their patterns of distribution differ somewhat from each other, both regionally and laminarly. Laminarly, there is a degree of complementarity in the two distributions, so that where one transmitter is plentiful the other is scarce, and *vice versa* (Bunney and Aghajanian, 1976; Björklund et al., 1978; Morrison and Magistretti, 1983; Levitt



**FIGURE 3.6** Noradrenergic innervation of three cortical areas of the squirrel monkey. Abbreviations: CS, central sulcus; SF, sylvian fissure; STS, superior temporal sulcus. (From *Morrison and Magistretti, 1983*, with permission.)

et al., 1984; Lewis et al., 1986a, 1987, 1988; Lewis and Morrison, 1989). In the prefrontal cortex, NE is less plentiful than DA. Analysis of the cellular sensitivity to the two transmitters, when they are applied microiontophoretically to the different layers of the prefrontal cortex, has shown that NE axons are more dense in superficial layers and DA-sensitive cells in

deep layers (Bunney and Aghajanian, 1976; Sawaguchi and Matsumura, 1985).

It is difficult to infer any specific function for NE from its patterns of distribution alone. Because this neurotransmitter is so widely distributed throughout the cerebral cortex, it can be assumed to mediate many different functions; indeed, given its reticular origin – that is,

its origin in parts of the brainstem tegmentum that constitute the ascending reticular activating system – the noradrenergic coeruleocortical system probably has a role in the regulation of the excitability and specific functions of vast cortical regions. That the NE system is to some degree self-regulated is suggested by the evidence of corticocerulear inhibitory as well as excitatory influences (Sara and Hervé-Minvielle, 1995; Jodo et al., 1998). Furthermore, it should be kept in mind that, at cortical as well as subcortical levels, catecholamine systems interact physiologically between themselves and with other neurotransmitter systems in ways that are still only partly understood (Hervé-Minvielle et al., 1989; Decker and McGaugh, 1991; Santiago et al., 1993; Smiley and Goldman-Rakic, 1993). Nevertheless, the relatively high NE concentration in prefrontal and postcentral somatosensory areas makes it reasonable to suppose that NE innervation plays a somewhat special role in the mediation of integrative cortical functions that support the processing of somatosensory information.

Whereas by virtue of its broad cortical distribution NE cannot be attributed any specific and exclusive function, it is now evident that it regulates many specific cortical functions. In any case, the particular function that NE performs in any given cortical region is largely determined by the neural substrate and connections of the region. Thus, the role of NE in the prefrontal cortex is closely tied to and defined by the nature of the cognitive functions of this cortex. Furthermore, the actions of NE in the prefrontal cortex are dependent on at least two other important factors: (1) the copresence and local release of other neurotransmitters, such as DA, with which NE interacts; and (2) the kinds of receptors that bind NE in the prefrontal cortex. The first factor will be further considered in the context of other transmitters. The second deserves some discussion here.

In the prefrontal cortex, there are three basic types of NE receptors:  $\alpha_1$ ,  $\alpha_2$ , and  $\beta$ . Each seems

to have a distinct role. The  $\alpha_2$ -NE receptor agonists (e.g., clonidine and guanfacine) restore cognitive functions, notably working memory in young monkeys, which have lost it as a result of local or general catecholamine depletion (Arnsten and Goldman-Rakic, 1985; Cai et al., 1993). Aged rats (Carlson et al., 1992) and monkeys (Arnsten and Goldman-Rakic, 1985; Arnsten et al., 1988; Rama et al., 1996) that have presumably undergone natural, age-dependent, depletion of the same kind also benefit from  $\alpha_2$ -NE receptor agonists. Normal adult monkeys show similar effects but with higher doses of agonist (Franowicz and Arnsten, 1998). The direct infusion of  $\alpha_2$  antagonists, but not  $\alpha_1$  or  $\beta$  antagonists, impairs prefrontal function as tested by working-memory tasks (Li and Mei, 1994), and that of  $\alpha_2$  agonists improves it (Tanila et al., 1996; Arnsten et al., 1997; Mao et al., 1999). In agreement with these findings, the iontophoresis (cellular infusion) of an  $\alpha_2$  antagonist in prefrontal neurons induces a reduction of discharge related to working memory (Sawaguchi, 1998; Li et al., 1999).

Because stress induces high levels of NE (Finlay et al., 1995; Goldstein et al., 1996), and these high levels stimulate  $\alpha_1$  receptors (Birnbaum et al., 1999), it has been speculated (Arnsten and Robbins, 2003) that the deleterious effects of high NE on cognition, as attained by high doses of  $\alpha_2$  agonists, are the result of  $\alpha_1$  stimulation, which overpowers and pre-empts  $\alpha_2$  stimulation. These findings and the speculation about them suggest the interesting possibility that low or high levels of NE, simulating either  $\alpha_1$  or  $\alpha_2$  receptors, respectively, subserve alternatively cognition or the stress response. This, for one thing, would help to explain the detrimental effect of stress on cognition. NE may act as a kind of "chemical switch": at moderate levels, by activating  $\alpha_2$  receptors, NE would enhance the cognitive functions of the prefrontal cortex, whereas at high levels, by activating  $\alpha_1$ , perhaps also  $\beta$ , receptors, it would turn off the tending to those functions

as it responds to the demands of stress. Another possibility is that, at high concentrations, cortical NE may activate corticocortical connections (Jodo and Aston-Jones, 1997) and thus activate a positive-feedback loop, increasing anxiety and impairing cognition.

It is important to note, in general terms, that NE cells in the locus coeruleus fire according to arousal state (off during rapid eye movement sleep, low tonic and phasic firing during slow-wave sleep or drowsiness, moderate tonic/high-phasic firing during alert waking, and high tonic firing during stress). In more specific conditions, locus coeruleus cells respond phasically to highly relevant stimuli, which impact directly on prefrontal function at a given time (Foote et al., 1980; Aston-Jones et al., 1999). Conversely, it has been said that the prefrontal cortex is the only “intelligent” input to the locus coeruleus and is likely to have important regulatory influences on this nucleus (Arnsten and Goldman-Rakic, 1984; Sara and Hervé-Minvielle, 1995; Jodo et al., 1998). The locus coeruleus also receives important excitatory influences from the orexin neurons in the hypothalamus for the control of arousal (Horvath et al., 1999; Carter et al., 2013), and from the amygdala during stress (Goldstein et al., 1996; Van Bockstele et al., 1998). In turn, NE from the locus coeruleus increases the signal-to-noise ratio in sensory cortex (Foote et al., 1975; Mouradian et al., 1991).

Although most previous studies focused on the role of DA in prefrontal cortical physiology, it is now known that the effects of NE are just as important, and may have special relevance to the development of pharmacological therapies to treat prefrontal deficits and mental disorders. Like DA, NE is subject to an “inverted-U” function, where either too little or too much is harmful to prefrontal cognitive function. However, in contrast to dopamine D<sub>1</sub> actions (below), the beneficial versus detrimental effects of NE are dissociated by receptor subtype: the beneficial effects of moderate levels of NE are mediated by high-affinity α<sub>2A</sub>-adrenoceptors

localized postsynaptically to noradrenergic terminals, whereas the detrimental actions result from stimulation of lower affinity α<sub>1</sub>- and β<sub>1</sub>-adrenoceptors. The second messenger mechanisms underlying these opposing effects have been characterized to an extraordinary degree. The α<sub>2A</sub>-adrenoceptor stimulation improves working memory by inhibiting cAMP production, which in turn closes hyperpolarization-activated cyclic nucleotide-gated (HCN) channels on the dendritic spines of prefrontal pyramidal cells (Wang et al., 2007). This strengthens the functional connectivity of prefrontal cortical networks, and increases delay-related firing for the preferred direction in a spatial working-memory task (i.e., increased “signal”). In contrast, high levels of cAMP (such as occurs during stress or β-adrenoceptor stimulation, or from inhibition of phosphodiesterases), open HCN channels and induce a collapse of prefrontal cortical network firing (Wang et al., 2007). High levels of NE during stress also engage α<sub>1</sub>-adrenoceptors, which activate phosphatidyl inositol protein kinase C signaling (Birnbaum et al., 2004). High levels of protein kinase C activity dramatically impair prefrontal cortical cognitive function and reduce prefrontal cortical firing, possibly through actions on potassium channels (Birnbaum et al., 2004). Genetic studies suggest these stress pathways are probably dysregulated in serious mental illness (see below). Based on this research, the α<sub>2A</sub>-adrenoceptor agonist guanfacine is now used for the treatment of attention deficit/hyperactivity disorder (ADHD) and related prefrontal disorders (Scahill et al., 2001), whereas prazosin, an α<sub>1</sub>-adrenoceptor antagonist, is used for the treatment of both combat- and civilian-related post-traumatic stress disorder (PTSD) (Taylor and Raskind, 2002; Raskind et al., 2003).

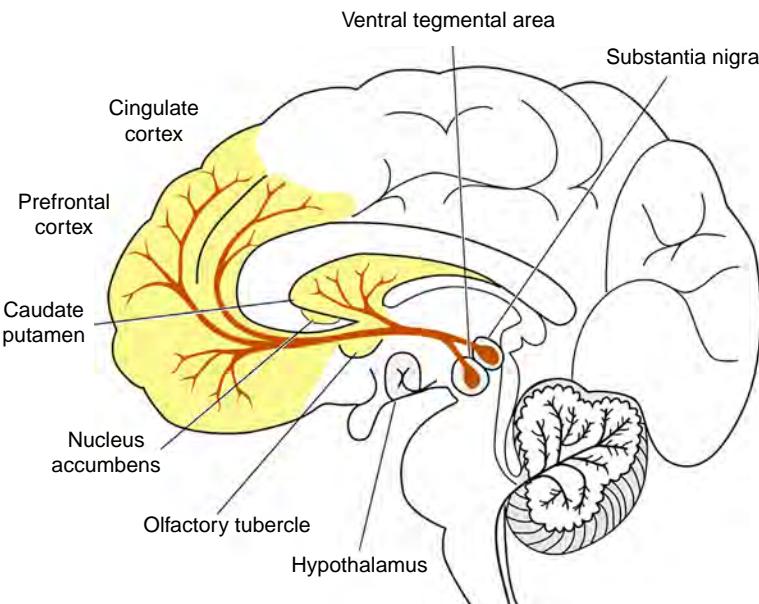
## D. Dopamine

Dopamine (DA), an intermediate product in the synthesis of NE, is also a neurotransmitter in its own right; accordingly, there are in

the brain DA-specific terminals and receptors. Dopaminergic systems, like NE systems, originate in the brainstem (see [Figure 3.3](#)). The most prominent and best known DA systems are (1) the mesostriatal DA system, which includes projections from the substantia nigra and the subjacent reticular formation to the striatum (caudate-putamen) and the nucleus accumbens; and (2) the mesocortical DA system, which includes projections from the ventral reticular tegmentum of the midbrain – the VTA – to the cerebral cortex, bypassing the thalamus (as does the cortical NE system). One part of the mesocortical DA system, especially conspicuous in the primate, flows into the ventral (orbitomedial) prefrontal cortex, the amygdala, the nucleus accumbens, and the septum. It is commonly designated the “mesocorticolimbic” DA system.

The dopaminergic innervation of the cortex by the mesocortical system has been the object of intense study since 1973, when Thierry and collaborators ([Thierry et al., 1973a, 1973b](#))

first described, in the rat, the presence of cortical DA that could not be attributed to metabolism in NE terminals. The principal targets of that dopaminergic system are the frontal, piriform (periamygdalar), and entorhinal cortices ([Bannon and Roth, 1983; Felten and Sladek, 1983](#)). These are, therefore, the cortical territories richest in DA terminals and receptors. In the monkey ([Figure 3.7](#)), as in the rat, the prefrontal cortex stands out as a prominent terminal field of DA innervation ([Berger et al., 1976; Kehr et al., 1976; Lindvall and Divac, 1978; Björklund et al., 1978; Brown et al., 1979; Deniau et al., 1980; Felten and Sladek, 1983; Kalsbeek et al., 1989](#)). The same seems to be true in the human ([Gaspar et al., 1989](#)). In fact, the neocortical field with the greatest dopaminergic projection has been found to largely overlap, if not coincide, with that of mediodorsal thalamic projection ([Beckstead, 1976; Björklund et al., 1978; Divac et al., 1978](#)). However, considerable differences exist between the cortical distribution of DA in the rodent and in the primate ([Berger et al.,](#)

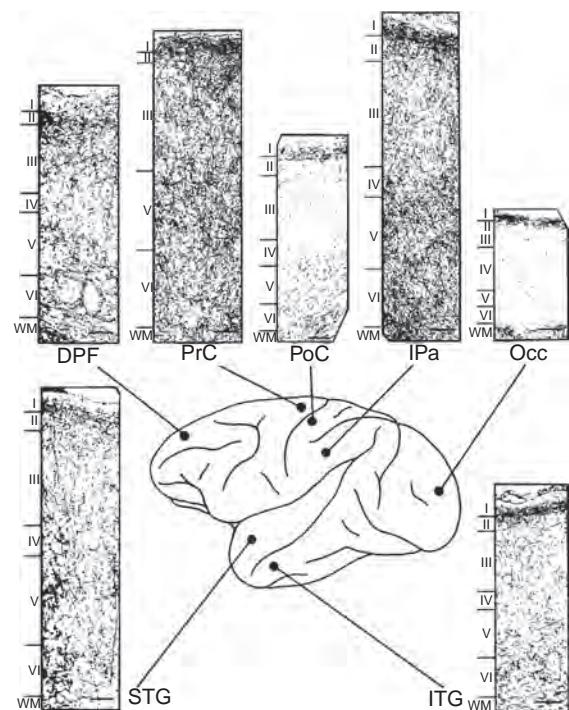


**FIGURE 3.7** Dopamine innervation in the primate brain.

1991). Whereas, in the former, dopaminergic axons are relatively restricted to the prefrontal cortex, in the primate – including the human – such axons appear to be present in every other neocortical region, albeit in less quantity.

The mesoprefrontal DA subsystem (subdivision of the mesocortical system) has been identified as a functionally and pharmacologically separate entity, at least in rodents (Bannon and Roth, 1983; Glowinski et al., 1984; Thierry et al., 1990). It remains to be determined whether that subsystem is present in all mammalian species, as neuroanatomical observations indicate (Björklund et al., 1978; Divac et al., 1978). A homolog of that subsystem seems to be present even in some non-mammalian species, such as the pigeon (Mogensen and Divac, 1982; Divac and Mogensen, 1985). There is evidence, however, that at least in primates the frontal DA distribution extends beyond the prefrontal cortex (i.e., the mediodorsal projection area) and into premotor and motor cortex; the highest DA concentration in the frontal lobes can be found in the precentral primary motor area (Brown and Goldman, 1977; Björklund et al., 1978; Brown et al., 1979). In any event, in all mammalian species thus far examined a prominent and distinct dopaminergic pathway, originating in cells of the ventral mesencephalic tegmentum, courses through the ventral diencephalon and innervates mainly, if not exclusively, frontal areas, including the prefrontal cortex.

The rostrocaudal gradient of cortical DA concentration (maximum frontal, minimum occipital), suggested by biochemical studies in the monkey (Brown and Goldman, 1977; Björklund et al., 1978; Brown et al., 1979), is generally matched by the results of histochemical analysis of DA fibers (Levitt et al., 1984; Lewis et al., 1986a, 1987; Gaspar et al., 1989). That analysis shows not only the frontal predominance of such fibers but also their heavy concentration in precentral – motor – cortex (Figure 3.8); in addition, it shows a peak of DA fiber density in posterior parietal



**FIGURE 3.8** Dopaminergic innervation of cortical areas of the cynomolgus monkey. Abbreviations: DPF, dorsomedial prefrontal cortex (area 9); IPa, posterior parietal cortex (area 7); ITG, rostral inferior temporal gyrus; Occ, primary visual cortex (area 17); PoC, primary somatosensory cortex (area 3); PrC, primary motor cortex (area 4); STG, rostral superior temporal gyrus. (From Lewis et al., 1986a, with permission.)

cortex (area 7). Furthermore, the histochemical data highlight the substantial dopaminergic innervation of deep layers (V and VI) indicated by other methods (Berger et al., 1976; Divac et al., 1978; Lindvall and Divac, 1978; Ferron et al., 1984; Glowinski et al., 1984). Histochemistry also shows, however, a heavy superficial plexus of DA fibers. Consequently, the internal granular layer (IV) of the granular frontal cortex appears to be relatively poor in DA terminals. In the rat, DA innervates uniformly the entire frontal cortex in addition to piriform and entorhinal cortices. In the monkey and the human, DA also innervates the entire

frontal mantle, with highest levels in motor and premotor cortex. In both primates, prefrontal DA has exceptionally rapid DA turnover.

Autoradiographic, pharmacological, and molecular studies have identified several types of DA receptors (up to five main ones, D<sub>1</sub>–D<sub>5</sub>) in brain structures where DA axon terminals have been located by other methods (Tassin et al., 1978; Onali et al., 1985; Boyson et al., 1986; Savasta et al., 1986; Goldman-Rakic et al., 1990, 1992). Thus, the findings of some of these studies match the noted regional and laminar distributions of DA terminals in prefrontal cortex. Here, D<sub>1</sub> receptors appear chiefly concentrated in superficial layers, whereas the less common D<sub>2</sub> receptors abound in layer V.

There are indications that the DA prefrontal system has certain peculiar properties and that DA plays in it a somewhat different transmitter or modulator role than elsewhere (Bannon and Roth, 1983; Bunney and Chiodo, 1984). To summarize the conclusions that Bannon and Roth (1983) reached in their review of the subject, the prefrontal DA system, in comparison with the nigrostriatal and limbic DA systems, is generally characterized by a higher DA turnover rate, a higher and more irregular discharge of its neurons, and a lower responsiveness to DA agonist and antagonist substances. The authors attribute the latter trait to the apparent absence, in DA system cells, of autoreceptors regulating DA production. Later studies have contributed to clarifying the modulating role of DA within the prefrontal cortex and in structures connected with it. It has become apparent that DA's effects vary considerably as a function of (1) the types and sites of cells it acts upon; and (2) the kinds of receptors that bind it. Furthermore, prefrontal DA cells project to many cortical and limbic structures whose functions they modulate, although these functions and the modulating mechanisms are not yet fully understood.

In brain-slice preparations of prefrontal area 46 of the macaque, dopaminergic modulation

has been shown to increase the excitability of layer III pyramids (Henze et al., 2000). However, by microelectrode recording *in vivo*, DA has been observed to decrease the excitability of prefrontal pyramidal cells, while enhancing that of interneurons, with the net effect of inhibiting activity in some prefrontal circuitry (Gao and Goldman-Rakic, 2003; Gao et al., 2003). In the rat, D<sub>1</sub> receptor stimulation attenuates dendroaxonic transmission to some pyramidal cells, while facilitating local transmission between pyramids of the same layer (V and VI) (Yang and Seamans, 1996). This suggests a kind of dual and reciprocal DA gating mechanism that would serve the selectivity of extrinsic and local transmission within the prefrontal cortex. Because the actions of DA in different cells and cell sites are subtle and complex, it has been reasonably argued that DA should be considered a neuromodulator, rather than a neurotransmitter, either excitatory or inhibitory (Seamans and Yang, 2004). Complicating our understanding of its mechanisms of action is the evidence that DA induces opposite postsynaptic responses depending on its concentration: at low or moderate concentration it can enhance those responses, and at high concentration depress them. This leads to characteristic dose-dependent inverted-U responses to DA agonists that have been observed at all levels, from the cellular to the regional and, as we see below, to the cognitive level.

Some prefrontal DA cells send projections to the nucleus accumbens (Brady and O'Donnell, 2004), a structure of well-recognized importance for the integration of sensory and limbic inputs. Other prefrontal DA projections flow into the basolateral amygdala (Rosenkranz and Grace, 1999), apparently enhancing the sensory filtering capability of this limbic structure. Conversely, prefrontal neurons are innervated by DA projections from the hippocampus (Carr and Sesack, 1996), which is known to play a central role in memory acquisition and retrieval, especially – in lateral prefrontal cortex – motor or executive memory.

In the prefrontal cortex, as elsewhere in the nervous system, some neurons contain different transmitters, especially if these are of the same molecular family or are precursors of one another (Deutsch and Roth, 1999; Waxham, 1999). A case in point is the colocalization of NE and DA in some prefrontal neurons, as the second is a precursor of the first. The colocalization of transmitters or receptors in the same presynaptic or postsynaptic units may or may not signify functional synergism, but it is an indication of the numerous interactions between neurotransmitter systems at the root of probably all prefrontal functions. Those interactions extend to the structures that are the source or recipients of prefrontal projections. DA systems have been shown to interact at many levels and structures, including the prefrontal cortex, with NE (Devoto et al., 2001, 2005; Berridge and Stalnaker, 2002; Weinshenker et al., 2002; Ventura et al., 2003; Pan et al., 2004), with glutamate (Abecawa et al., 2000; Sesack et al., 2003; Feenstra et al., 1998), and with GABA (Abecawa et al., 2000; Wang et al., 2002).

In light of the facts reviewed above, it is obvious that DA, like any other chemical transmitter or modulator, cannot be ascribed any particular prefrontal function. It does, however, serve some functions more than others by virtue of its distribution in the prefrontal cortex and by virtue of the restraints noted above related to cell type, location, concentration, and connectivity. Accordingly, there are three broad domains of frontal function in which DA plays a critical role: movement, cognition, and affect – the latter including the disparate yet related aspects of stress, reward, and drive. We shall briefly discuss the facts in those three domains, in that order.

From the patterns of its regional distribution in the brain, it can be readily inferred that DA plays a role of prime importance in the neural integration and support of motor action. This inference is partly based on, and underscored by, the crucial involvement of the nigrostriatal

system in movement and the disorders of movement (e.g., Parkinson's disease) that result from deficient DA levels in that system. Consistent with this, damage to the mesoprefrontal DA system, at either subcortical or cortical level, induces motor symptoms or deficits. In the rat, lesions of the VTA, the root of the system, induce motor hyperactivity and hyper-reactivity (Le Moal et al., 1976; Stinus et al., 1978; Simon, 1981), both common results of prefrontal injury as well (see Chapter 4). Lesions of prefrontal DA terminals (e.g., DA depletion by local application of 6-OHDA) have comparable effects (Carter and Pycock, 1980). The heavy concentration of DA and DA terminals in the primary motor cortex of the primate reinforces the motor DA hypothesis. The reasoning behind this hypothesis can be extended and applied to the frontal cortex at large, especially its dorsolateral aspects. One can reasonably assume that DA is there in high concentrations to mediate the organization and execution of motor behavior.

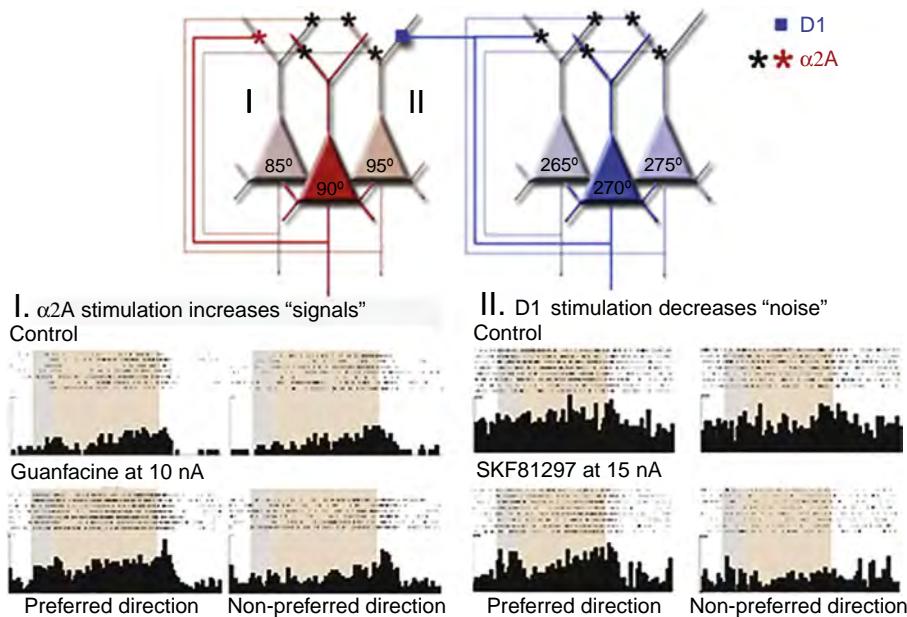
A further extension of that line of reasoning, in agreement with concepts and evidence discussed later in this volume, is the inference that dorsolateral prefrontal DA is critical for the cognitive processes that support the temporal organization of motor behavior, such as working memory. There is now abundant experimental support for this inferential extrapolation. Lesions of the VTA, or depletion of prefrontal DA by 6-OHDA, in the rat (Simon et al., 1980; Simon, 1981), the monkey (Brozoski et al., 1979), or the marmoset (Roberts et al., 1994; Collins et al., 1998) cause marked deficits in performance of delayed alternation, a behavior paradigmatic of working memory that is typically disrupted by prefrontal ablation. That deficit is reversed by DA agonists such as L-dopa and apomorphine (Brozoski et al., 1979). Furthermore, the iontophoretic infusion of DA on to prefrontal cells enhances not only motor-related (Sawaguchi et al., 1986) but also memory-related (Sawaguchi et al., 1988b)

firing. Conversely, a microdialysis study of the monkey's prefrontal cortex provided evidence of increased extracellular DA during the performance of a working-memory task (Watanabe et al., 1997). The increase was evident in dorsolateral, but not orbital, prefrontal cortex. No prefrontal DA increment was observed in a simple sensory-guided motor task. Both tasks, however, led to DA increase in premotor cortex, a further indication of the importance of DA in motor systems. In a comparable rat study (Phillips et al., 2004), the magnitude of the prefrontal DA efflux was commensurate with the accuracy of performance of the working-memory task.

There is now considerable evidence that DA exerts its facilitative action on working memory through D<sub>1</sub>, in animals (Sawaguchi et al., 1988b; Sawaguchi and Goldman-Rakic, 1991; Arnsten et al., 1994; Cai and Arnsten, 1997; Williams and Goldman-Rakic, 1995; Yang and Seamans, 1996; Muly et al., 1998; Robbins et al., 1998; Gao et al., 2001) as well as humans (Kimberg et al., 1997; Muller et al., 1998). It has been postulated (Durstewitz et al., 2000) that DA, through D<sub>1</sub> receptors, has a stabilizing effect on the delay-period activity of memory cells in the prefrontal cortex. This stability, which would render those cells and their memory encoding resistant to distraction, would be achieved by DA-induced enhancements of persistent sodium ion (Na<sup>+</sup>) and NMDA conductances – concomitant with reduction of AMPA conductance. More recent evidence, however, implicates also D<sub>2</sub> receptors in working memory (Wang et al., 2004). In working memory (Brozoski et al., 1979; Murphy et al., 1996b; Williams and Goldman-Rakic, 1995), as in other cognitive functions of the prefrontal cortex, the effects of DA agonists show the characteristic inverted-U dose-response function – not unlike that seen for NE – that seems to reflect the relationship between input and output, through D<sub>1</sub> receptors, at the synaptic level (Yang and Seamans, 1996). A moderate DA increase facilitates cognition, while a large

increase disrupts it. This accords with the relationship between arousal and performance, as stated by the Yerkes-Dodson principle of optimal levels. The optimal DA level may differ with cognitive function or behavioral paradigm (review by Arnsten and Robbins, 2003).

The dopamine D<sub>1</sub> receptor family has an inverted-U influence on spatial working memory function at both the electrophysiological and behavioral levels. This inverted U was first discovered by Arnsten and Goldman-Rakic in their studies of the effects of stress on cognitive function (Arnsten and Goldman-Rakic, 1990, 1998). Although Goldman-Rakic noted the necessity of DA for proper working-memory abilities (Brozoski et al., 1979), the finding that stress impaired working memory showed that excessive D<sub>1</sub> actions could be as harmful as insufficient D<sub>1</sub> receptor stimulation to prefrontal cortical functions. Indeed, infusion of a higher dose of D<sub>1</sub> agonist, or a cAMP agonist, into the prefrontal cortex mimics the stress response (Zahrt et al., 1997; Taylor et al., 1999). Electrophysiological recordings from prefrontal cortical neurons in monkeys performing working-memory tasks have revealed the cellular basis for this phenomenon. Some D<sub>1</sub> receptor stimulation is necessary for the persistent activation of prefrontal neurons (Sawaguchi et al., 1988b; Williams and Goldman-Rakic, 1995). However, higher levels of D<sub>1</sub> receptor stimulation in awake monkeys have suppressive effects on delay-related firing (Williams and Goldman-Rakic, 1995; Vijayraghavan et al., 2007). At optimal levels, D<sub>1</sub> receptor stimulation preferentially suppresses delay-related firing to non-preferred directions; that is, it reduces "noise" (Figure 3.9), thus enhancing spatial mnemonic tuning (Vijayraghavan et al., 2007). However, at higher levels of D<sub>1</sub> stimulation, such as is likely to occur during stress, all delay-related firing is suppressed (Vijayraghavan et al., 2007). These suppressive effects occur via a cAMP mechanism (Vijayraghavan et al., 2007) probably involving the opening of HCN channels.



**FIGURE 3.9** Optimal noradrenergic and dopamine modulation of prefrontal cortical networks enhances spatial tuning of delay-related firing. *Top:* A model based on the work of Goldman-Rakic (1995). Networks of prefrontal cortical pyramidal cells engage in recurrent excitation to maintain representations of spatial position over the delay period in a delayed response task. Spatial tuning of these pyramidal cells is enhanced by  $\gamma$ -aminobutyric acid (GABA) and by the appropriate level of catecholamines. *Bottom:* Recordings from dorsolateral prefrontal cortical neurons in monkeys performing a spatial working memory task (oculomotor delayed response). In “neuron I,” stimulation of noradrenergic  $\alpha_2A$ -adrenoceptors, such as with the drug guanfacine, increases delay-period firing to the preferred direction (i.e., increases “signals” from neurons with similar tuning characteristics). Research has shown that this effect arises from  $\alpha_2A$ -adrenoceptor inhibition of cyclic adenosine monophosphate (cAMP), closing HCN channels on dendritic spines and strengthening functional connectivity of prefrontal networks. Conversely, application of a D<sub>1</sub> agonist on to “neuron II” reduces firing during the delay period for the non-preferred directions (i.e., decreases “noise”). These suppressive effects involve production of cAMP, probably via opening of HCN channels. Background color of the rasters indicates different periods in the delayed response task: gray = presentation of the cue; beige = 2.5 s delay period; white = response period. Drugs are iontophoresed directly on to the neurons during the recordings. (Adapted from Arnsten, 2007, with permission.)

These detrimental effects of cAMP may be amplified in patients with mental illness (see below). The D<sub>1</sub> inverted U has now been seen in mice, rats, monkeys, and humans; it helps to explain the differences in cognitive abilities linked to the COMT genotype (Egan et al., 2001; Mattay et al., 2003).

It is important to note that the D<sub>2</sub> receptor family also influences prefrontal cortical function. D<sub>4</sub> receptors are concentrated in interneurons, but are also evident in pyramidal

cells (Mrzljak et al., 1996). D<sub>4</sub> receptor stimulation can alter both types of cells, thus having a complex effect overall (Wang et al., 2002, 2003). Dopamine D<sub>2</sub> receptors had been thought to have little effect on prefrontal physiology, but D<sub>2</sub> receptor stimulation has been shown to markedly alter response-related, but not delay-related, firing of prefrontal cortical neurons (Wang et al., 2004). Some of the response-related firing was initiated after the monkey had made a saccade to the remembered location,

possibly thereby providing efferent copy (corollary discharge) regarding the initiation of a movement. Weakened corollary discharge may contribute to hallucinations in schizophrenia (Ford et al., 2002); thus, this mechanism may have special relevance to positive symptoms of the disease.

By producing local excitotoxic lesions in different regions of the DA prefrontal system of the marmoset, Dias et al. (1996a, 1996b, 1997) observe area-dependent dissociations of effects on a set-shifting task (an analog of the Wisconsin Card Sorting Test for humans) and a reversal learning task. From their results they conclude that prefrontal areas (i.e., dorsolateral and orbital) are differentially involved in two different attentive functions (both based on inhibitory DA control) that are specifically tested by one or the other task. O'Reilly et al. (2002), however, by use of a computational model, offer a different interpretation of those results. Their model is based on the assumption of quantitative differences in the level of categorization of the information processed by the two areas in the performance of the tasks: orbital cortex represents the concrete aspects of that information, whereas dorsolateral cortex represents the more abstract ones.

Whereas the emphasis of cognitive studies of DA actions in the prefrontal cortex has been so far on short-term processes (e.g., working memory), there are reasons to suspect that prefrontal DA has a decisive role in the more basic, long-term processes of cognition, such as learning and long-term memory. *A priori*, there are two main reasons for that conjecture: (1) the prefrontal cortex interacts with a number of limbic, cortical, and subcortical structures that are known to be intimately involved in such processes; and (2) the prefrontal cortex is known to contain the neuronal substrate for very important aspects of one form of long-term memory, namely, executive memory. Moreover, there is growing evidence (summarized by this author elsewhere: Fuster, 1995) that those short-term

processes for which DA has been shown to be important, such as working memory, use the same substrate, that is, the very same cortical networks, that represent long-term memory. In accord with these premises and hypotheses, the dopaminergic connections of the prefrontal cortex with other structures involved in learning, such as the hippocampus, the amygdala, the nucleus accumbens, and the posterior association cortex, are gaining relevance. Although the precise mechanisms of DA participation in learning are still obscure, empirical evidence has been cumulating that prefrontal DA neurons play probably critical roles in synaptic plasticity in the hippocampus (review by Jay, 2003), learning avoidance behavior (Stark et al., 2004), long-term potentiation (Otani et al., 2003), and transactions with NMDA receptors (Verma and Moghaddam, 1996).

Stress and anxiety, especially if severe, are known to impair cognitive performance in humans and animals. Both stress and anxiety are also known to increase catecholamine levels in blood and brain. Because of the well-documented role of DA in prefrontal neuromodulation, and because of the evidence of interactions between stress level and the performance of working-memory tasks for which prefrontal function is crucial, it has been inferred that prefrontal DA plays a role in the neural response to stress. Loud noise, supposedly a mild stressor, in monkeys (Arnsten and Goldman-Rakic, 1998), or pharmacologically induced stress in rats (Murphy et al., 1996a; Birnbaum et al., 1999), induces working-memory deficits. There are indications that these deficits are correlated with prefrontal DA turnover (Murphy et al., 1996a) and can be to some extent prevented or reversed by DA antagonists (Arnsten and Goldman-Rakic, 1990, 1998; Murphy et al., 1996b). Furthermore, there is evidence (reviewed by Pezze and Feldon, 2004) that the neural response to fear, stress, or anxiety is mediated by the so-called mesocorticolimbic dopaminergic system, which prominently

involves the medial prefrontal cortex, the amygdala, and the nucleus accumbens.

The mechanisms of prefrontal DA action in stress, as in cognition, are not yet entirely clear. One complicating issue, again, is the absence of linear, or even monotonic, relationships between magnitude of DA concentration and postsynaptic change. The absence of such relationships leads to imponderable or poorly controllable dose-dependent responses to DA agonists and antagonists. The problem is compounded by the evidence of apparently different "optima" of DA effect on different variables, whether these variables are behavioral or biological. This may lead to paradoxical results; for example, an operational measure of stress was modified by local infusion of DA agonists or antagonists in the prefrontal cortex that failed to impair working memory (Broersen et al., 1994; Broersen, 1995). Nevertheless, the bulk of the available evidence from chemical interventions (reviewed by Arnsten and Robbins, 2003) indicates that cognitive deficits from stress are the result of excessive stimulation of D<sub>1</sub> (DA) and α<sub>1</sub> (NE) receptors in the prefrontal cortex.

Finally, there is the increasingly relevant issue of the role of prefrontal DA in the related functions of motivation and experience of reward. Again, the neuroanatomy of the mesocorticolimbic DA system, that is, the destination of its brainstem projections and the connectivity between the structures of destination (ventral prefrontal cortex, amygdala, nucleus accumbens, and hypothalamus), provides clear indications of the involvement of this system in motivation and reward. These indications are borne out by experimental evidence. An electrochemical study in the rat shows that medial prefrontal DA levels are correlated with food reward, as estimated by timing and amounts of food ingestion (Richardson and Gratton, 1998). The discharge of some cells in the medial prefrontal cortex of the rat, which is rich in DA, has been found to be associated with the accessibility to food in a behavioral task (Kursina et al., 1994). The amygdala, the nucleus

accumbens, and the prefrontal cortex have been shown to be intimately involved in dynamic interactions at the root of the regulation of feeding behavior and its regulation by the level of satiety (Jackson and Moghaddam, 2001; Ahn and Phillips, 2002). DA plays a key role in those interactions, which also involve other neurotransmitters, notably glutamate.

Current thinking and research on the relationships between reward and prefrontal DA, with the designation of DA as the "reward transmitter," originated with experimentation on the phenomenon of intracranial self-stimulation (ICSS): if given the opportunity, animals will press a lever-switch to deliver electrical current through implanted electrodes in certain parts of their brain. This phenomenon is most readily demonstrable in the rat, where it was first discovered (Olds and Milner, 1954). It can most predictably be elicited with electrodes in limbic structures, particularly in some portions of the hypothalamus. The physiological significance of ICSS is poorly understood, but it is generally agreed that the stimulation of certain brain sites is rewarding to the animal and that this is probably so, at least in part, because those sites are normally somehow involved in the physiology of drive and motivation.

Electrodes in neocortical regions do not lead to ICSS behavior, with one exception: the prefrontal region (Routtenberg and Sloan, 1972; Rolls and Cooper, 1973; Rolls, 1975). This is somewhat understandable because the prefrontal cortex is the only part of the neocortex that projects to hypothalamic nuclei (see Chapter 2) that readily yield ICSS. Not all prefrontal sites lend themselves to ICSS, however. To the monkey, only the stimulation of certain orbital areas of the prefrontal cortex appears to be rewarding; this may be so because it is in orbital areas that corticohypothalamic projections arise. At any rate, in the rat as in the monkey, prefrontally induced ICSS behavior has been shown to be markedly susceptible to pharmacological manipulations that affect the production, release,

and reuptake of neurotransmitters, especially DA (for a review, see [Mora and Ferrer, 1986](#)). By such means, the prefrontal DA system has been shown to be depressed by DA antagonists such as haloperidol, pimozide, and spiroperidol ([Mora et al., 1976a, 1976b](#); [Phillips et al., 1979](#)) and, somewhat paradoxically, also by apomorphine, a DA agonist ([Mora et al., 1976c](#); [Phillips et al., 1979](#)), although the paradox may be to do with the aforementioned reversals at high DA concentrations. Furthermore, some of these substances have been noted to depress prefrontal neuron discharge ([Mora et al., 1976c](#)).

In the prefrontal cortex, ICSS has been reported to release DA *in situ* ([Mora and Myers, 1977](#)), whereas DA depletion, by 6-OHDA, induces a decrease in ICSS ([Phillips and Fibiger, 1978](#)). It would appear from such reports that presynaptic prefrontal DA plays an important role in the mediation of ICSS. However, such a conclusion is called into question by failures to reproduce a prefrontal ICSS decrease by lesions of the VTA, the source of dopaminergic terminals to the prefrontal cortex ([Simon et al., 1979](#)), or by prefrontal DA depletion ([Gerfen and Clavier, 1981](#)). The last-cited study also included a test of injections of kainic acid in prefrontal cortical layers V and VI. These injections, which destroyed cell bodies in those layers, did produce a decrease in prefrontal ICSS. This result suggests that prefrontal ICSS is mediated by descending, corticofugal, fibers acting upon parts of the striatum, the lateral hypothalamus, the substantia nigra, and the VTA; such fibers are well substantiated by anatomical evidence (see Chapter 2 and earlier in the present chapter). The idea that those subcortical dopaminergic structures are normally under the regulatory control of descending influences from the prefrontal cortex is further supported by neuropharmacological and behavioral data from animals in which those influences have been abolished by prefrontal lesion ([Carter and Pycock, 1980](#); [Pycock et al., 1980](#); [Scatton et al., 1982](#); [Itoh et al., 1985](#)).

The idea of a prefrontal DA region associated with reward has gained considerable momentum as a result of investigations of neuronal activity in the orbital prefrontal cortex of the monkey in behavioral performance. Earlier electrophysiological research had shown that when food or drink was delivered to a monkey as the reward for good performance, some prefrontal cells showed distinct activation of firing ([Niki et al., 1972](#); [Rosenkilde et al., 1981a](#); [Fuster et al., 1982](#); [Inoue et al., 1985](#); [Watanabe, 1990, 1992](#)). By appropriate controls, it was ascertained that some units were activated by the ingestion of the reward, while others were activated by its absence when it was due and expected ([Rosenkilde et al., 1981b](#)). Some units were attuned to only the expectancy of reward or even to the specific nature of the reward ([Watanabe, 1996](#)). "Reward" units were found practically anywhere in the prefrontal cortex, probably because associations between reward and behavioral action are widely distributed in prefrontal networks, but were noted to be most common in orbital prefrontal areas. This orbital prevalence of reward units makes sense in the light of the limbic connectivity of orbital cortex and with the presence within it of cells receptive to gustatory stimuli ([Thorpe et al., 1983](#); [Rolls, 1989](#)). It also makes sense in the light of the key role of DA in orbital prefrontal cortex as the "reward transmitter."

The reward role of DA cells in orbitomedial prefrontal cortex is highlighted by the research of Schultz and his colleagues ([Schultz et al., 1993, 1997, 2000](#); [Schultz, 1998, 2011](#); [Hollerman et al., 2000](#)). The major conclusions of this research, which in many respects confirm or complement those of other studies, can be summarized as follows:

- The DA neurons of orbital prefrontal cortex are components of a vast system of DA cells represented at various levels of the nervous system, including the VTA and striatal nuclei engaged in the signaling of reward at the service of goal-directed behavior.

- Some DA cells, especially in orbital cortex, signal very specific aspects of reward, such as its peculiar physical nature.
- Other cells signal error in reward prediction.
- Most DA cells signal not only the reward itself, but also sensory stimuli that by virtue of prior training have become behaviorally associated with it. The latter characteristic indicates that DA cells are part of widely distributed cognitive networks that probably include parts of posterior cortex, in addition to dorsolateral prefrontal cortex, and that encode all the associated features of integrative goal-directed behavior, including the goal itself, that is, the reward.

In the light of these observations – especially the last one above, and the comment that follows it – the concepts of something akin to a pleasure center in orbital prefrontal cortex and of DA as the reward transmitter become almost meaningless. The aggregates of DA cells in orbital prefrontal cortex are undoubtedly at the crossroads of the frontolimbic circuitry of the mesocortical DA system and, at the same time, nodular components of cognitive networks representing the reward in the context of its history; that is, the associations it has formed with other elements of the environment by prior learning and experience. On both counts, the responses of DA cells to present or anticipated rewards are quite understandable. But this responsiveness, however intense or concentrated in time or brain space, does not justify the inference of a neural “center” for reward or anything related to it. Even more implausible is the attribution of reward to a neurotransmitter with such diverse actions, excitatory and inhibitory, in so many parts of the central nervous system. Instead, on the basis of the available evidence (reviewed by Jentsch et al., 2000), it is reasonable to conclude that DA promotes behavioral and neural responses to conditioned or reward-related stimuli by integrating activity in multiple cerebral sites.

## E. Serotonin

The third monoamine of interest in prefrontal physiology is 5-hydroxytryptamine (5-HT), an indoleamine also known as serotonin. Like NE, 5-HT is present in many organs of the body, especially in the gastrointestinal, respiratory, and cardiovascular systems. The brain contains only about 1% of the total 5-HT in the body, yet in the brain it is almost ubiquitous. Just as in the catecholamine systems already discussed, the serotonergic system has its cells of origin in the brainstem. Serotonergic cells were located first by Dahlstrom and Fuxe (1964) in the raphe (midline) nuclei of the pons and the mesencephalon (see Figures 3.3 and 3.5). These cells project upward to various regions of the diencephalon, the limbic system, and the cortex (Ungerstedt, 1971; Felten and Sladek, 1983; Fallon and Loughlin, 1987). The neocortical 5-HT concentration and projections are diffuse and more uniform than those of catecholamine systems (Brown et al., 1979; Lidov et al., 1978; Lewis et al., 1986a; Voigt and De Lima, 1991). In the cortex of the primate, however, a preponderance of 5-HT metabolites and terminals has been observed in somatosensory and visual cortices (Brown et al., 1979; Takeuchi and Sano, 1983; Lewis et al., 1986a). A dense plexus of terminal 5-HT innervation has been described in layer IV of the monkey’s primary sensory areas; it is most conspicuous in the visual cortex (Figure 3.6). In the prefrontal cortex, 5-HT innervation and receptors, 5-HT<sub>1</sub> and 5-HT<sub>2</sub>, seem to concentrate in layers III and IV (Lidow et al., 1989b).

Serotonin, which does not cross the blood-brain barrier, is synthesized from the amine tryptophan – which does cross that barrier – by intervention of the enzyme tryptophan hydroxylase. The gene encoding the latter substance has been cloned and sequenced. The synaptic vesicles that store 5-HT are similar to those that store the catecholamines, but differ from these in that they express a high-affinity serotonin

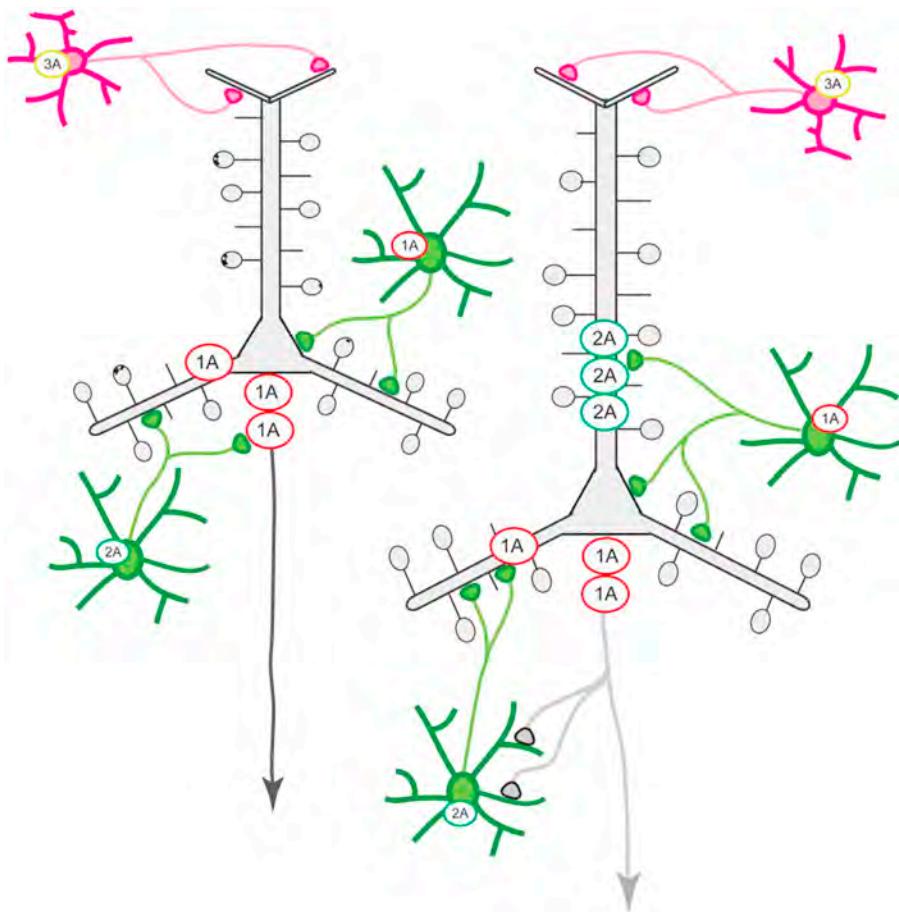
binding protein. There are four major serotonin receptors, 5-HT<sub>1</sub>–5-HT<sub>4</sub>, with certain subcategories of each. All of them couple to G-proteins to produce their actions in the postsynaptic intracellular milieu. Serotonin release and synthesis are regulated by specific autoreceptors. Its inactivation occurs by reuptake with intervention of a plasma membrane serotonin transporter (SERT). SERT is the target of a broad class of antidepressant drugs called selective serotonin reuptake inhibitors (SSRIs).

Because of its pattern of distribution in the cerebral cortex, especially the heavy density of its terminals in the layer of sensory thalamic projection of posterior sensory cortices, for a long time it was thought that cortical 5-HT was mainly if not exclusively involved in the processing of sensory information. Compared to that of DA, the role of 5-HT in the prefrontal cortex appeared in the past to be of secondary importance. Now, however, prefrontal 5-HT research has risen to first rank of importance for a number of reasons, including: (1) 5-HT's role in synaptic development; (2) its growing neuropharmacological role in psychiatric syndromes, such as depression and schizophrenia, presumed to implicate the prefrontal cortex; and (3) evidence of interactions with other prefrontal neurotransmitters, notably DA (see review by Chamberlain et al., 2006). Thus, for different though related reasons, the prefrontal functions of 5-HT have become at least as relevant in cognitive neuroscience as its well-documented roles in sleep, circadian rhythms, and eating.

Artigas and his colleagues found that prefrontal pyramidal neurons are activated by 5-HT agonists (Puig et al., 2003) and colocalize (80%) both 5-HT<sub>1</sub> and 5-HT<sub>2</sub> receptors (Amargós-Bosch et al., 2004). The same receptors are colocalized by some GABA neurons (Santana et al., 2004). Furthermore, the electrical stimulation of the raphe nuclei (the origin of 5-HT) induces reciprocal effects on those neurons: inhibition through 5-HT<sub>1</sub> receptors – including autoreceptors – and excitation through 5-HT<sub>2</sub> receptors

(Romero and Artigas, 1997; Puig et al., 2004). Raphe stimulation has been noted to induce the GABA- and 5-HT-mediated inhibition or excitation of prefrontal pyramidal neurons (Santana et al., 2004; Puig et al., 2005). Conversely, the medial prefrontal cortex has been shown to regulate, downstream and through AMPA and NMDA receptors, raphe serotonergic neurons (Celada et al., 2001; Martín-Ruiz et al., 2001). Electron microscopy reveals that the dendritic shafts of prefrontal interneurons are important targets of 5-HT axons (Smiley and Goldman-Rakic, 1996). Since some pyramidal neurons – by way of 5-HT<sub>1</sub> receptors – as well as interneurons are inhibitory, it is reasonable to assume that 5-HT plays a critical role in the inhibitory control exerted by the prefrontal cortex over some of its circuitry and over some of the structures to which it projects. Indeed, prefrontal 5-HT has been shown to excite cells that mediate inhibition through GABA transmitters and receptors, both in the prefrontal cortex itself (Yan, 2002) and, downstream, in the raphe nuclei (Jankowski and Seasack, 2004). More recently, Puig and Gullede (2011) have demonstrated that the most abundant 5-HT receptors in the prefrontal cortex (Figure 3.10) are selectively expressed in pyramidal neurons and interneurons. Through these cells, 5-HT plays critical roles of both excitatory and, especially, inhibitory modulation of cortical activity – some of which is manifest in rhythmic electrical oscillations under certain behavioral conditions.

The 5-HT-mediated inhibition of and by prefrontal DA neurons is probably related to a general inhibitory control function of the prefrontal cortex on behavior, drive, and emotion. As we will see in Chapter 4, this function is most important for the control of instinctual impulses and the organization of goal-directed behavior. Its disruption in the rat, by depletion or excess of prefrontal 5-HT, entails decontrol of impulsivity (Dalley et al., 2002) and maladaptive perseveration tendencies (Clarke et al., 2004, 2005). Also in the rat, and



**FIGURE 3.10** Localization of serotonin (5-HT) receptors (1A, 2A, and 3A) in prefrontal microcircuits. Pyramidal neurons in deep layers coexpress receptors 1A and 2A, which are innervated by inhibitory interneurons. Other interneurons innervate 3A receptors in apical dendrites of the superficial layer. (From Puig and Gullede, 2011, with permission.)

by microdialytic assessment, stress has been reported to increase 5-HT levels in prefrontal cortex (Kawahara et al., 1993). In the monkey, Williams et al. (2002) show large effects of iontophoresis of 5-HT<sub>2</sub> antagonists on prefrontal neurons.

The experimental analysis of the role of 5-HT in the human prefrontal cortex is as difficult as that of any other neurotransmitter in human cortex. The main reasons for this difficulty are obvious: limitations in brain studies imposed

by ethical concerns and limitations in our ability to derive physiological inferences from *in vitro* or pathological material. There are, however, two lines of research that circumvent or mitigate those limitations. One is the study of the behavioral effects on prefrontal functions of pharmacological agents, agonists or antagonists of 5-HT, or dietary manipulations of the 5-HT precursor, tryptophan; the other is the combined application of pharmacology and neuroimaging in the healthy human subject. Both bear fruit.

The reaction of an endogenous hormonal substance, prolactin, to the 5-HT agonist fenfluramine has been used as a neuroendocrine assay of response to cerebral 5-HT. Thus, fenfluramine-induced changes in regional glucose metabolism can serve as indicators of neuronal activity changes resulting from variations in 5-HT. Further, regional analysis of 5-HT concentration can be assessed by 18-fluorodeoxyglucose (FDG) positron emission tomography (PET). By these means it was determined in healthy volunteers that reactive 5-HT reaches above-average values in left prefrontal cortex, notably the left anterior cingulate and dorsolateral areas of the prefrontal convexity (Mann et al., 1996).

A working-memory task dependent on dorsolateral prefrontal areas, however, does not seem to be facilitated by 5-HT. Fenfluramine impairs monkeys' performance of delayed alternation, whereas the same behavior is facilitated by the DA agonist bromocriptine (Luciana et al., 1998). Prefrontal 5-HT depletion has been shown to selectively impair reversal learning (Robbins and Roberts, 2007). Thus, DA and 5-HT appear to have opposite actions on working memory mediated by the dorsolateral prefrontal cortex. In fact, Rogers et al. (1999a, 1999b) extend this DA/5-HT dichotomy into a double dissociation of prefrontal areas and the behavioral actions of the two neurotransmitters. Whereas methylphenidate – a DA agonist – has been shown to impair working memory (a dorsolateral-supported function), it does not affect a decision-making gambling task (an orbital-supported function). The evidence on methylphenidate, however, is not uniform. Elliott et al. (1997) found that the drug improves, not impairs, working memory on a spatial task, as well as planning, in young adults.

Rogers et al. (1999a) also found that the dietary depletion of tryptophan (the precursor of 5-HT) did not affect working memory, but had a deleterious effect on the gambling task. This task is similar to one devised by Bechara et al. (1998), which they found to be sensitive to

orbitofrontal damage. The task requires the subject to weigh decisions based on magnitude and probability of expected success against commensurate risks of loss. Basically, the subject must choose between a small but highly probable reward and a large but highly improbable reward. The individual with an orbitofrontal lesion chooses the latter, incapable of forgoing a large measure of gratification even if that entails the risk of losing all chances for reward, large or small. Clearly, the orbitofrontal patient suffers from an incapacity to inhibit the drive toward immediate and maximum reward. In the orbital patient, as in the tryptophan-depleted subject, disinhibition has other manifestations, such as trouble in learning reversal tasks (Park et al., 1994; Rogers et al., 1999a). Along with uncontrollable impulsivity and drive, those manifestations, which are also common in the orbital monkey (see Chapter 4), suggest the role of the orbitofrontal cortex in inhibitory control. Thus, although many questions remain on the subject, the evidence of modulation of GABA activity by prefrontal 5-HT suggests that the orbital prefrontal cortex may exert its function of inhibitory control of emotion and impulsivity by way of 5-HT mechanisms, possibly among others.

## F. Acetylcholine

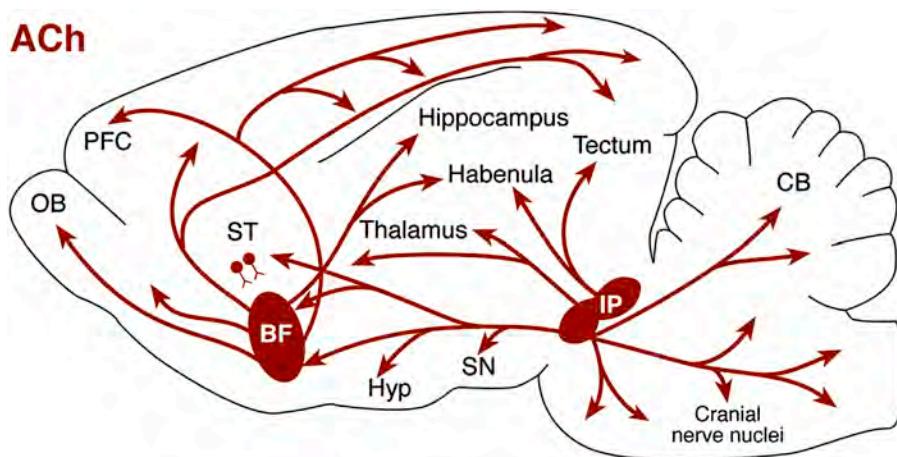
Acetylcholine (ACh), the first neurotransmitter to be discovered (Loewi, 1921), is also a pervasive neurotransmitter. It operates in assorted synapses: in neuromuscular junctions (where it was first identified), in the autonomic system, and in the peripheral as well as central nervous system. It has two types of target receptors: (1) nicotinic receptors (central nervous system type), through which it mediates rapid (in the millisecond range) excitatory transmission; and (2) muscarinic receptors, through which it mediates slower (in the second range) excitatory or inhibitory transmission. (It should be pointed out that nicotine receptors in the central nervous system have very different properties

from those in the periphery and neuromuscular junction.) Nicotine is an agonist and curare an antagonist of ACh transmission in the first type of receptors; muscarine (a mushroom alkaloid) and atropine are, respectively, an agonist and an antagonist in the second type. Two enzymes, choline-acetyltransferase (AChT) and acetylcholinesterase (AChE), subserve, respectively, the synthesis and catabolism of ACh; both are useful markers for determining, immunohistochemically or otherwise, its presence and concentration in neural tissue. At least one of the principal ACh receptors is very similar to that of other ionotropic receptors, especially 5-HT<sub>3</sub>. ACh binding is relatively straightforward and well understood at the molecular level (Waxham, 1999). The inactivation of ACh occurs enzymatically and through muscarinic cholinergic autoreceptors, although the latter also regulate release.

ACh-containing and cholinceptive neurons are widely distributed throughout the brainstem and the basal forebrain of the rat (Armstrong et al., 1983; Woolf et al., 1984; Deutsch and Roth, 1999), the cat (Kimura et al., 1981), the monkey (Hedreen et al., 1983), and

the human (Mackay et al., 1978). Various cholinergic pathways and systems have been identified, connecting subcortical structures with one another and with the cortex (Figure 3.11). Some of the best known ACh neurons are the cholinergic interneurons of the striatum, which are modulated by DA. In the absence of that modulation, as occurs in Parkinson's disease, those interneurons are pharmacologically targeted with anticholinergic substances in attempts to control the disordered motility of the disease.

A very important source of cholinergic influences over the neocortex in general, and the prefrontal cortex in particular, is a vast array of ACh neuron populations in the basal forebrain (Shute and Lewis, 1963; Jones et al., 1976; Johnston et al., 1979; Mesulam et al., 1983; Hedreen et al., 1984). These neuron populations form nuclear aggregates in the septum, the nuclei of the diagonal band, the ventral pallidum, and the nucleus basalis of Meynert, which is part of the substantia innominata. That aggregate system projects diffusely to the cortex, with some preponderance of projection to precentral and temporal regions in the monkey (Lehmann et al., 1984). It can be safely assumed



**FIGURE 3.11** Schematic of the major collections of cholinaminergic (ACh) neurons and their projections in the rat's brain. Abbreviations: BF, basal forebrain; CB, cerebellum; Hyp, hypothalamus; IP, interpeduncular nucleus; OB, olfactory bulb; PFC, prefrontal cortex; SN, substantia nigra; ST, striatum. (From Deutsch and Roth, 1999, modified, with permission.)

that the largest share of terminal ACh in the neocortex derives from the cholinergic system of the basal forebrain and that only a small part is generated intrinsically, that is, in cortical neurons (Johnston et al., 1981). According to the results of some studies (Shute and Lewis, 1963; Mitchell, 1963; Kanai and Szerb, 1965; Lewis and Shute, 1967; Phillis, 1968), that system, like the NE system from the locus coeruleus – which is also diffusely projecting – is a constituent of the ascending reticular activating system and therefore critical for arousal. Electrical stimulation of the brainstem reticular formation or peripheral sensory stimulation causes the release of ACh in widespread cortical areas and, with it, electrocortical arousal (low-voltage and fast-frequency electroencephalography).

The prefrontal cortex is part of the cortical projection field of the basal forebrain cholinergic system (Emson, 1978; Mesulam et al., 1983). The laminar distribution of ACh axons terminating in prefrontal areas is similar to that of DA terminals: they are especially abundant in deep cortical layers (Emson, 1978; Kimura et al., 1981), although some immunoreactive studies have found them to be most dense in layers I–III (Lewis, 1991). Upon microiontophoretic application of the transmitter (Inoue et al., 1983; Sawaguchi and Matsumura, 1985), the highest numbers of ACh-sensitive neurons can be found in layers III–VI. Fine autoradiographic analysis has revealed some interspecies differences in the laminar distribution of muscarinic receptors ( $M_1$  and  $M_2$ ) in the prefrontal cortex of the rat (Zilles et al., 1989), the monkey (Lidow et al., 1989a), and the human (Cortés et al., 1986; Zilles et al., 1989).

By microiontophoresis, one study found that ACh, through muscarinic receptors, increased the spontaneous firing rate of more than half of the cells in the dorsolateral prefrontal cortex of the monkey (Inoue et al., 1983); the excitatory or inhibitory responses of certain cells to task events in a simple instrumental feeding task were enhanced by ACh and diminished

by an ACh antagonist (atropine); furthermore, the activity of prefrontal units could be driven by electrical stimulation of the nucleus basalis of Meynert, and this effect was also blocked by atropine.

The prefrontal cortex seems to regulate ACh release in posterior sensory or association cortex. The mechanism is unclear; it may involve prefrontal projections down to cholinergic cell bodies, which in turn act upon posterior cortices. Alternatively, prefrontal projections (see Chapter 2) may act on cholinergic axon terminals in posterior cortex. Nelson et al. (2005) investigated the functional chemical interactions between prefrontal and posterior parietal cortex. Upon stimulating the prefrontal cortex by direct application of AMPA, they observed an increase in ACh efflux in parietal cortex. That increase was antagonized by administration of an AMPA receptor antagonist. The study indicates the capacity of the prefrontal cortex to regulate the release of ACh in posterior cortex. It is reasonable to suppose that such mechanisms are essential to the “top-down” influences from prefrontal upon posterior cortex that, as we will see in Chapter 6, are at the basis of attention and working memory. In the rat, Sarter and coauthors (Sarter et al., 1997; Gill et al., 2000; Himmelheber et al., 2000; Sarter and Bruno, 2000) have provided evidence on the role of ACh in attention regulation and the participation of the prefrontal cortex in that regulation.

In a neuroimaging study, Furey et al. (2000) substantiated the cholinergic enhancement of posterior cortex in working memory. By potentiating ACh with administration of the cholinesterase inhibitor physostigmine, they were able to improve visual working memory, apparently by enhancing the representation of the visual memorandum in extrastriate cortex. The authors derived this inference from the evidence that, whereas under the influence of physostigmine the prefrontal cortex itself did not show increased activity, the posterior – extrastriate – cortex did. The authors argued that working

memory benefited from the facilitation, probably by the prefrontal cortex, of the encoding of the visual image to be subsequently retained by the subject in short-term memory.

A study in the monkey shows that the orbital prefrontal cortex is an important source of downward prefrontal regulating projection to the cholinergic cell bodies (Mesulam and Mufson, 1984). This is in accord with the finding that basal cholinergic cells fire to the presentation of the reward in a delayed-response task (Richardson and DeLong, 1986). It is also in accord with the evidence (Chapters 4–6) that the orbital prefrontal cortex plays a crucial role in the evaluation of reward.

## G. Neuropeptides

Until now, this chapter has dealt with the major, classical, neurotransmitters and neuromodulators. All are known to intervene in the prefrontal cortex, even if their functions are not yet fully understood. We will see that some of them play (or misplay) a major role in a score of psychiatric syndromes (see next section). Now we must deal, albeit briefly, with a large category of non-classical neurotransmitter/modulators whose functions in the prefrontal cortex are yet more obscure, but that deserve some discussion, at the very least to alert the neuroscientist to their potential importance in affect or cognition and to instigate further research on them. Among the “non-classicals” is a vast slate of neuropeptides, and two gases, nitric oxide and carbon monoxide, that fall outside the definition of neurotransmitters but appear to play at least a coadjuvant role with them in the prefrontal cortex.

Neuropeptides conform to the conventional definition of neurotransmitters in that they are synthesized within neurons, stored in synaptic vesicles, and released in calcium-dependent mode. Furthermore, they mediate electrochemical transactions between neurons and are subject to regulation and inactivation, much like

the other neurotransmitters. They differ from these, however, in very important ways. In the first place, a peptide is synthesized in the cell body, rather than in axon terminals, and is transported slowly down the axon to the synapses in a slow process that may take days. Release is prompted by relatively high rates of firing, but it is slower than for classical transmitters. Moreover, compared with these, the neuropeptides are subject to a much slower turnover. The inactivation of a peptide is enzymatic or by diffusion, in the absence of high-activity reuptake. Release and depolarization need not be at the terminal synapses, but may be ephaptic, for example, between axons.

There are about two dozen neuropeptides that are demonstrated or putative neurotransmitters. The best known thus far identified in the mammalian nervous system are somatostatin, substance P, cholecystokinin (CCK), neuropeptide Y, vasoactive intestinal polypeptide (VIP), angiotensin, and neuropeptidin. The physiological actions of neuropeptides are still poorly understood. In some fundamental respects they behave like the conventional neurotransmitters: their release at nerve terminals is  $\text{Ca}^{2+}$  dependent, and they can induce firing changes in adjacent neurons. These changes, however, are relatively slow and rarely induced through morphologically discrete and well-identifiable synapses. For these and other reasons, neuropeptides have been viewed as hormone-like substances, and their actions more as those of neuromodulators than of true neurotransmitters. Reinforcing these concepts is the observation that certain peptides coexist in certain cells, notably non-pyramidal cortical neurons, with unequivocal transmitters such as GABA or ACh (Hendry et al., 1984a; Jones and Hendry, 1986). From observations of this kind derives the notion that peptides possibly modulate, within those cells, the production or release of other transmitters. Aside from that, peptides have also been suspected of performing trophic functions; in this respect, they resemble

growth factors, another category of substances to which neurotransmitter functions have been attributed.

All the neuropeptides mentioned above have been found in the cerebral cortex of rats and monkeys (Emson and Lindvall, 1979; Jones and Hendry, 1986; Deutsch and Roth, 1999). Somatostatin, substance P, and CCK have been observed in both fibers and cells of the neocortex (Hendry et al., 1984b; Bouras et al., 1986). All three appear to be particularly abundant in the prefrontal cortex (Emson, 1978; Hayashi and Oshima, 1986; Lewis et al., 1986b; Oeth and Lewis, 1990, 1993; Lund and Lewis, 1993; Condé et al., 1994). In the prefrontal cortex, as elsewhere, however, neuropeptides coexist in the same cells as other neurotransmitters, and they may potentiate these neurotransmitters or contribute to their synthesis. A case in point is the interaction between neurotensin and DA, which by microdialysis have been found to coexist in prefrontal cells (Bean and Roth, 1992). Neurotensin release increases when the cell enters a bursting pattern of firing, which is common in DA neurons. Furthermore, the DA auto-receptors are sensitive to neurotensin release. Thus, DA release and neurotensin release seem to be reciprocally regulated. Another sign of DA-neurotensin interactions is the evidence that the activation of neurotensin receptors in prefrontal cortex stimulates brainstem DA cell firing (Rompre et al., 1998).

In recent years, considerable interest has been devoted to another neuropeptide of wide-ranging influence: orexin or hypocretin. This substance is secreted by hypothalamic cells and neurally transported to other subcortical and cortical structures. Apparently by interacting with ascending and descending reticular systems of the brainstem, orexin plays important roles in sleep, arousal, attention, and autonomic functions. Either indirectly through the thalamus or circumventing it, orexin terminals interact in the diencephalon with other neurotransmitters, notably glutamine, DA, and ACh,

that have wide distribution and actions in the prefrontal cortex (Fadel et al., 2005; Huang et al., 2006; Vittoz and Berridge, 2006). Orexin has been found to modulate DA neurons from the brainstem and their effects on medial prefrontal cortex, presumably by this mechanism affecting arousal, attention, and emotional responsiveness (Vittoz and Berridge, 2006; Moorman and Aston-Jones, 2010). Orexin/hypocretin also has a major excitatory effect on the NE cells of the locus coeruleus (Horvath et al., 1999), through which it may also contribute to cortical activation in those states.

Nitric oxide, another non-conventional “neurotransmitter” (Dawson and Snyder, 1994), may play an important role in prefrontal physiology. Glutamate prefrontal pyramids, through NMDA receptors, can be assisted by nitric oxide in the elicitation of LTP and its consequent protein changes in the hippocampus (Böhme et al., 1993). The reverse relationship (hippocampus to prefrontal) may occur by intervention of those transmitters, glutamate and nitric oxide, in the formation of the associative executive memory of the prefrontal cortex.

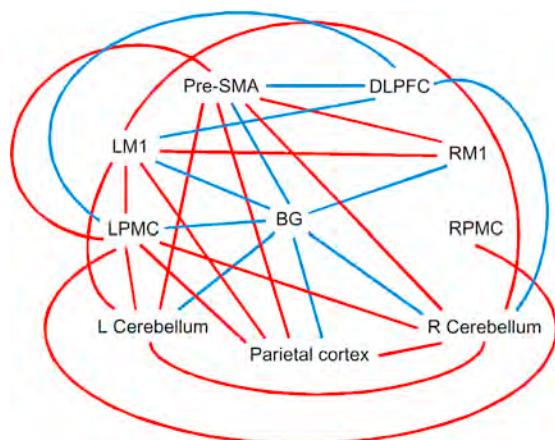
#### IV. NEUROPSYCHIATRIC IMPLICATIONS

When the dopaminergic cells of the basal ganglia degenerate, the result is Parkinson's disease, with all its clinical manifestations. Arguably, this is the clearest example of failure of a given neurotransmitter in a given part of the brain leading to a clear-cut disease syndrome. Yet, this picture is not quite correct. In fact, on close analysis Parkinson's disease epitomizes to some degree the common misattribution of a disease syndrome such as those to be reviewed in this section to solely one failing neurotransmitter in a discrete cerebral structure. Although the dopaminergic disorder in the basal ganglia is unmistakably at the nucleus of the Parkinson's disease, DA is not the only

transmitter failing in this disease, nor are the basal ganglia the only affected structures in it. Two categories of clinical data suggest that to be the case: (1) the cognitive and autonomic symptoms commonly accompanying its characteristic motoric manifestations; and (2) evidence that other structures and neurotransmitters are involved in the disease other than the basal ganglia and DA, even if these may be primary and the others secondary. We could add the variability with which different Parkinson's patients respond to different treatment modes, pharmacological or surgical, a variability that suggests differences in pathogenesis between patients with the same disease.

To emphasize the multiplicity of brain structures affected in Parkinson's disease, as well as the interactions between those structures and between neurotransmitters in the disease, it is illustrative to consider the altered patterns of cerebral connectivity that modern neuroimaging (Wu et al., 2011) reveals in Parkinson's patients (Figure 3.12). This example from a relatively well-defined disease entity that affects the prefrontal cortex can be used to emphasize the general rule that more than one neurotransmitter and structure are involved in any of the neuropsychiatric conditions that affect that cortex. If the case of Parkinson's is paradigmatic, it is easy to infer how much more complicated the chemical interactions probably are in cognitive and emotional disorders that are subject to more complex genetic, environmental, and metabolic factors, such as schizophrenia.

Below, we review the role of the various neurotransmitters in some of the major neuropsychiatric syndromes. In the light of previous considerations, in no case can we unequivocally attribute a disease entity to a deficit or malfunction of one specific transmitter, although in each syndrome some disordered neurotransmitters play more of a role than others. The reasons for the lack of pathogenetic neurotransmitter specificity are to be found in the fact that those chemicals work in complex systems, such as the



**FIGURE 3.12** Differences in effective connectivity between Parkinson's patients and normal controls during performance of self-initiated movements, assessed by functional magnetic resonance imaging. Red/blue lines indicate increased/decreased connectivity in patients versus controls. Abbreviations: BG, basal ganglia; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area; L, left; R, right. (From Wu et al., 2011, with permission.)

neurons they serve. Beginning at the lowest level with the neuron, Dale's principle (i.e., that each neuron releases only one type of neurotransmitter at all of its synapses) is no longer valid. The idea that a cell uses only one transmitter is false, as now we know that neurons can contain more than one transmitter. For example, as we have seen, a cell can use DA and neuropeptides, or glutamate and NE. A given neuron can contain as many as four transmitters. Then, a transmitter does different things in different brain structures, since what it does is defined by the structure and the connectivity that it serves within it. Such is the case in the prefrontal cortex, with its many transmitters and myriad connections. Nevertheless, despite our ignorance on the nature of many electrochemical transactions in this part of the brain, there is an emerging body of knowledge about the malfunction of neurotransmission in some major disease categories that affect the frontal lobe, as well as

a solidifying rationale about how to treat them by chemical means. Much of that knowledge is empirical, derived from experiment and clinical experience; some of it is inferential.

### A. Attention Disorders

Attention is a complex cognitive function biologically based on the limitations of the nervous system to process an excessive amount of relevant or adaptive information at a given time. The prefrontal cortex, as we shall see, has much to do with selective and adaptive processing. The narrow phenomenological definition of attention coincides with that of the so-called focus of attention, which refers to the selective informational content that is in the field or "stream" of consciousness at any given time. The ability to willfully and persistently maintain that selective content in consciousness is what we understand as the capacity to concentrate attention. It may be argued that this concept of attention, based on focused and maintained content, includes working memory ([Fuster, 2003](#)), which is attention focused on an internal representation.

That narrow definition of attention, however, which may be called "inclusionary" (for what the focus of attention includes), is incomplete because it does not account for the exclusionary (inhibitory) aspect of attention. The adaptive behavior of an organism depends not only on attending to a particular item, sensory, emotional, or otherwise, but also, equally important for adaptation, on suppressing or inhibiting everything else, or at least what is not immediately relevant. [James \(1890\)](#) was the most prominent proponent of the first aspect of attention, [Broadbent \(1958\)](#) of the second. The prefrontal cortex is important for both.

In the primate, we know that all three major prefrontal regions – lateral, medial, and orbital or ventral – play major roles in attention. The medial prefrontal cortex, which includes anterior cingulate, paralimbic, and medial premotor areas,

is the prime recipient of inputs from the limbic, mesencephalic, and diencephalic structures (see Chapter 2) involved in arousal, drive, and motivation. Oversimplifying somewhat for the sake of clarity, we could conclude that the medial areas contribute to attention the elementary neural "energy" it needs. The lateral prefrontal cortex, which in addition to receiving subcortical and limbic inputs is widely interconnected with other neocortical areas, contributes the focusing and concentrating capacity of attention, which is commonly part of what has been named cognitive control. Indeed, its well-known role in working memory supports this view. Finally, for reasons that will be made explicit in the next three chapters, the orbital prefrontal cortex contributes most of the inhibitory aspects ("exclusionary") of attention. Thus, to sum up, it seems appropriate to attribute to the medial, lateral, and orbital prefrontal cortices the major roles in the intensive, inclusionary, and exclusionary aspects of attention, respectively. It should be kept in mind, however, that the three "functions" work intimately together, and that none of the three regions has the exclusive control of any function.

As we have seen earlier in this chapter, there are certain differences in the regional distribution of neurotransmitters in the prefrontal cortex. But these, too, are differences of degree and far from clear-cut. In any region it seems to be the rule that any pyramidal neuron colocalizes more than one transmitter, each transmitter possibly serving a different cognitive function depending on the connectivity of the neuron. It is not surprising, therefore, that several transmitters are implicated in practically any of the attentive functions of the prefrontal cortex. If we accept the reasonable proposition that working memory is attention directed to an item of sensory information for prospective action, we are forced to conclude that DA, NE, and glutamate in particular, are clearly involved in the inclusionary, focusing, aspect of sustained attention, which is mainly the purview of the lateral cortex in the monkey, and the dorsomedial in the

rat. This conclusion is certainly supported by the results of using agonists and antagonists of those transmitters in delay tasks, as reviewed above in the relevant sections. That conclusion is also supported by the neuropsychology of brain lesions (see Chapter 4) and the neurophysiological and neuroimaging data in Chapters 6 and 7.

In the past three decades, the neurobiochemistry of a particular attention disorder of children and young adults has attracted considerable interest: ADHD ([Hinshaw, 1994](#); [Barkley, 1997a, 1997b](#)). This heritable disorder is characterized by serious problems in all aspects of attention. The patient has difficulty concentrating attention on anything for any length of time, especially on cognitive tasks such as school requirements. He or she is also extremely distractible, seemingly unable to refrain from attending to the most trivial surrounding stimuli and events. In addition, he or she is beset with an irrepressible need to move, incapable of staying still despite all reasonable restraint and admonition. Parents and teachers labor usually without success to control the unruly behavior and to reverse the lagging scholastic advance of the child with ADHD. In many cases, the patient outgrows the trouble in adolescence or later. In others, the trouble persists into adulthood and may lead to sociopathy.

Since the mid-1990s, there have been several important discoveries in the field of ADHD. Some of these pertain to the genetics of the disorder (reviewed by [Faraone et al., 2005](#); [Banaschewski et al., 2010](#); [Cortese, 2012](#)). A surprising number of genes having to do with catecholamine transmission is involved in ADHD, including the DA transporter, and the D<sub>1</sub>, D<sub>5</sub>, D<sub>4</sub>, and α<sub>2A</sub> receptors. Inasmuch as proper catecholamine transmission is needed to enhance the signal-to-noise in the prefrontal cortex, patients with mutations in those genes may have weaker prefrontal regulation of attention and behavior. This could, in principle, be normalized by medications that augment or mimic

NE and/or DA ([Prince, 2008](#); [Robbins and Arnsten, 2009](#); [Arnsten and Pliszka, 2011](#); [Del Campo et al., 2011](#)).

Because of the favorable evolution of many untreated cases of ADHD, it is reasonable to suspect, at the root of the problem, the delayed maturation of a neurochemical or structural system affecting the ontogenesis of the prefrontal cortex. Some neuroimaging evidence points in that direction. Imaging studies (reviewed by [Bush et al., 2005](#)) show smaller/weaker prefrontal cortex in ADHD. This has functional implications that are relevant here. The right inferior prefrontal cortex, in particular, is important for response inhibition ([Aron et al., 2004](#)), and that region is hypoactive in ADHD patients engaged in inhibition-control tests ([Rubia et al., 1999, 2005](#)). Furthermore, as discussed in ensuing chapters, the anterior cingulate cortex is important for error correction, and the orbital cortex for inhibitory control in both emotion and cognition.

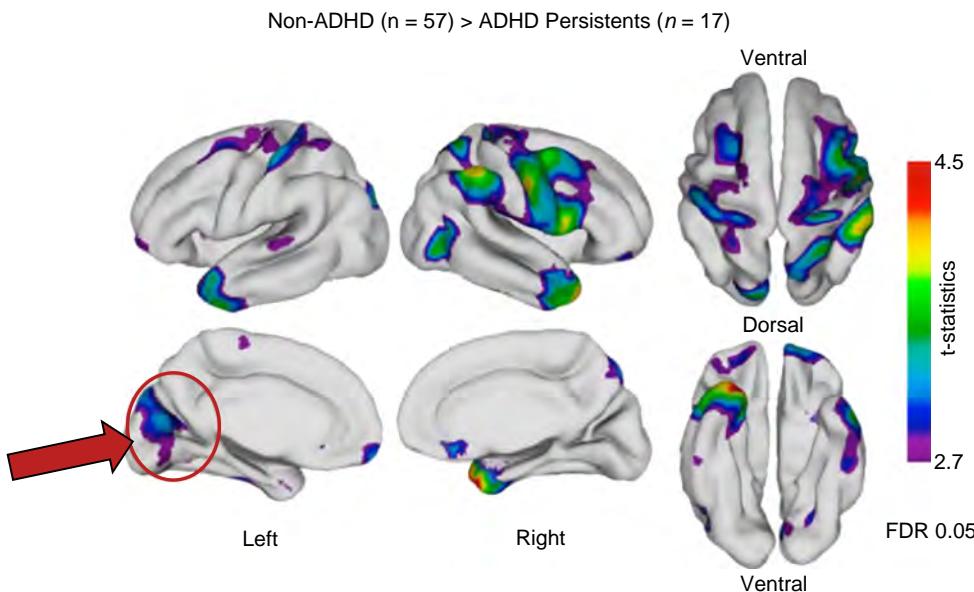
Like the genetic factors, animal models of ADHD, notably rats after pharmacological intervention or with a spontaneous tendency to hyperactivity, point to disorders in catecholamine systems, more specifically the mesocortical DA system, with congruent phenomena such as the underexpression of tyrosine hydroxylase ([Sullivan and Brake, 2003](#); [Viggiano et al., 2004](#)). In the same vein, according to the analysis of findings compiled in two extensive reviews of the problem ([Carlsson, 2001](#); [Todd and Botteron, 2001](#)), ADHD appears to arise from hypcatecholamine function (especially DA) in subcortical and prefrontal cortical regions that secondarily results, among other alterations, in glutamate and GABA deficiencies in pyramidal and striatal neurons, leading to a variety of manifestations of disinhibition. The disorder would seem to be essentially developmental ([Sagvolden et al., 2005](#)). The principal clinical manifestations of ADHD, namely, the difficulty in concentration, the distractibility, and the disinhibition of motility, would appear to be attributable to that glutamate/GABA deficit in the prefrontal cortex

and the basal ganglia. In this respect, as [Carlsson \(1981\)](#) has noted, ADHD would be antithetical to obsessive-compulsive disorder (OCD), which is another prefrontal-striatal disorder, this one characterized by hyperglutaminergic activity and “hyperattention” (In my view, an appropriate characterization of obsessive thinking and compulsive behavior).

Although previous research focused on the dopaminergic role of stimulant medications, it is now known that low doses of stimulants that mimic those given to children actually have a greater effect on NE than on DA ([Kuczenski and Segal, 2002](#); [Berridge and Waterhouse, 2003](#)). Low-dose methylphenidate increases NE and DA levels, especially the former, in the prefrontal cortex, and has much greater effects on this cortex than subcortical catecholamines. These low methylphenidate doses reduce locomotor activity ([Kuczenski and Segal, 2002](#)) and improve cognitive abilities linked to the prefrontal

cortex in rats ([Berridge and Waterhouse, 2003](#); [Arnsten and Dudley, 2005](#)), the latter via both  $\alpha_{2A}$ -adrenoceptor and dopamine D<sub>1</sub> mechanisms ([Arnsten and Dudley, 2005](#)). New medications for treating ADHD, such as atomoxetine (Strattera®) and guanfacine, similarly increase or mimic the actions of NE ([Scalhill et al., 2001](#)). Conversely, one can recreate all the symptoms of ADHD in monkeys by blocking  $\alpha_{2A}$ -adrenoceptors in the prefrontal cortex, thus increasing locomotor activity ([Ma et al., 2005](#)), weakening impulse control ([Ma et al., 2003](#)), and impairing working memory ([Li and Mei, 1994](#)).

Research indicates that ADHD may affect cortical systems in addition to the prefrontal-striate system and its catecholamine receptors. In a morphological imaging study of adult ADHD patients diagnosed in infancy, [Proal et al. \(2011\)](#) demonstrated subnormal levels of gray matter and diminished cortical thickness in several regions ([Figure 3.13](#)): prefrontal,



**FIGURE 3.13** Cortical thickness analysis in attention deficit/hyperactivity disorder (ADHD). A 33-year longitudinal follow-up study shows that adults with ADHD have significantly decreased cortical thickness in several cortical areas. Arrow points to a major decrease in visual cortex. (From [Castellanos and Proal, 2012](#), with permission.)

parietal, temporal, and notably occipital, involving the visual cortex. Subsequent functional magnetic resonance imaging at rest indicated that the areas in question harbor large-scale cortical networks, including some that come under the category of “default” networks, which are predominantly active in the resting state. These morphological and functional data suggest that the abnormalities of chemical neurotransmission in ADHD may extend well beyond the commonly implicated prefrontal–striate system ([Castellanos and Proal, 2012](#)).

From these considerations, it is reasonable to conclude that ADHD probably results from a genetically determined developmental delay in the maturation of prefrontal–striate catecholamine systems. This inference is supported by two essential clinical facts: the positive response of many cases to certain catecholamine agonists, such as methylphenidate, and the favorable spontaneous evolution of many cases with age, presumably by eventual, though laggard, maturation of deranged prefrontal transmitter systems. Furthermore, whether coincidentally or secondarily, other cortical and subcortical neurotransmitter systems may be involved in the disease.

## B. Schizophrenia

Schizophrenia is a heritable mental illness of usually young adulthood that presents itself in the form of at least four different syndromes, each with its particular constellation of symptoms, although in the course of the illness one syndrome may evolve into another. Certain cardinal symptoms are characteristic of schizophrenia, namely, the disorders of the formal thought process, of affect, and of behavior, although these diagnostic symptoms may not coexist at the same time in the same patient. Other symptoms, for example, delusions and hallucinations, are not diagnostic, as schizophrenia shares them with other mental disorders. In any event, when considered as a

whole throughout the course of the illness, its manifestations are nothing short of protean and severely incapacitating at practically any stage of its evolution.

In all probability the polymorphism of the clinical manifestations of schizophrenia is a reflection of, among other things, its genetic polymorphism. Indeed, a long tradition of epidemiological studies, family studies, and twin studies has provided ample evidence that the illness has a genetic basis. Yet, as of now, no particular alteration in a gene or combination of genes has been unmistakably and consistently identified as the cause of, or even as a risk factor for, schizophrenia ([Tiwari et al., 2010](#)). On the other hand, as we note below, certain genetic alterations have been associated with defects in the development of the prefrontal cortex or in the physiology of some of its neurotransmitters, both of which play an important role in the pathogenesis and the cognitive and emotional manifestations of the illness. In very general terms, the genes most commonly associated with schizophrenia ([Owen et al., 2005](#)) are the following: (1) genes involved in the development of the cortex (e.g., NRG1, PRODH, DISC1); (2) genes involved in glutamate transmission (e.g., DTNBP1, DAOA, RGS4); and (3) genes that inhibit intracellular signaling pathways, which are activated by stress (e.g., DISC1, PDE4B, RGS4, COMT). Among the latter are genes that impact on DA in the prefrontal cortex, notably COMT. Some of the same genes are implicated in other psychiatric conditions, notably bipolar disorders.

COMT is an enzyme involved in the degradation of DA, among other neuroactive substances. Since the early work of Weinberger and his colleagues at the US National Institute of Mental Health (NIMH) ([Egan et al., 2001](#)), several studies have supported the notion that a variant of the COMT gene is responsible for the defective breakdown of DA in the prefrontal cortex of schizophrenic patients. The evidence in support of that notion derives from genetic,

clinical, neuropsychological, and behavioral data in patient populations as well as in animal models. Nonetheless, largely because of the polymorphism of the gene in question and its apparent involvement in other mental conditions (e.g., ADHD, bipolar disorders), the demonstration of a direct and specific link with schizophrenia remains elusive. Yet, because of the polymorphism of both the disease and the gene, it remains plausible to assume that, at least in part, a COMT alteration in the prefrontal cortex plays a role in at least some of the aspects of the pathogenesis of schizophrenia (Lewandowski, 2007; Williams et al., 2007; Durstewitz and Seamans, 2008). If that notion is correct, it would appear that D<sub>1</sub> and D<sub>2</sub> DA receptors would be those most affected by the genetic defect.

For more than half a century, ever since the start of its empirical treatment with so-called neuroleptic drugs, the quest has been on to elucidate the disordered neurochemistry of schizophrenia. Neurotransmitters have been at the center of that quest. Despite considerable success in some aspects of this research, there is a growing consensus that, just as there is probably no one single gene responsible for the disease, there is probably no one single deranged neurotransmitter in it. This would be expected, anyhow, from the complex and intimate interactions between transmitters. At the same time, the evidence that several neurotransmitter are implicated in schizophrenia, together with the clinical evidence, has given rise in the minds of some investigators to the idea that schizophrenia is essentially a “disconnection” syndrome (Friston and Frith, 1995), much as are syndromes in the realm of aphasias and agnosias (Geschwind, 1965). Indeed, we now know that several cortical, subcortical, and limbic structures are affected in schizophrenia. That fact by itself points to the centrality of the prefrontal cortex in the pathogenesis of the illness, as that cortex is the best interconnected with those other structures (see Chapter 2).

All the cardinal symptoms of schizophrenia suggest frontal pathology. Furthermore, as we will see in Chapter 7, structural abnormalities of the frontal lobe have been found in the disease. We should resist and reject, however, the simplistic inference that “schizophrenia is a disease of the frontal lobe.” Just as the frontal cortex does nothing physiologically alone by itself, rarely is it ill alone by itself, least of all in a condition as complex and polymorphous as schizophrenia. Nonetheless, there are at least three neurotransmitter systems operating in that cortex that seem exceptionally vulnerable in the psychotic process: DA, GABA, and glutamate.

It has long been suspected or postulated that at the basis of the pathogenesis of schizophrenia is a malfunction of DA mechanisms (Stevens, 1973; Matthysse, 1974; Toda and Abi-Dargham, 2007; Durstewitz and Seamans, 2008; Howes and Kapur, 2009). More specifically, it has been hypothesized that the psychosis is due to an excess of DA in some cerebral structures, including the neocortex, or a dysfunction of the corticofugal feedback system descending upon subcortical structures, notably the VTA and the basal ganglia. The early empirical grounds for the concept of a DA disorder in schizophrenia, possibly involving DA overactivity in some brain locations, could be summarized as follows: (1) amphetamine, a DA agonist, induces a psychotic syndrome resembling acute schizophrenia (Connell, 1958); (2) some neuroleptic or antipsychotic drugs, the most efficacious pharmacological agents for the treatment of schizophrenia, are DA receptor blockers known to reverse the behavioral effects of amphetamine in animals (Randrup and Munkvad, 1965); (3) the clinical antipsychotic efficacy of neuroleptics is directly correlated with their ability to block DA at synapses (Seeman et al., 1975, 1976); and (4) neuroleptic treatment commonly induces parkinsonian, extrapyramidal symptoms which reflect DA depletion, at least in the nigrostriatal system.

In any event, the hypothesis that schizophrenia results solely from an overall increase in DA activity in the brain can be ruled out. Studies on the cerebrospinal fluid of people with schizophrenia have failed to demonstrate consistent increases in central DA turnover rates (Post et al., 1975; Van Kammen et al., 1986). Furthermore, schizophrenia can coexist with Parkinson's disease, and there is no clear evidence, in patients in which it does, of reciprocal relationships in the symptoms from the two diseases (Crow et al., 1976). There is, however, evidence that L-dopa treatment in Parkinson's patients can ameliorate cognitive functions under prefrontal control, possibly – as at least one neuroimaging study indicates (Cools et al., 2002) – by increasing blood flow in the lateral prefrontal cortex.

Whereas the idea of a global increase in dopaminergic activity in schizophrenia is untenable, that of selective increases – such as by region or by receptor type – has gained considerable support. DARPP-32, a phosphoprotein essential in DA metabolism, has been found to be deficient in the prefrontal cortex of schizophrenic patients (Albert et al., 2002). Also, it has been proposed that the lack of prefrontal feedback regulation upon subcortical dopaminergic structures may account for increased DA activity in those structures and, as a result, for many of the symptoms (affective, cognitive, and motoric) that afflict the schizophrenic patient (Bannon and Roth, 1983). Subcortical DA deregulation of prefrontal origin may lead to the overproduction of D<sub>2</sub>-type DA receptors in the basal ganglia, as indicated by a PET study (Wong et al., 1986).

Chemical models of schizophrenia also support some aspects of the prefrontal DA rationale for the disease. Phencyclidine (PCP) is a psychomimetic drug that, in humans and animals, induces a variety of cognitive and affective disorders akin to those observed in schizophrenia. When administered to monkeys, PCP produces a reduction of DA usage in dorsolateral

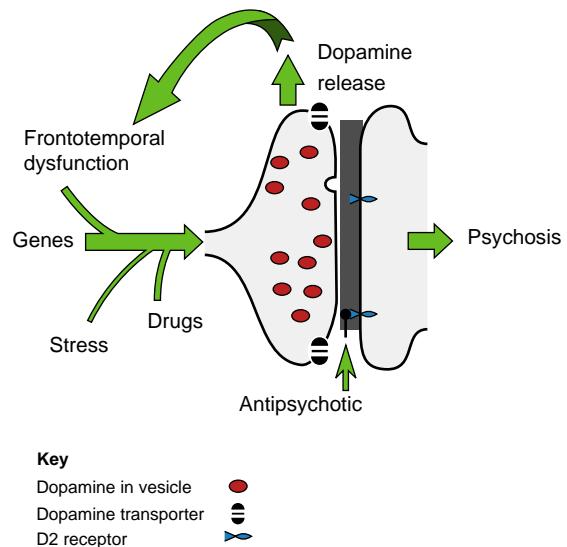
prefrontal cortex and a concomitant deficit in working memory that can be reversed by the antipsychotic clozapine (Jentsch et al., 1997a). Similar effects of subchronic PCP administration on behavior and on mesocortical DA level were observed in the rat (Jentsch et al., 1997b). In the monkey, the chronic administration of amphetamine, a substance that presumably impedes the reuptake of DA, also leads to prefrontal cognitive deficits and a reduction of local DA turnover (Castner et al., 2005). Another animal model of schizophrenia, the neonatal hippocampal lesion, shows abnormal DA responses in nucleus accumbens in adult but not prepubertal animals, an abnormality that could be prevented by antipsychotic treatment (Goto and O'Donnell, 2002). These phenomena suggest a delayed, possibly developmentally determined, result of early hippocampal lesion on the appearance of abnormal DA transactions present in schizophrenia. Hippocampal and prefrontal cell densities have been found to be reduced in schizophrenic patients in neuroimaging studies, which have also confirmed the abnormalities of the mesolimbic DA system in the disease (Jann, 2004).

It has been widely assumed that D<sub>2</sub> receptors are those most directly implicated in schizophrenia. Much of the support for that notion derives from the evidence that antipsychotic drugs blockade D<sub>2</sub> receptors, in some cases in proportion to their clinical efficacy (Seeman et al., 1975; Creese et al., 1976; Westerink et al., 1998, 2001; Westerink, 2002). Furthermore, D<sub>2</sub> receptors have been found in excess in the brain of schizophrenic patients (Lee et al., 1978; Mita et al., 1986; Seeman, 1992). Modern neuroreceptor imaging methods corroborate that finding (Abi-Dargham, 2004). Nonetheless, other studies (Seeman et al., 1993; Lauzon and Laviolette, 2010) point to D<sub>4</sub> receptors, which have been found to be increased six-fold in the brain of schizophrenics. These cases are particularly susceptible to improvement under clozapine, a neuroleptic to which D<sub>2</sub> receptors are exceptionally

resistant. However, three commonly used neuroleptics, including clozapine, down-regulate D<sub>1</sub> receptors in the prefrontal cortex of the monkey (Lidow and Goldman-Rakic, 1994). D<sub>1</sub> receptor dysfunction has been associated with cognitive dysfunction of the dorsolateral prefrontal cortex (Goldman-Rakic et al., 2004). The chronic administration of antipsychotic drugs has been found to down-regulate both D<sub>1</sub> and D<sub>5</sub> receptors (Lidow et al., 1997). An immunological study has identified prefrontal layer VI as the site of most DA receptor disorder in schizophrenic patients (Akil et al., 1999).

In a remarkably thorough and critical review of the data from several methodologies, Howes and Kapur (2009) developed an unusually comprehensive version of the DA theory of schizophrenia in particular and of psychosis in general. At the center of their theory is the tenet that multiple environmental and genetic risk factors for schizophrenia converge in a common pathway that leads, funneled down, to a presynaptic hyperdopaminergia, that is, excess DA, on cells of the basal ganglia (Figure 3.14). Because of that excess, and the inability of striatal receptors to absorb it, DA spills back into the system, notably – we say – the prefrontal cortex, and by positive feedback rekindles the clinical manifestations of psychosis. In particular, that pathological feedback leads to what the authors call “aberrant salience,” by which they mean what is clinically commonly called delusional interpretation. For obvious reasons, they name their DA-based theory the “final common pathway” theory of psychosis. Since its formulation in 2009, it has not been refuted by any empirical evidence of which the author is aware.

DA, however, is not the only neurotransmitter affected in schizophrenia; the other three relevant amines also appear to be involved. Westerink et al. (1998, 2001), among others, have shown that a wide range of antipsychotic agents (haloperidol, clozapine, risperidone, olanzapine, and ziprasidone) increase extracellular NE, as well as DA, in the prefrontal



**FIGURE 3.14** The final common pathway theory of dopamine in schizophrenia. Multiple external and internal neural influences interact to result in striatal dopamine dysregulation, altering the appraisal of stimuli and resulting in psychosis. (From Howes and Kapur, 2009, modified.)

cortex of the rat. Furthermore, the second study (Westerink et al., 2001) shows that the drugs increase DA through a synergistic interaction of 5-HT<sub>2</sub> as well as DA receptor blocking. With regard to 5-HT, it is significant that some studies have shown 5-HT receptor abnormalities in the prefrontal cortex of people with schizophrenia (Mita et al., 1986; Hashimoto et al., 1991; Laruelle et al., 1993).

Glutamate and GABA have become the focus of serious scrutiny in the pathogenesis of schizophrenia. Neuropharmacological actions of antipsychotic drugs have also indirectly implicated glutamate. Those drugs lower glutamate release from nerve terminals in the rat's prefrontal cortex (Yang and Wang, 2005). As noted above, PCP, which has been considered to induce a schizophrenia-like syndrome, induces a surge of glutamate, presumably by blocking NMDA receptors. By pharmacologically reducing glutamate in rats pretreated with PCP, the

cognitive abnormalities induced by the latter have been reversed (Moghaddam and Adams, 1998). In other words, lowering glutamate levels ameliorates one animal model of schizophrenia, suggesting that the disease is caused by deregulation not only of monoamine systems but of glutamate turnover as well. On the basis of findings such as that one, a glutamate theory of schizophrenia emerged (Javitt, 2010; Moghaddam and Javitt, 2012). This theory is *a priori* of importance given that glutamate is the most pervasive excitatory neurotransmitter in the brain. The central tenet of the theory is that in the schizophrenic process there is a critical problem in the availability of *N*-methyl-D-aspartate receptors (NMDARs) for glutamate. The defect is substantiated by disturbances of NMDAR gene expression and metabolism in people with schizophrenia. In the absence of those receptors on inhibitory (GABA) neurons, there is a disinhibition of glutamate neurons, which leads to the unregulated increase of glutamate, especially in the prefrontal cortex. This would be the root cause of a considerable degree of psychotic symptomatology.

Finally, in the past couple of decades, GABA itself, the prime inhibitory transmitter, has also been decidedly implicated in schizophrenia. An early study (Akbarian et al., 1995) showed reduced levels of GAD messenger RNA in the dorsolateral prefrontal cortex of people with schizophrenia, without reduction in the number of cells. The reduced expression of GAD, which is the essential enzyme for the synthesis of GABA, implied a deficit in concentrations of the neurotransmitter. Significantly, the deficit was especially evident in upper (supragranular) layers of the cortex, which are the origin and termination of most corticocortical connections (see Chapter 2). A later immunological study confirmed that finding: signal intensity for parvalbumin, a calcium-binding protein in GABA-containing cells, was markedly diminished in layers III and IV (Hashimoto et al., 2003). These observations suggest an explanation for the

disintegration of cognitive processes, including thinking and speech, which is one of the phenomenological hallmarks of schizophrenia. In a series of postmortem studies of the brains of schizophrenic patients, Lewis and his colleagues were able to identify precisely the type of GABA cells most affected in the illness (Woo et al., 1998; Lewis et al., 1999, 2004; Lewis, 2000). These cells are the so-called chandelier cells, a class of interneurons first described by Cajal and named after their peculiar histological features. Chandelier interneurons are GABAergic cells that, through their axon terminals ("cartridges"), exert a powerful inhibitory action on the initial segment of neighboring pyramidal neurons. In this manner, the chandelier cells, which receive substantial dopaminergic input, control the excitatory glutaminergic output of mostly layer III pyramids. Chandelier cells normally develop in late adolescence, a time of common onset of schizophrenia. A genetically or epigenetically determined pathological alteration of GAT-1 protein in the axon terminals of chandelier cells could be at the root of the schizophrenic process.

In more general terms, altered markers for GABA neurotransmission in the dorsolateral prefrontal cortex are one of the most consistent findings in the brain of schizophrenic patients postmortem (Lewis et al., 2008; Lewis, 2011). Pathophysiologically, it would stand to reason, as other studies have indicated, that alterations of GABA cells would fundamentally disturb, in chain-like fashion, the glutaminergic output of supragranular pyramids (Costa et al., 2004) and glutamine receptors – notably NMDA (Coyle, 2004) – with the end result of disrupting, literally interrupting critical cognitive associations in the cerebral cortex. In addition to the GABA disorders in the dorsolateral prefrontal cortex, we have to take into account those that occur in the anterior cingulate prefrontal cortex of schizophrenic patients (Benes, 2010). Those disorders would fundamentally affect the amygdalocortical circuitry, which is so critical in emotion.

Inasmuch as the prefrontal cortex is affected in these ways, the explanation may lie there for many of the disorders in the integration in all domains (thinking, speech, emotion, and behavior) that are characteristic of the disease.

In summary, the etiology and pathogenesis of schizophrenia remain unclear, but there is growing evidence that a profound alteration of DA mechanisms, particularly in the prefrontal cortex, is at the basis of the disorder. The DA system, however, may not be the only neurotransmitter system affected by the disease in the prefrontal cortex. Primarily or secondarily, GABA, glutamine, NE, and 5-HT neurotransmission may also be affected. Conceivably, the clinical characteristics and symptomatology of a particular schizophrenic syndrome depend on the neurotransmission system most affected, which would determine the most indicated form of pharmacological treatment of the disease. Both genetic and exogenous factors apparently play a causal role in the dysfunction of whichever neurotransmission mechanisms are disturbed in the prefrontal cortex of the schizophrenic patient.

### C. Drug Abuse

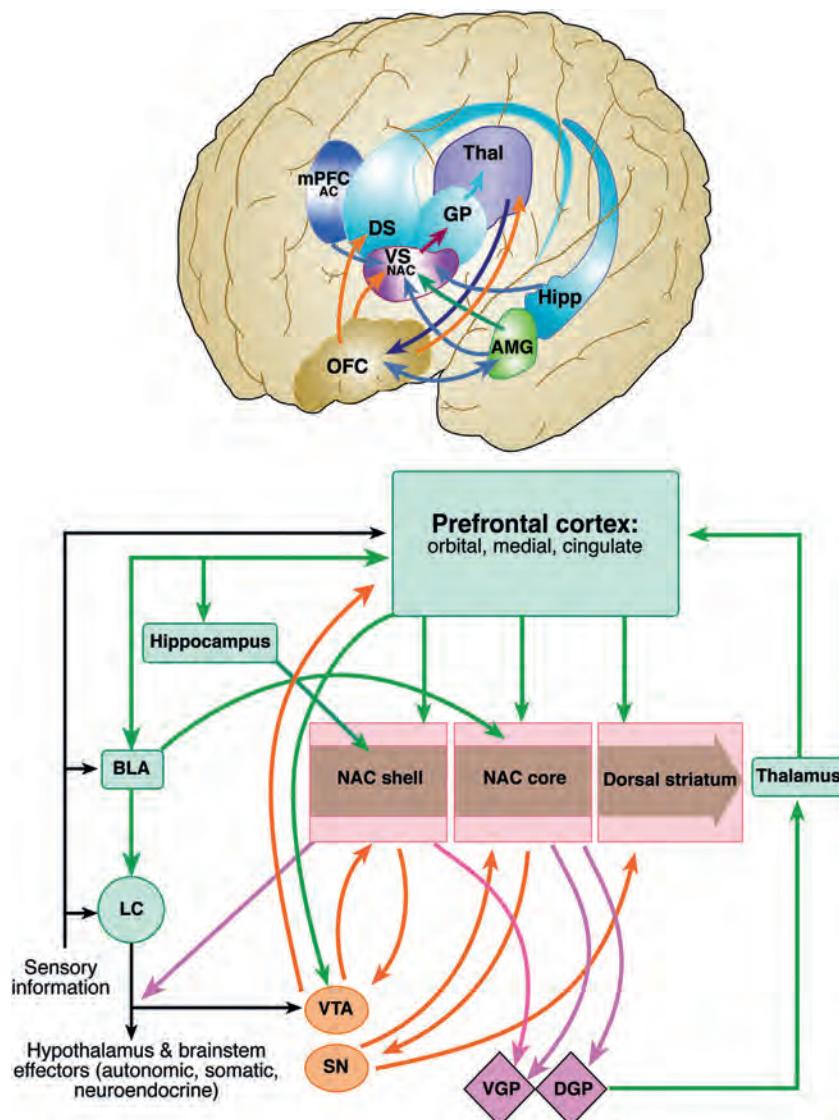
All known substances of abuse induce neurochemical alterations in several neurotransmitter systems and the structures that harbor them. Most prominently, those substances affect DA, NE, GABA, glutamate, and 5-HT systems. The structures affected – at one stage or another of intoxication or addiction – include the brainstem nuclei of neurotransmitter origin, the ventral striate, notably the nucleus accumbens therein, the amygdala, and the prefrontal cortex, especially its orbital and medial regions.

Most of those structures, depicted in [Figure 3.15](#) with their neurotransmitter linkages, are of limbic character and known to participate in the experience of reward as well as compulsive behavior or habit. Furthermore, those structures are critically implicated in emotion and in the

evaluation of the motivational significance of sensory information. Many of them exhibit the phenomenon of ICSS, discussed above under Dopamine: animals with electrodes implanted in those structures will press a bar that, by mechanically closing an electrical switch, stimulates them with electrical current, apparently because of the rewarding nature of that stimulus. Hence the inference that those structures, the orbital prefrontal cortex among them, constitute a series of so-called pleasure centers ([Olds, 1956](#)). By and large, those are structures with heavy DA innervation. They have been shown to be “targets” of practically all known substances of abuse, inasmuch as the consumption of those substances increases DA levels in these structures, and the local infusion of the same substances within them has rewarding effects on the animal.

In terms of regions and neurotransmitters affected, drugs of abuse have proven commonalities with natural rewards and behavior reinforcers, such as sex and hunger. In acute intoxication (the “high”) a large variety of addictive substances, including opiates, nicotine, amphetamine, cocaine, cannabis, PCP, and alcohol, raise DA levels in the mesocorticolimbic DA reward system, prominently in the orbitomedial prefrontal cortex and the nucleus accumbens ([Wise, 1996](#); [Bonci et al., 2003](#); [Volkow et al., 2004](#)). Some substances, in addition to increasing DA, act directly on certain receptors, thereby becoming habit forming: opioids on opiate receptors, nicotine on nicotinic acetylcholine receptors, and PCP on NMDA receptors ([Wise, 1996](#); [Mansvelder et al., 2009](#)).

The reward-DA-drug linkage has been known since [Phillips and LePiane \(1980\)](#) demonstrated the reinforcing effects of morphine injected into the VTA of rats. Whereas drug intoxication commonly leads to DA increases in DA systems, it is now also well established that the withdrawal from chronic intoxication with practically any drug of abuse leads to DA depletion in those systems ([Robertson et al.,](#)



**FIGURE 3.15** Critical connectivity in drug addiction. *Top:* Representation of limbic circuitry with structures most directly affected by addiction, craving, and withdrawal. Abbreviations: AC, anterior cingulate; AMG, amygdala; DS, dorsal striatum; GP, globus pallidus; Hipp, hippocampus; mPFC, medial prefrontal cortex; NAC, nucleus accumbens; OFC, orbital prefrontal cortex; Thal, thalamus; VS, ventral striatum. *Bottom:* Diagram of critical structures, arrows indicating neurotransmitter connections most affected. Abbreviations: BLA, basolateral amygdala; DGP, dorsal globus pallidus; LC, locus coeruleus; NAC, nucleus accumbens; SN, substantia nigra; VGP, ventral globus pallidus; VTA, ventral tegmental area. Green arrows, glutaminergic projections; orange arrows, dopaminergic projections; pink arrows, GABAergic projections. (From Everitt and Robbins, 2005, modified, with permission.)

1991; Parsons et al., 1991; Rossetti et al., 1992; Wise, 1996; Williams and Steketee, 2005). The DA depletion of the addicted patient is usually accompanied by metabolic hypoactivity, demonstrable by imaging, in a number of limbic and paralimbic structures, especially the medial and orbital prefrontal cortex (Volkow et al., 2004; Dackis and O'Brien, 2005). Most particularly in striatal regions, including the nucleus accumbens, the depletion affects D<sub>2</sub> receptors (Myrick et al., 2004; Volkow et al., 2004).

The precise mechanisms by which the various substances of abuse affect neurotransmitter systems are not well understood. Whereas most substances increase DA by direct action upon DA systems, probably by blocking DA reuptake, some of those substances do it indirectly, that is, through the intervention of other transmitters. Thus, DA in the nucleus accumbens increases as a result of drug-induced activation of glutaminergic afferents to that nucleus from the orbital prefrontal cortex (McFarland et al., 2003; Kalivas et al., 2005); this is especially apparent after reinstatement of the drug in a subject under withdrawal. Opioids excite DA neurons by hyperpolarizing local – GABAergic – interneurons (Johnson and North, 1992). Opioids can also increase DA in the nucleus accumbens by NE release in the prefrontal cortex (Ventura et al., 2005). NE has been implicated in opiate withdrawal (Maldonado, 1997; Aston-Jones et al., 1999) and reinstatement (Wang et al., 2001; Ventura et al., 2005). The role of NE in addiction, however, extends beyond opiates. NE, as well as 5-HT, is depleted in orbitofrontal cortex and/or the nucleus accumbens after repeated administration of the powerful psychostimulant methamphetamine (Mayerhofer et al., 2001; Buchert et al., 2004; Morgan et al., 2006). 5-HT depletion, which in part results from the degeneration of terminal axons of cells in the raphe nuclei, has been shown in alcoholism and cocaineism (Esteban et al., 2002; Bradberry and Rubino, 2004; Clarke et al., 2004), where it is accompanied by the compulsion-

that is characteristic of orbitofrontal pathology (see Chapters 4 and 5).

The compulsion induced by cocaine on the behavior of the addict is evidently attributable to a loss of inhibitory prefrontal control. This is well demonstrated by two procedures that reverse or counteract that behavior. One is the infusion of brain-derived neurotrophic factor (BDNF) into the dorsomedial prefrontal cortex of cocaine-addicted and self-administered animals (McGinty et al., 2010). That infusion has a dual effect: it attenuates cocaine-seeking behavior and normalizes the suppressed glutamate levels in the nucleus accumbens. The second procedure is the direct optogenetic stimulation of the prelimbic prefrontal cortex (Chen et al., 2013): it decreases compulsive cocaine-seeking behavior.

Drug craving and seeking behavior are easily associated with sensory environmental cues that accompany the availability, immediate or predictable, of the addicting substance. Thus, in the addicted animal or human, especially in the state of withdrawal, those cues can easily trigger and enhance both the craving and the drug-seeking behavior. Manipulating those cues, and making drug availability contingent on them, facilitates the study of the neurometabolism of craving, reinstatement, and dependence. By those means, in conjunction with imaging methods, it has become possible to substantiate the central role that the ventral striatum and orbitomedial prefrontal regions play in substance abuse (Volkow and Fowler, 2000; Bonson et al., 2002; Myrick et al., 2004; Volkow et al., 2004; Vollm et al., 2004; Wilson et al., 2004).

Addictive illness creates widespread neurochemical dysregulation of the aforementioned structures, especially the prefrontal cortex and the ventral striate. That dysregulation, usually associated with such phenomena as drug withdrawal symptoms and tolerance, leads to the subjective experience of craving, the biochemical basis for which has been postulated to be the sensitization of neural systems to the

drug (Robinson and Berridge, 1993). With the craving, the patient's drives, as well as attention, become severely distorted. The drug gathers all-encompassing salience at the expense of everything else, including natural drives and values. Craving, which is negative reinforcement, also leads to disinhibition of impulses and drug-seeking behavior that, in turn, will lead to the only positive reinforcement left for the patient: the drug and the euphoria that results from activation of the reward pathways. Here is where the pathology of drug addiction intersects with the pathology of the orbital and medial prefrontal cortex (see review by Jentsch and Taylor, 1999).

As we shall see in the next two chapters, those cortices are heavily involved in a number of emotional, cognitive, and behavioral functions that are severely deranged in drug addiction. To summarize, the neuronal populations of the orbital prefrontal cortex, a crucial substrate of DA systems, play a key role in reward (Rolls, 2000; Schultz et al., 2000; Schultz, 2010); Watanabe et al., 2002; Kringselbach, 2005). At the same time, that cortex is known to play a key role in the inhibitory control of attention, drive, and motivation. In the light of this evidence it is understandable that the addictive illness, which creates such havoc in the reward and control systems of the orbitofrontal cortex, should result in compulsive drug-seeking behavior, poor decision-making, and disinhibition of impulses, as well as the overvaluing of the drug and the undervaluing of normal reinforcements and habits (Jentsch et al., 2000; Volkow and Fowler, 2000; Goldstein and Volkow, 2002; Fillmore, 2003; Adinoff, 2004; Bechara, 2005; Everitt and Robbins, 2005).

## D. Depression

As could be predicted *a priori* by simply considering the connectivity of prefrontal areas with limbic structures (emotional connectivity;

see Chapter 2), several affective disorders have long been associated with prefrontal disorder. One of them is depression. Depression accompanies a number of prefrontal syndromes; it is a common manifestation of injuries to the prefrontal cortex. Another clinical manifestation of prefrontal lesion is the opposite of depression, that is, mania or abnormally elevated mood, especially in its mild form (hypomania). Whereas depression can result from substantial lesion of practically any prefrontal region, hypomania, along with impulsivity, disinhibition, and increased excitability, occurs more commonly after orbitomedial lesion. Even in the absence of morphological alteration, however, affective disorders, notably endogenous depression and bipolar illness, have been empirically attributed to imbalances in the neurochemistry of the prefrontal cortex.

Depression has been related to monoamine disorder ever since the seminal observation by Freis (1954) that patients under treatment for hypertension with reserpine, a catecholamine antagonist, would show a tendency to become depressed. That was the origin of the biogenic amine theory of depression (Bunney and Davis, 1965; Pryor and Sulser, 1991). It is now well established that, in the converse manner, drugs that somehow prevent the degrading or reuptake of monoamine neurotransmitters are effective in the treatment of most forms of depression. This is the case for monoamine oxidase (MAO) inhibitors as well as SSRIs. Tricyclic antidepressants compete with NE and 5-HT transporters. Other neurotransmitters, notably GABA and glutamate, have also been implicated in the pathogenesis of depression and mania.

Inasmuch as neurotransmitters are pervasive throughout the cortex, prefrontal circuitry is liable to abnormalities in any of them. In the light of present knowledge, however, 5-HT abnormalities seem to stand out for both their apparent genetic basis and prefrontal involvement in

depression, especially in its severe endogenous form, which is frequently associated with the tendency to suicide. A review of the literature (Arango et al., 2003) reveals abundant suggestive evidence of genetic abnormalities in the serotonergic system, notably pertaining to certain biosynthetic enzymes, transporters, and receptors essential for the metabolism and actions of 5-HT. At the same time, there are numerous postmortem studies indicating lowered levels of 5-HT metabolites or formal elements in the prefrontal cortex of severely depressed patients or suicide victims (Meyerson et al., 1982; Stanley et al., 1982; Mann et al., 1999; Vawter et al., 2000; Arango et al., 2002). In an extensive study of 5-HT signaling genetic markers in the brain of depressed patients (Perroud et al., 2010), the gene expression for tryptophan hydroxylase, a critical enzyme involved in the reuptake of 5-HT from the synaptic gap (TPH2), was found to be significantly increased in the ventral prefrontal cortex of patients who had completed suicide.

The functional imaging of depressed patients reveals a blunting in prefrontal cortex of the 5-HT-releasing effect of the drug fenfluramine (Mann et al., 1996; Anderson et al., 2004). It would appear that the weak 5-HT response to that chemical challenge is attributable to an underlying deficit in the prefrontal substrate for the formation and transport of that neurotransmitter. Functional imaging (PET) in depressed patients (Winsberg et al., 2000) also suggests a prefrontal deficit in the excitatory amino acid aspartate. A subsequent PET study (Bauer et al., 2005) showed that supraphysiological doses of thyroxine alter local metabolism in ventral and anterior cingulate prefrontal cortex, with the effect of improving mood and potentiating the action of antidepressant agents in severely depressed patients. In fact, thyroxine supplementation may overcome the resistance of some patients to those agents (Altshuler et al., 2001). Those pharmacological effects of thyroxine may be produced by the hypothesized and

substantiated synergism of the hormone with both NE (Whybrow and Prange, 1981) and 5-HT (Bauer et al., 2002). With regard to the latter, the euthymic effect of thyroxin is probably related to the evidence that hypothyroidism results in increased 5-HT turnover.

In any case, the role of any neurotransmitter in depression, whether in the prefrontal cortex or elsewhere in the brain of the depressed patient, cannot be easily dissociated from that of other transmitters. 5-HT illustrates the point, although that transmitter is the main target of the most widely used antidepressants (Clark et al., 2009). For one thing, 5-HT, like the other monoamines, induces postsynaptic changes in G-protein, which in turn affect the cells' responsiveness to other neurotransmitters, such as glutamate and GABA, which play their own role in depression (Vawter et al., 2000; Kalia, 2005). For another, 5-HT abnormalities in the prefrontal cortex, for example, may be secondary to, or the source of, abnormalities in other neurotransmitter systems in subcortical or limbic structures with which the prefrontal cortex maintains connections. Alterations in those systems or structures, therefore, may compound the pathogenesis from deficit of 5-HT in the raphe nuclei or the prefrontal cortex of the depressed patient.

At least one putative genetic alteration for bipolar affective disorder has been substantiated (Baum et al., 2008). The gene encoding for diacylglycerol (DAG) kinase is the most affected in that disorder. This is of singular interest, as the loss of DAG kinase activity would lead to excessive DAG, the molecule that activates protein kinase C. Excessive protein kinase C activity has been shown to dramatically impair prefrontal function and suppress the firing of prefrontal neurons (Birnbaum et al., 2004). Accordingly, certain medications indicated for the treatment of bipolar disorder – lithium and Depakote® – inhibit protein kinase C activity (Manji and Lenox, 1999).

## E. Neurodegenerative Disease

Most forms of neurodegenerative disease affecting the prefrontal cortex have a more or less evident genetic root. Genetic determinacy is clearest in Pick's or frontotemporal dementia (Rohrer and Warren, 2011) and in the familiar form of Alzheimer's disease (Lendon et al., 1997; Donix et al., 2012). In some of these dementias, as in Parkinson's disease, chromosome 17 has been heavily implicated (Foster et al., 1998; Alberici et al., 2011).

Whereas other monoamine systems, notably the NE system, seem to be disturbed in Parkinson's disease, the etiology of this disease lies primarily on a disorder of the nigrostriatal DA system. However, given the prominent role of subcortical DA projections to the prefrontal cortex, it is to be expected that the disease will somehow impair cognitive prefrontal functions as well. In fact, it can do so at any time in the course of the illness, but in the majority of cases it does so long after the onset. Generally speaking, there is a well-recognized dissociation between the onset of the illness in the nigrostriatal DA system, with its characteristic motor manifestations, and the onset of cognitive disorders; when these appear, they do so in large part as a result of DA deficit in the prefrontal cortex. Late Parkinson's, however, may also be accompanied by, and to some extent result from, cholinergic deficit from degeneration in the nucleus basalis of Meynert and other subcortical cholinergic nuclei (Perry et al., 1985; Vale, 2008) or in the cortex itself (Ruberg et al., 1982).

Indeed, Parkinson's dementia tends to be a late development (Canavan et al., 1989). At any time in the disease, however, a deficit in DA-modulated outflow from the basal ganglia may cause cognitive deficits that have been likened to a "frontal-lobe syndrome" (Caltagirone et al., 1985; Taylor et al., 1986, 1990; Carbon and Marie, 2003; Carbon et al., 2004; Vale, 2008). In some cases, Parkinson's is accompanied by visual attention disorders and hallucinations that

are indicative of temporal lobe and upper brainstem involvement (Botha and Carr, 2012). By and large, current thinking is that the early deficits result from impairment in the function of the caudate–cortical connective loops, at a time when prefrontal L-dopa uptake may actually be elevated (Kaasinen et al., 2001), whereas the late deficits result mainly from degeneration of mesocortical DA connections that impact more directly on the prefrontal cortex (Mattay et al., 2002), especially the orbitomedial prefrontal cortex (Poletti and Bonuccelli, 2012).

The primary cellular pathology of Alzheimer's dementia consists of damage to and loss of cortical pyramidal cells in widespread areas of the cortex. Practically all the neurotransmitter systems are adversely affected by the disease. However, it has long been known (see review by Mann and Yates, 1986) that the cholinergic system is the most prominently impacted in Alzheimer's and related dementias. Whether that system is first or primarily affected at subcortical level, the cortex of dementia patients has been consistently found to be deficient in muscarinic receptors (Mash et al., 1985; Nordberg and Winblad, 1986; Rinne et al., 1984; Weinberger et al., 1991). In Alzheimer's disease, large losses of cholinergic fibers have been observed in supragranular cortical layers (Geula and Mesulam, 1996), although these losses are more common in temporal than in prefrontal cortex. However, inasmuch as many of the cognitive impairments characteristic of dementia (e.g., deficits in attention and short-term memory) indicate prefrontal pathology, a dysfunction of the prefrontal sector of cortical projections of the cholinergic system can be reasonably assumed in the pathogenesis of the dementia. Consistent with this assumption, data from rodents implicate the prefrontal cholinergic system in short-term memory: the infusion of scopolamine, an ACh antagonist, in the prefrontal cortex impairs the performance of delayed matching to position (Broersen, 1995), whereas that of a DA antagonist does not (Broersen et al., 1994). Bartus et al.

(1982) hypothesize that a cholinergic disorder is at the basis of dementia and its memory disorders. Therein lies the rationale for using cholinergic substances, especially AChE inhibitors, to treat dementia (Iversen, 1998). Prominent among such substances is physostigmine, which in the monkey reverses the scopolamine-induced deficit in delayed response behavior (Rupniak et al., 1990). Similar substances have been licensed in the USA and Europe for the treatment of dementia. Their use has limitations and mixed results (Bartus, 1990; Iversen, 1998; Pouryamout et al., 2012; Salomone et al., 2012; Tricco et al., 2012; Noetzli and Eap, 2013).

Unlike Alzheimer's dementia, Pick's dementia is characterized by degeneration and atrophy largely circumscribed to the frontal lobe, though commonly involving also the pole of the temporal lobe – hence it is also called "frontotemporal dementia" (FTD). In most cases, the behavioral manifestations reflect prefrontal pathology (Seeley, 2013). Like Alzheimer's dementia, however, FTD commonly affects the cholinergic system, as demonstrated by deficits in acetyltransferase and decreased acetylcholinesterase activity in the nucleus basalis of Meynert (Sparks and Markesberry, 1991); this occurs together with muscarinic receptor deficits in the frontal cortex (Yates et al., 1980; Francis et al., 1993). In addition, serotonergic binding and cell numbers are deficient in raphe nuclei and other subcortical structures innervating this cortex with 5-HT terminals (Sparks and Markesberry, 1991; Francis et al., 1993; Yang and Schmitt, 2001).

## V. SUMMARY

The prefrontal cortex shares with the other regions of the neocortex a variety of neurotransmitter substances. These substances and their synaptic receptors are already present in the prefrontal cortex at birth. Thereafter, they generally develop in synchrony to reach the

highest levels in young adulthood. In the prefrontal cortex, as elsewhere in the cortex, normal aging is accompanied by a general diminution in the concentration of neurotransmitters and receptors.

Glutamate is the prime excitatory neurotransmitter in the cortex. It serves not only the local prefrontal circuitry, but also the excitatory connectivity of the prefrontal cortex with striatal, thalamic, and limbic structures. NMDA, a glutamine receptor of widespread distribution in the cortex and the hippocampus, is thought to play a critical role in learning and the formation of memory.

GABA is the prime inhibitory neurotransmitter in the cortex. It serves all the inhibitory interneurons, which are found practically everywhere in the nervous system. In the prefrontal cortex, as elsewhere, GABA supports local inhibitory functions, including lateral inhibition, that enhance the saliency of excitatory responses.

In the microcircuitry of the prefrontal cortex, NMDA receptors and recurrent inhibition through GABA<sub>A</sub> are thought to play a critical role in the persistent neuronal activity of working memory.

The three monoaminergic systems, with their cells of origin in the brainstem, innervate the prefrontal cortex by way of ascending fiber paths that bypass the thalamus: (1) the noradrenergic system (its transmitter is norepinephrine, NE) from the nucleus coeruleus; (2) the dopaminergic system (its transmitter is dopamine, DA) from the ventral tegmentum; and (3) the serotonergic system (its transmitter is serotonin, 5-HT) from the nuclei of the raphe. Whereas the NE system innervates the neocortex diffusely (with a maximum in somatosensory cortex) and the 5-HT system innervates mostly sensory areas, the cortical DA system innervates predominantly and distinctively, although not exclusively, the prefrontal cortex. Terminal DA innervation concentrates mainly on the deep cortical layers (V and VI).

Because of its diffuse cortical distribution, NE can be assumed to serve both a global modulator role and a variety of specialized cortical functions. Moderate increases in NE, as may be attained by agonist drugs, facilitate prefrontal cognitive functions such as working memory, mainly through certain adrenoreceptors. Larger amounts, however, have detrimental effects on those functions. These phenomena indicate an inverted-U curve of benefits from NE concentration. Data from DA manipulations suggest a similar curve for the effects of this second catecholamine transmitter on prefrontal cognitive functions. These effects are largely mediated by D<sub>1</sub> and D<sub>2</sub> receptors. The orbitomedial prefrontal cortex is the recipient of profuse DA terminal fibers from the VTA and limbic structures. They are part of the mesocorticolimbic system, which is heavily involved in motivation and the experience of reward. 5-HT, like the other two monoamines, interacts with other transmitters in the prefrontal cortex and in other structures with which it is connected. Such interactions involve GABA, the inhibitory neurotransmitter, which serves cortical lateral inhibition in cognitive functions as well as subcortical structures in emotional functions. The orbital prefrontal cortex, through 5-HT neurons, exerts some of its controls on emotion and impulsivity by GABA modulation of the brainstem 5-HT nuclei.

In addition to the monoamines, the prefrontal cortex, like the rest of the neocortex, receives profuse afferents from the subcortical components of the cholinergic system. These include the mesencephalic reticular formation and the nucleus basalis of Meynert. The postsynaptic effects of ACh are largely excitatory. The prefrontal cortex is the recipient of substantial and widespread cholinergic influences that modulate its neuronal circuits in cognitive functions.

Also active in the prefrontal cortex are a number of neuropeptides (somatostatin, substance P, CCK, angiotensin, neurotensin, and others) that act there as neurotransmitters or

neuromodulators. Some of them interact at synapses with other transmitter substances, such as DA and glutamate. One of them, hypocretin or orexin, is under considerable scrutiny, as it has powerful influences on the cortex in general states, such as sleep and arousal, through the NE system.

A number of pathological conditions of more or less definite genetic etiology have been attributed to disorders in neurotransmitter systems. In most if not all of those conditions, more than one neurotransmitter is implicated. Prominent among the apparently familial disorders of neurotransmission are the attention disorders of childhood, especially ADHD. One of the underlying troubles in this disease is the underexpression of tyrosine hydroxylase, which leads to a DA deficit in orbitomedial prefrontal cortex. This deficit, in turn, leads to disorder in the inhibitory (GABA) functions of that cortex, with resulting disinhibition and hyperactivity.

Genetic factors also play a role in schizophrenia (genes involved in cortical development, glutamate transmission, intracellular signaling pathways, and DA receptor expression). The beneficial effects of antipsychotic medication rely to a considerable extent on the down-regulation of DA receptors. According to well-substantiated current thinking, schizophrenia is a disorder of DA systems resulting from multiple confluent factors, possibly including genetics, drug abuse, and environmental stress. The end result ("pathway") of that pathogenic confluence of factors would be excess DA from failure of the basal ganglia to incorporate it. This excess DA would return upon parietal and frontal cortex to exacerbate the schizophrenic syndrome. DA, however, is not the only prefrontal neurotransmitter implicated in schizophrenia; GABA, 5-HT, glutamine, and NE are also affected, either primarily or secondarily, as a result of alterations in other neurotransmitters.

Drugs of abuse induce neurochemical alterations in numerous limbic and paralimbic structures, notably the nucleus accumbens in the

ventral striatum, the amygdala, and the orbitomedial prefrontal cortex. In these structures, the transmitters – and their receptors – most commonly affected in drug abuse, craving, and withdrawal are DA, NE, GABA, glutamate, and 5-HT.

Endogenous depression, as it occurs in bipolar illness, is a heritable disorder that is generally accompanied, if not caused, by deficits in one or more monoamine systems, notably serotonergic. Accordingly, the most potent antidepressants impede the degrading of monoamines (MAO inhibitors) or somehow block their reuptake (tricyclics and SSRIs).

The major neurodegenerative diseases affecting the prefrontal cortex are to some degree heritable. Parkinson's disease characteristically results from degeneration of DA systems at subcortical level (nigrostriatal). In advanced Parkinson's, prefrontal DA and ACh are also affected. Certain forms of Alzheimer's disease and especially FTD are characterized by their familial tendency to the disease. All dementias are accompanied by loss of pyramidal cells and some degree of ACh deficit in the prefrontal cortex. That deficit commonly extends to temporal and parietal cortices.

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# Animal Neuropsychology

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## I. INTRODUCTION

Traditionally, studies on the functions of the prefrontal cortex in animals have relied on the effects of total or partial experimental lesions of this cortex on behavior. Most of these studies are based on the following assumption: if a certain area is indispensable for a certain function, the lesion of that area will degrade that function and whatever behavior depends on it. We will thereby be able to infer the function of the area from the consequences of its absence. This

time-honored rationale and the ablation procedures it calls for have played a crucial role in the scrutiny of the functions of the prefrontal cortex. The evaluation of the massive literature on this subject is exceedingly difficult, however, because of discrepancies in the methods used by different investigators, the variability of lesions and behaviors tested, and above all, the not always tenable assumption that a brain deprived of prefrontal cortex is simply a brain without the function(s) of that cortex. Indeed, any ablation procedure results in morphological changes

and functional readjustments in the remaining structures that make the behavior of the postablation organism hardly interpretable as merely the product of a subtractive maneuver. Besides, in the final analysis, ablations can answer questions about which functions are where, but not about how any function works. Later in the chapter, we will see how the use of reversible lesions can obviate some of those difficulties, at least with respect to the pre-eminent prefrontal function of working memory. In any case, for all the difficulties that encumber the interpretation of its results, experimental lesion, in the prefrontal cortex as elsewhere, has remained a prime tool of neuropsychology for a long time. In this chapter, we shall review the effects of prefrontal lesions on animal behavior. In Chapter 5, we will address human neuropsychology; that is, the effects of prefrontal damage in people.

## II. HISTORICAL BACKGROUND

The earliest descriptions of the behavioral effects of frontal ablations are based largely on naturalistic observations and riddled with anthropomorphic interpretations. The insight of some of those early accounts, however, cannot be denied. Observations of the behavior of animals after frontal ablation led [Hitzig \(1874\)](#) to conclude that the prefrontal cortex is the substrate of abstract intelligence. For [Ferrier \(1886\)](#), attention was the primary function of the prefrontal cortex; he drew this inference from observing the behavioral effects of ablation and electrical stimulation of certain portions of that cortex on ocular motility, which is essential for spatial attention. [Bianchi \(1895, 1922\)](#) was one of the first to examine systematically the consequences of frontal ablations in animals of several species. The prefrontal cortex, according to him, was a major center for the association and synthesis of percepts. [Bechterew \(1911\)](#) and [Pavlov \(1949\)](#), on the other hand, emphasized the importance of the prefrontal cortex for the

integration of goal-directed movements and behavior. In the light of present evidence, none of those functions seems to have its seat exclusively in the prefrontal cortex, yet it seems that the prefrontal cortex, more than any other cortical region, participates in every one of them. Thus, to date, none of those old ideas is inappropriate. Their generality, as well as the limitations of the available methods, however, make their refutation or corroboration impractical, but do not deprive them of heuristic value or preclude their potential verification.

[Shepherd I. Franz \(1902, 1907\)](#) was the first to test the effects of frontal ablation with structured behavioral methods. He observed that in dogs, cats, and monkeys, large lesions of prefrontal cortex induced deficits in the execution of learned motor habits and in the solving of certain problems, such as the operation of Thorndike's puzzle-boxes. He also noted that, with time and adequate retraining, performance of the impaired behaviors was eventually restored to preoperative levels. After Franz's publications there was a relative pause in the frontal ablation literature until the 1930s, when [Jacobsen \(1935, 1936\)](#) published his discovery of the deleterious effect of prefrontal ablation on delayed reaction. The following sections present a review of the most important and well-substantiated findings. For a better appreciation of controversial points and a more extensive bibliography of early work on the subject, the reader may wish to consult the published proceedings of two international symposia that were largely devoted to it ([Warren and Akert, 1964](#); [Konorski et al., 1972](#)). More modern accounts can be found in [Stuss and Knight \(2013\)](#).

## III. MOTILITY

### A. Hyperactivity

Hyperactivity is one of the most common effects of prefrontal ablation. It manifests itself

primarily by aimless locomotion, but may involve practically all sectors of the somatic musculature. Hyperactivity was first discovered in monkeys after frontal lesions and reported in several early studies (Jacobsen, 1931; Richter and Hines, 1938; Kennard et al., 1941; Mettler, 1944; Isaac and DeVito, 1958; French, 1959a; Miller and Orbach, 1972). However, the phenomenon was not observed in certain primates, such as the squirrel monkey (Miles and Blomquist, 1960; Miles, 1964). When apparent, the postablation hyperactivity is frequently accompanied by disorders of top-down attention or cognitive control (Rossi et al., 2007).

With respect to carnivores, the evidence is conflicting: frontal hyperactivity is reported in some studies (Kalischer, 1911; Langworthy and Richter, 1939; Smith, 1942; Konorski, 1957; Villablanca et al., 1976b) and not in others (Brutkowski et al., 1956; Lawicka and Konorski, 1961; Warren et al., 1962, 1972; Warren, 1964). Immediately after frontal ablation, a transient period of hypoactivity is sometimes observed, which may or may not be followed by hyperactivity (Kennard et al., 1941; Wade, 1952; Brutkowski, 1965; Butter et al., 1970).

Although in the monkey lateral prefrontal lesions often induce hyperactivity (Gross, 1963a; Gross and Weiskrantz, 1964; Delacour et al., 1971), the phenomenon is more consistently observed after orbital lesions, even if such lesions avoid injury to the head of the caudate, which by itself may result in hyperactivity (Richter and Hines, 1938; Mettler and Mettler, 1942; Ruch and Shenkin, 1943; Davis, 1958; Villablanca et al., 1976a). In the rat, hyperactivity has been most reliably elicited by lesions of the orbital paralimbic prefrontal cortex. This has allowed relating this finding to the genetic, neurotransmitter, and pharmacological aspects of hyperactivity (Viggiano, 2008).

Lesions limited to area 8 elicit peculiar disorders of ocular motility. Unilateral lesions cause deviations of the eyes and the head toward the side of the lesion, forced circling in the same

direction, and neglect of stimuli in the opposite side of the visual field (Kennard and Ectors, 1938; Kennard, 1939; Welch and Stuteville, 1958; Latto and Cowey, 1971a, 1971b; Schiller et al., 1980; Crowne et al., 1981; Deuel and Collins, 1984). One study (Watson et al., 1978) suggests that this neglect is due to a disruption of the intentional component of orienting reactions. After bilateral lesions, in the monkey, an overall reduction of eye movements has been observed (Kennard and Ectors, 1938; Latto and Cowey, 1971b). Such lesions also impair the performance of visual search tasks (Latto, 1978a, 1978b; Collin and Cowey, 1980; Collin et al., 1982; Lynch, 1987). Similarly, in the cat, bilateral eye-field lesions are seen to induce a deficit in conditioned anticipatory visual attending (Schlag-Rey and Lindsley, 1970). All these findings, as do those of certain electrophysiological studies (Chapter 6), emphasize the importance of area 8 for the motor components of visual attention.

## B. Disinhibition

Numerous studies indicate that the increased motility of animals with prefrontal lesion is not spontaneous but determined by events in the environment. The abnormality may be corrected by placing the animals in the dark or by otherwise diminishing their exposure to external stimuli (Kennard et al., 1941; Mettler, 1944; Isaac and DeVito, 1958; Orbach and Fischer, 1959; Gross, 1963a). Conversely, increasing sensory stimulation accentuates hyperactivity in proportion to the level or diversity of that stimulation (Mettler, 1944; French and Harlow, 1955; Isaac and DeVito, 1958; Gross, 1963a). For these reasons, many have interpreted the hyperactivity of frontal animals as the expression of an underlying tendency to overreact to external stimuli; in other words, the hyperactivity seems secondary and reducible to hyperreactivity. The relevance of this inference to issues of attention is obvious. One of the effects of orbital lesion

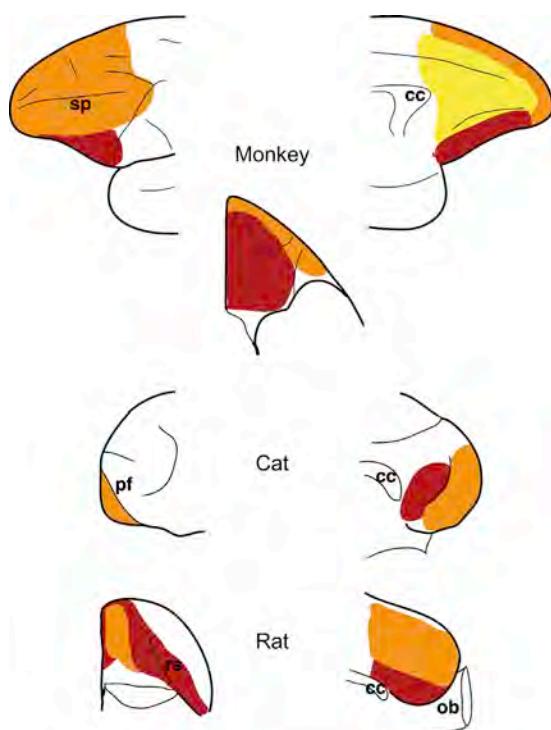
is increased distractibility, that is, the overreaction to stimuli that are irrelevant to ongoing behavior or extraneous to its context (Klüver, 1933; Konorski and Lawicka, 1964; Grueninger and Pribam, 1969). Especially vulnerable is the attention to the motivational value of stimuli (Dias et al., 1996a). It is easy to see how, in a rich or changing environment, distractibility would result in increased motility, and this increase in motility would be proportional to the diversity and frequency of environmental influences.

Thus, it seems that the animal with a frontal lesion, especially if that lesion is ventral or orbital, suffers from a basic inability to inhibit behavioral reactions when they need to be inhibited. This difficulty can best be observed and quantified in structured experimental situations that require the animal to withhold responses to conditioned sensory stimuli or discriminanda (see below). The monkey with orbitofrontal lesion (Figure 4.1) fails in those tests (Brutkowski et al., 1963; Mishkin, 1964; Butter, 1969; McEnaney and Butter, 1969; Iversen and Mishkin, 1970, 1973; Passingham and Ettlinger, 1972; Oscar-Berman, 1975), and so does the dog with lesion of the medial frontal cortex, which is the homolog of the monkey's orbital cortex (Brutkowski and Mempel, 1961; Stepien et al., 1963; Brutkowski, 1964; Dabrowska, 1971). Let us briefly review further signs and implications of behavioral disinhibition.

The animal with orbitofrontal lesion has trouble suppressing orienting reactions. Its attention changes often and rapidly, attracted by practically any stimulus without regard to its value or relevance. This disorder is also observed in monkeys after certain other operations, such as temporal lobe resection (Klüver and Bucy, 1939). It is strongly reminiscent of the phenomenon of "hypermorphosis" (Wernicke, 1906), frequently observed in human cortical syndromes, not necessarily frontal. In the frontal lesion animal, orienting

motor reactions is generally difficult to habituate, although the animal may concomitantly show a paradoxical drop in the autonomic components of an orienting reaction (Grueninger et al., 1965; Kimble et al., 1965; Zernicki, 1972). Also difficult is the extinction of conditioned and discriminant motor responses (Butter, 1969; Warren et al., 1969b). Responses that were once effective for obtaining a reward are persistently emitted long after they have become useless.

Defective inhibition is maladaptive, not only because it allows the execution of purposeless or unproductive acts but also because some of



**FIGURE 4.1** Schematic diagram of the prefrontal cortex of the monkey (lateral, medial, and orbital views), the cat (lateral and medial views), and the rat (inferior or "sulcal" and medial views). Areas in the same color – across species – are connected to approximately the same subcortical structures (see Chapter 2). Abbreviations: cc, corpus callosum; ob, olfactory bulb; pf, presylvian fissure; rs, rhinal sulcus; sp, sulcus principalis.

those acts may short-circuit the attainment of goals that are predicated on the integration of spatially or temporally distant elements of the environment. A vivid illustration is the so-called magnet reaction, which cats, dogs, and monkeys with prefrontal lesions exhibit if spatial discontiguities are present between stimulus and reward, as when two spatially separate stimuli require crossed responding (e.g., stimulus A requires a response in the location of stimulus B and *vice versa*). In such a situation the frontal animal tends to approach "magnetically" the location of the stimulus, wherever it may be, apparently unable to overcome the impulse to orient to it and to substitute, for the spatially immediate response, a mediate, more distant, and more adaptive response (Stepien and Stepien, 1965; Stepien and Stamm, 1970a; Stepien, 1972).

Understandably, the frontal animal is said to be stimulus bound (Konorski and Lawicka, 1964). Consequently, during performance of instrumental tasks, its reactions to extraneous stimuli tend to interfere with or pre-empt adaptive responses. Changes in spatial relationships are particularly disruptive (Pribram, 1969; Anderson et al., 1976; Brody et al., 1977). The encumbrance that spatial discontiguities impose on frontal animals has also been shown by other methods (McClean and Harlow, 1954; French, 1962).

In summary, the animal with orbitofrontal lesion is disinhibited in a variety of conditions. This disinhibition manifests itself in the inordinate ease with which a host of sensory stimuli and perhaps internal impulses and tendencies can release maladaptive motor responses. Whatever the determinants of that behavioral disinhibition, it is so patent and pervasive that it has led to constructs of prefrontal function based on various concepts of inhibition. Stanley and Jaynes (1949), in a review on the prefrontal cortex, proposed that act inhibition is a fundamental function of this cortex. To bolster their argument, they used the

neuronographic evidence of frontal suppressor areas, although most of these areas are not in the prefrontal cortex proper. Brutkowski (1965), in another review, ascribed to the prefrontal cortex a role in two forms of inhibition: drive inhibition and response inhibition. He arrived at that conclusion from evidence of the difficulties that frontal animals have in inhibiting reactions to both appetitive and aversive stimuli (see next section). Mishkin (1964) propounded the concept of central-set inhibition. In any event, by a number of electrophysiological and behavioral measures, the fact has now been well substantiated that the animal disinhibited by prefrontal lesion is subject to a severe loss of cognitive control and flexibility (Gruber et al., 2010).

## IV. EMOTIONAL BEHAVIOR

Animals that have sustained substantial lesions of prefrontal cortex are prone to abnormalities of temperament and emotion. David Ferrier, as early as 1875, spoke of monkeys that, after frontal lobe amputation, became strangely indifferent to others and to events around them. Bianchi (1922) remarked in vivid terms on the fearful and withdrawn appearance of frontal dogs and monkeys. Early reports of investigations that were primarily intended to elucidate the effects of prefrontal ablation on learned behavior contain references to changes in the affective disposition of the experimental animal after operation (Blum, 1948; Crawford et al., 1948; Evarts and Nissen, 1953). Those observations have since been complemented and expanded by formal studies of the emotional interactions of monkeys with prefrontal lesions in social settings. These studies are summarized below.

A related line of investigations has revealed a degree of involvement of the prefrontal cortex in the control of drives. Some early reports refer to the abnormal voracity and aggressiveness of

animals with large frontal lesions (Fulton et al., 1932; Langworthy and Richter, 1939; Kennard, 1945). More recent studies attempt to elucidate the relationships between the prefrontal cortex and motivation by the use of instrumental conditioning techniques.

From the beginning, however, the study of the motivational and emotional aspects of prefrontal function by means of ablations in animals suffered from the difficulty of defining motives and emotions in a manner that made them amenable to assessment. Experiments were hampered by problems in operationally differentiating various motives or instincts (hunger, fear, sex, etc.) from one another and from the emotions that attended them. The pertinent literature contains disparate and contradictory interpretations of fact, and the reviewer's task is complicated by the imprecision description of reported lesions and of the observations that purportedly reflect alterations of motives or their actualization. In any case, as we will see, it is in the affective and social domains that some of the most striking similarities between the frontal syndromes of humans and animals can be seen. It is of more than passing historical significance that certain remarks by Jacobsen and his colleagues on the placidity of primates after prefrontal lesions (Fulton and Jacobsen, 1935; Jacobsen et al., 1935) led Egas Moniz (1936) to introduce prefrontal lobotomy as a form of treatment for certain emotional disorders in the human, however questionable his rationale for doing it may have been.

### A. Biological Drives

Lesions of anterior frontal cortex induce increased appetite in cats (Langworthy and Richter, 1939; Soltysik and Jaworska 1967), dogs (Shustin, 1959; Wolf-Jurewicz, 1982), and monkeys (Fulton et al., 1932; Anand et al., 1958; Butter et al., 1970). Such lesions can also make cats (Fulton and Ingraham, 1929; Kennard,

1945) and dogs (Brutkowski et al., 1961; Soltysik and Jaworska, 1967) exceedingly irascible. Judging from the published reports, some of the lesions in question appear to have encroached on the limbic cortex behind prefrontal areas; all seem to have involved to a large extent in the prefrontal cortex of the medial or orbital areas, which is cortex anatomically related to the limbic system (see Chapter 2). The results of these studies, therefore, imply that the cortex is under the control of the limbic mechanisms of hunger and aggression. The manner in which such control may be mediated is unclear, but it is appropriate to note here the evidence of autonomic representation in the areas involved and, more important, of inhibitory influences from those areas on certain autonomic functions (see Chapter 6). It is largely on that evidence that Fulton (Fulton and Ingraham, 1929), Kennard (1945), and others argued for a frontal cortical region exercising control, through the hypothalamus, over the efferent mechanisms of aggressive drive.

That point of view has received support from demonstrations that prefrontal lesions, especially of the orbital cortex, increase aggressiveness in the rat (De Bruin et al., 1983; De Bruin, 1990). The same lesions lower the threshold for emotional reactions induced by hypothalamic stimulation, rage in particular (Sato, 1971; Sato et al., 1971). Conversely, prefrontal stimulation suppresses attack behavior and raises the threshold for inducing that behavior by hypothalamic stimulation (Siegel et al., 1974, 1977; Kruck et al., 1979).

The voracious appetite and the aggressiveness that result from certain prefrontal lesions may thus be interpreted as release phenomena of basic drives that are essentially subserved by the hypothalamus and other limbic structures. The observations of such phenomena are in harmony with the concept of drive disinhibition, proposed by Brutkowski (1965) in his attempt to characterize the effects of medial and orbital prefrontal lesions on conditioned behavior.

Practically all the reports of excessive eating and uncontrolled rage derive from studies of carnivores with large ablations probably trespassing the limits of the prefrontal cortex. Smaller lesions of the prefrontal (proreal) cortex in the cat do not seem to increase either hunger or aggressiveness. On the contrary, the animal with such a lesion tends to be less aggressive than before the operation, more submissive to other animals, and less successful in competing for the food that it needs to satisfy an apparently normal appetite (Warren, 1960, 1964; Warren et al., 1962, 1972; Nonneman and Kolb, 1974).

Ablation studies in rats provide evidence of the involvement of the prefrontal cortex in reward and motivation. Most of these studies implicate the orbital prefrontal cortex (DeCoteau et al., 1997; Balleine and Dickinson, 1998; Gallagher et al., 1999; Mobini et al., 2002; Killcross and Coutureau, 2003; Kheramin et al., 2005). This evidence is, of course, in line with the evidence that this cortex harbors important neurochemical substrates – notably a dopamine system – involved in the experience and utilization of reward in learning and behavior (see Chapter 3). In the rabbit, lesions of medial prefrontal cortex lead to abatement or abolition of heart-rate responses in the course of instrumental conditioning (Chachich and Powell, 1998; McLaughlin and Powell, 1999). The aggregate of this evidence points to the importance of the orbitomedial prefrontal cortex for the evaluation of the environment and the integration of emotional behavior consequent to that evaluation.

Also in the rat, considerable evidence has been obtained from lesion studies pointing to the role of the prefrontal cortex in fear, anxiety, and more generally in the regulation of emotional behavior. Lesions of inferior medial and orbital prefrontal cortex have been shown to block the normal extinction of fear responses to no longer fear-associated stimuli (Morgan et al., 1993; Morgan and LeDoux, 1995, 1999; Tian

et al., 2011), the recall of previous extinction (Quirk et al., 2000), and context-induced anxiety (Lacroix et al., 2000).

Pavlovian extinction blockage has also been observed in the monkey after orbital prefrontal lesion (Izquierdo and Murray, 2005). Also in the monkey, lesions of both ventrolateral and anterior orbital prefrontal cortex have been shown to induce fear and other negative emotions (Agustín-Pavón et al., 2012). In sum, lesion data from animals, as some reviewers have concluded (Kim and Jung, 2006; Sotres-Bayon et al., 2006), indicate that the orbital prefrontal cortex is the source of critical inhibitory output, probably mediated by the amygdala, over aversive emotional behavior and experience, whether these are conditioned or unconditioned.

## B. Social Behavior

In the monkey, total or almost total ablations of the prefrontal cortex elicit even more distinctly some of the features mentioned above of the carnivore with prefrontal lesion. In addition, the prefrontal monkey generally displays varying degrees of apathy, increased tolerance to frustration, indifference to others, and withdrawal. Although these effects of the lesion had been previously observed in the context of behavioral testing on structured tasks (Jacobsen et al., 1935; Crawford et al., 1948), they have been most vividly demonstrated in studies of animals in social groups (Deets et al., 1970; Myers, 1972; Franzen and Myers, 1973; Myers et al., 1973; Peters and Ploog, 1976).

In the prefrontal monkey, all emotions seem obtunded. Myers and his colleagues point to the animal's characteristic loss of vocalization, of facial expression, and, generally, of all forms of communication. Sometimes afflicted with hyperactivity, mute, and poker-faced, the animal gives the appearance of an automaton. It is incapable of adequately interacting with others and of securing a stable position in the group. Grooming and all other forms of affiliative

behavior, including maternal behavior, are diminished. After the frontal operation, females become poor sexual partners and bad mothers. Both males and females become generally less aggressive and seem to have lost both the zest and the ability to compete for food, shelter, sex, and the company of others. As a consequence of its deficit and the reactions of normal monkeys to it, the prefrontal monkey is chased from the group or abandoned, and thus becomes an isolate. That condition in the wild is incompatible with life; dramatic cases of solitary death are reported in a study of prefrontal monkeys in an island colony (Myers et al., 1973). Of course, the sheltered environment of the laboratory prevents the frontal animal from reaching such extremes.

To what extent are the two orders of difficulties, emotional and cognitive, related to each other? Do the emotional difficulties result from cognitive deficit, or is it the other way around? How are the apathy and social indifference of the lobectomized animal related to its distractibility and hyperreactivity to sensory stimuli? There are no clear answers yet to these questions, but there is evidence indicating that those answers may rest, at least partly, on anatomical grounds.

Lesions of the orbital cortex do not seem to be as devastating to emotional life as are comprehensive ablations of the prefrontal cortex, but lesions of the orbital cortex are more detrimental to social adaptation than are lesions confined to the lateral cortex. The monkey with an orbital lesion appears withdrawn and helpless, although capable of some expression and emotional reaction (Kling, 1976; Kling and Steklis, 1976; Peters and Ploog, 1976; Raleigh et al., 1979; Raleigh and Steklis, 1981; Rudebeck et al., 2006). Perhaps its most striking characteristic is the inability to deal with aggression. Fear and flight gain the upper hand and consequently the animal loses its standing in the community. Butter and collaborators (Butter et al., 1970; Butter and Snyder, 1972) show that

rhesus monkeys with orbital lesions display increased aversion and reduced aggression in threatening situations, as could be ascertained by examining their reactions to humans, animal-like objects, and other monkeys in a colony, where they lose their dominance (alpha position) if they had it before the lesion. Furthermore, those researchers determine that the critical focus for the observed emotional changes is a relatively small parcel of the basal cortex, the posteromedial orbital cortex.

The apparent increase in aversion amid fear-motivated behavior of the monkey with an orbital lesion leads to the logical expectation that conditioned avoidance behavior, such as instrumental shock avoidance, would be facilitated by the same lesion. However, it does not seem to be (Butter and Snyder, 1972). One reason may be the inadequacy of some of the instrumental tasks utilized as indicators of fear (Brutkowski, 1965). This inadequacy applies to many studies in which lesions have been shown to affect either active or passive avoidance. Tanaka (1973) observed that one-stage lesions, but not *seriatim* lesions (Tanaka, 1974), involving the medial prefrontal cortex induced a deficit in instrumental avoidance of electric shock. However, the failure to perform the appropriate motor response to avoid shock was accompanied by obvious agitation and other signs of anxiety. Dissociations such as that between instrumental response and overt emotional behavior suggest the shortcomings of avoidance-task performance as a measure of fear. Less efficient performance does not necessarily indicate less fear, a point worth considering in the light of demonstrations, some of them mentioned in the previous section, that prefrontal lesions impair the learning, retention, or extinction of avoidance tasks in primates (Waterhouse, 1957; Tanaka, 1973, 1974; Izquierdo and Murray, 2005; Rudebeck et al., 2006), carnivores (Auleytnr and Brutkowski, 1960; Warren, 1964; Warren et al., 1972; Zielinski, 1972, 1974; Zielinski and

Czarkowska, 1973), and rodents (Streb and Smith, 1955; Brennan and Wisniewski, 1982; Morgan et al., 1993). The effects of large lesions on conditioned avoidance may be ascribed to several different effects of prefrontal lesion, each effect perhaps produced by the damage of a different cortical sector. Some of the effects undoubtedly pertain to the cognitive aspects of avoidance tasks and have little to do with fear reduction *per se*.

In the monkey, there are obvious similarities between the emotional orbital syndrome outlined above and that resulting from amygdalectomy or anterior temporal lobe resection (Klüver and Bucy, 1939), the diminution of aggressiveness being the most prominent common feature of the two. Other features of the temporal lobe syndrome, such as heightened orality, aberrant eating habits, and distractibility, have also been encountered in the orbital monkey (Ursin et al., 1969; Butter and Snyder, 1972; Kling and Steklis, 1976). The similarities in the results of the two kinds of ablation are so remarkable that they naturally evoke the close anatomical relations between the orbital cortex and temporal lobe structures, the amygdala in particular, and suggest that those temporal lobe structures, together with the orbital cortex, form a neural complex essential for the appraisal of the motivational significance of objects, for emotional expression, and for social bonding (Butter and Snyder, 1972; Kling and Steklis, 1976; Gaffan et al., 1993; LeDoux, 1993). A lesion study (Rudebeck et al., 2006) implicates the anterior cingulate cortex in the valuation of social stimuli.

Unlike orbital lesions, lesions of the dorsolateral cortex or large lobectomies that spare the posterior orbital area tend to increase the aggressiveness of the monkey (Brody and Rosvold, 1952; Kling and Mass, 1974; Miller, 1976b; Singh, 1976). The effect is peculiar because it occurs in conjunction with a general diminution of the communicative expressions that normally accompany aggression. There

is a decrement of threats and of all those symbolic gestures and moves with which the normal monkey precedes aggression or asserts dominance and position in the hierarchy. The dorsolateral monkey attacks other monkeys, often without apparent motive or the benefit of a warning, as if impelled by uncontrolled hostility that is not guided by the customary interchange of signals. Consequently, the social order is generally disrupted when the operated animal is introduced or reintroduced in the colony.

The abnormal social behavior of the monkey with an extensive dorsolateral lesion has been interpreted as a result of the inability to use previously learned patterns of avoidance (Brody and Rosvold, 1952). In a similar vein, Miller (1976b) commented that the animal is unable to sort out sensory stimuli and to inhibit the response tendency to flee. In the resulting confusion it may resort to aggression. Both these interpretations imply a cognitive-perceptual deficit at the foundation of the animal's abnormal behavior. Of special interest is the related notion that the dorsolateral cortex supports the integration and the recognition of communicative signals (Myers, 1975), a notion in turn related to the fact that, in humans, a part of the dorsolateral cortex plays a role in speech. Some caution is necessary here, however, for it cannot be assumed that speech is simply an elaboration of animal communication. Also, it is far from clear that animal vocalization and human speech are served by homologous brain structures; this applies to the prefrontal cortex as well as to other structures. It is plausible to assume, however, that some of the cognitive processes underlying the integration and recognition of language are also present in the non-human primate and, furthermore, that those processes depend to a large extent on the functional integrity of the dorsolateral prefrontal cortex. The plausibility of these assumptions will become clearer in ensuing chapters.

## V. COGNITIVE FUNCTION

As will be argued in subsequent chapters, a large body of empirical evidence from animals as well as humans now clearly indicates that the overriding function of the prefrontal cortex is the temporal organization of novel goal-directed behavior. Two major adaptive resources of the organism support that behavior. One is the neural infrastructure for the expression of emotion, drive, reward, and motivation, which in the human is largely represented in the orbital and medial prefrontal cortex, with close links to the limbic system and its neural structures for homeostasis, notably the hypothalamus and the autonomic nervous system. The other is the neural foundation for the cognitive aspects of temporal organization, which is largely represented in the dorsolateral prefrontal cortex. This second resource comprises the executive functions in charge of so-called cognitive control. Basically, these functions are three: (1) executive attention, with its subcomponents of top-down attention or set, working memory, and inhibitory control; (2) planning; and (3) decision-making. Only the first function, executive attention, with its components of set, working memory, and inhibitory control, can be suitably studied neuropsychologically (by lesions) in the animal. They will be the subject of the balance of this chapter. The other two, planning and decision-making, will be treated in Chapter 5, as they can be best approached in the human with clinical lesion of the cortex.

### A. Attentive Set

Attention is the cognitive expression or equivalent of a deeply seated and ubiquitous neurobiological function. This function is based on the limited capacity of neural processing systems as well as the necessity to allocate that capacity to the most effective processing of information at any given time and in any given

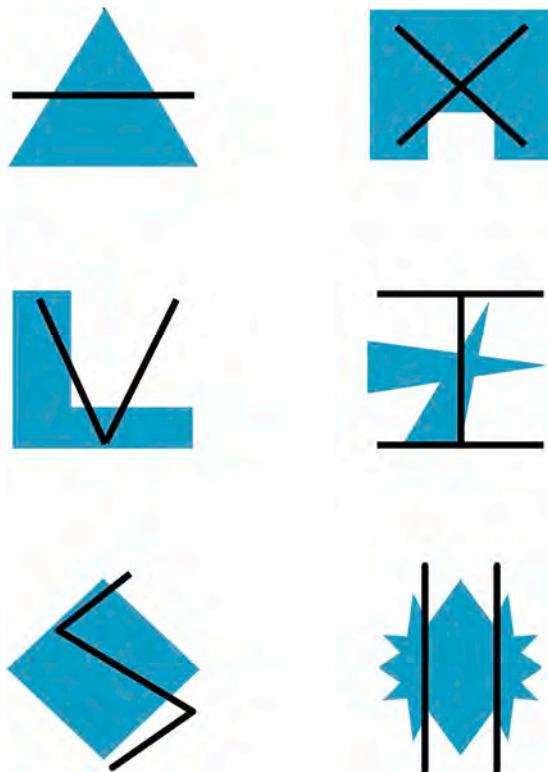
context. By definition, attention is selective: it is the selective processing of the most relevant information toward the attainment of a goal under present circumstances. All sensory and motor systems have rudiments of what in the cognitive sphere we call attention. Wherever a discrete sector of sensorium or motility is engaged in the selective processing of information, there lies the biological root of what in the realm of cognition becomes selective attention. In that sense, there is "attention," of sorts, in the eye as there is in the knee. In both places there can be selective processing (a sort of "focus"), whether of a discrete component of the visual scene or of locomotion. Note, however, that in both places the optimization of excitatory processing in a given sector of the sensory or motor apparatus is accompanied, collaterally, by the inhibition of other sectors: inhibition of retinal cells around the receptive fields at the center of the processing or inhibition of antagonistic muscles, both kinds of inhibition contributing to increased saliency or contrast of the image or the movement "in focus." As we ascend the neural hierarchies to the level of consciousness and cognition, those reciprocal excitatory-inhibitory processes become the essence of attention. Indeed, attention consists of two antagonistic and complementary cognitive processes, one of focusing, inclusive, and the other inhibitory, exclusionary. One exists to optimize the processing of the relevant, the other to suppress the irrelevant (see Chapters 3, 7, and 8).

The preceding general comments on attention have two purposes. One is to emphasize that attention is inseparable from other cognitive functions such as sensory perception and memory. For this reason, among others, it is futile to attempt the neuropsychological localization of attention, in the cortex or anywhere else. The other purpose is to lay the groundwork for the evidence that the prefrontal cortex plays a crucial role in attention whenever and wherever goal-directed behavior needs to

be integrated in time. This means that the two attentive processes, that is, focusing and inhibitory control, will emerge and re-emerge in the discussion, below, of the effects of prefrontal lesions on such functions as discrimination and working memory; indeed, there is no successful discrimination without attention, and working memory can be properly considered attention to an internal representation. The prefrontal cortex, we will see, is essential not only for the sensory aspects of attention but also for the motor (executive) ones.

Executive attention, however, for which the prefrontal cortex is indispensable, is an essentially prospective function. It is what has been called top-down attention, based on memory and experience more than on bottom-up sensory experience. Most importantly, it has a future dimension that, in human terms, makes it akin to expectancy and prediction. It is what can be best designated as attentive or preparatory set. By virtue of its temporally prospective aspect, attentive set prepares the animal for a choice, for an action, or for a decision, albeit a decision determined by previous events. That top-down attentive set is a critical component of what some have termed "executive cognitive control." It is the prospective aspect of temporally extended attention, much as working memory is the retrospective one. For the reasons noted, attentive set has been appropriately called "preparatory set" or "prospective memory."

To illustrate the interrelation of attentive set with discrimination behavior, and the role of the prefrontal cortex in both, here it is appropriate to consider, however briefly, the experiments by Dias, Robbins, and Roberts (Dias et al., 1996a, 1996b, 1997). They trained marmoset monkeys to discriminate between visual stimuli presented in pairs, such as those in Figure 4.2. Each of the stimuli was composed of a pattern of black lines superimposed on a geometric figure. In a series of consecutive trials, the stimuli were presented in pairs



**FIGURE 4.2** Examples of three pairs of test stimuli utilized by Dias et al. in their set-shifting experiments. (From Dias et al., 1996a, slightly modified, with permission.)

for the monkey to choose the "correct" one (the rewarded choice) of each pair. Some animals were trained to discriminate between line-patterns regardless of background figure; others were trained to do the reverse, to discriminate between figures regardless of the overlying lines. In other words, some monkeys had to concentrate their attention on the lines and ignore the figures (they developed a "line set," so to speak). The others had to do the opposite ("figure set"). The task is very similar to the Wisconsin Card Sorting Test (see Chapter 5), a test used to test humans with prefrontal damage, in which the subject is required to classify cards by the shape or color of the objects depicted in them.

After training the monkeys to a certain criterion of performance, Dias and colleagues surgically produced exotoxic lesions of lateral or orbital prefrontal cortex. Then the monkeys were tested for their ability to shift set: that is, line-set animals had to shift to figure set, and figure-set animals had to do the opposite. Subjects with lateral lesion were notoriously deficient in performing those shifts. They failed to transfer attention from lines to figures, and *vice versa*; presumably, they failed to inhibit the previous set. That failure to inhibit inappropriate attention was most conspicuously displayed by the orbital lesion animals on a simple discrimination reversal task (see next section). Here we have, therefore, in a visual discrimination task, the two aspects of attention impaired by prefrontal lesion. The first aspect of attention, set-shift, like working memory (see below), is most impaired by lateral prefrontal lesion (both set and working memory are forms of temporally based – “time-sensitive” – attention to internal representations). The second aspect of attention, inhibition, like inhibitory control in the previous and succeeding sections, is most impaired by orbital prefrontal lesion.

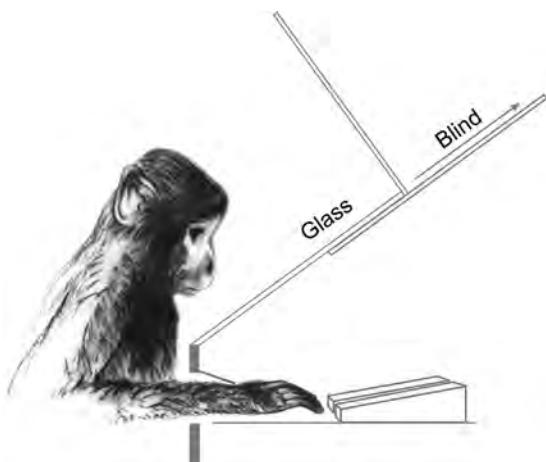
## B. Working Memory

Since the deficit induced by frontal ablation on delayed-response tasks was first described by [Jacobsen \(1935, 1936\)](#), it has been the fulcrum of behavioral research on the cognitive aspects of prefrontal function, and the rhesus monkey has been the standard species for this research. The delayed-response deficit is undoubtedly one of the clearest and best documented phenomena in physiological psychology. That deficit is complex, however, in large part because delayed-response tasks (“delay tasks” for short) are complex. From the deficit itself, no one single function can be inferred for the prefrontal cortex. Nonetheless, the deficit reflects at least one of those functions most

prominently: working memory, that is, the temporary retention of information – sensory or other – for the performance of a prospective act to solve a problem or to attain a goal. Note that working memory, like attentive set, has a critical future perspective that is part of the definition as formulated by [Baddeley \(1983\)](#) in human subjects. Another function, which also underlies other prefrontal deficits, is the inhibitory-control function that is emphasized in the next section. Which of those functions fails for the animal to fail at delayed response will depend to some extent on the prefrontal area affected.

In a typical delayed-response test, as devised by [Hunter \(1913\)](#) and adopted by Jacobsen for his primate experiments, the animal has to perform a task that essentially requires the short-term retention of a sensory cue for the performance of a choice ([Figure 4.3](#)). Each trial consists of the following seriatim events: (1) the display of a discrete item of information, namely, the placement of food under one of two or more identical objects; (2) an enforced delay of a few seconds or minutes, during which the objects are out of reach and, in some test versions, out of sight; (3) the simultaneous presentation of the objects for choice; and (4) the animal’s choice of one object. If it chooses the baited object, the animal is allowed to retrieve the food as the reward. The position of the bait is changed at random from one trial to the next. Thus far described is the classic, so-called direct-method delayed-response test, usually administered in the Wisconsin General Test Apparatus ([Harlow, 1949](#)) or a variant of it. Some versions of the test are administered in automated instruments, in which the site of the correct response is signaled at the start of a trial by a visual or an auditory stimulus (indirect method, [Figure 4.4](#), DR).

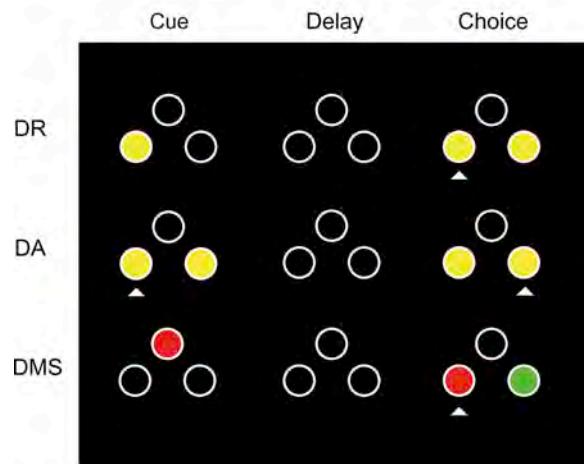
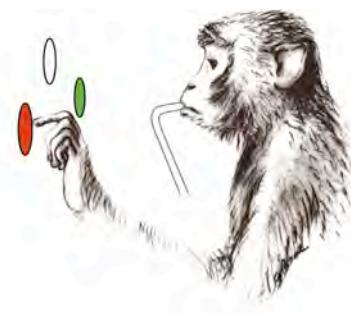
A somewhat different test is delayed alternation, in which the trials are temporally interlocked with one another ([Figure 4.4](#), DA).



**FIGURE 4.3** Monkey performing the classical delayed-response task (direct method). A trial begins with elevation of the opaque screen (blind) and the placement, in full view of the animal, of a piece of food under one of two identical objects behind the glass. The screen is then lowered, blocking the view of the objects for a period of a few seconds or minutes. At the end of that delay, the screen is again raised, and the monkey chooses one of the objects by introducing a hand through one of the two corresponding trap doors. If the chosen object is the correct (baited) one, the monkey is allowed to retrieve the food from under it. Otherwise, the trial is terminated without reward. The position of the bait is changed randomly between trials.

The animal is required to alternate the site of response, usually between right and left, with an enforced delay between responses. The correct site for each response is thus predicated on the previous response. The task is basically a form of place reversal (below).

Monkeys with frontal ablation fail a third type of delay test: delayed matching-to-sample (Spaet and Harlow, 1943; Glick et al., 1969). In this task (Figure 4.4, DMS), the animal is presented with a stimulus (sample) at the start of each trial; after an enforced delay, the same stimulus is presented in conjunction with another (or others). The animal's choice of the sample stimulus is then rewarded. The sample stimulus is changed randomly between trials, and so is



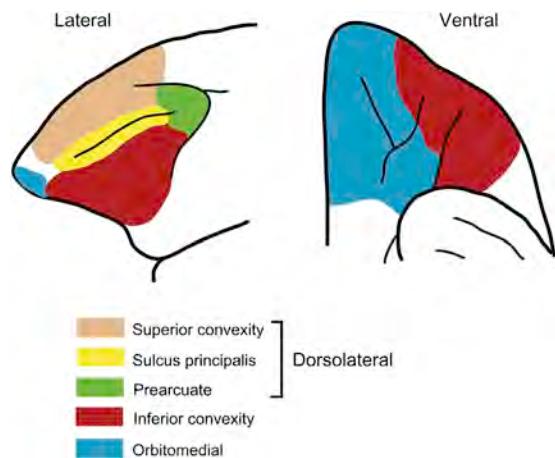
**FIGURE 4.4** Monkey facing a panel with stimulus-response buttons for performance of indirect-method delay tasks (mouth spigot is for delivery of liquid reward). Below is the sequence of events in three such tasks: delayed response (DR), delayed alternation (DA), and delayed matching-to-sample (DMS). A DR trial begins with brief illumination of a button (right or left, randomly changing); after a delay, two buttons are simultaneously lit, and the animal must press the one that was lit at the start of the trial. In DA, the animal must alternately press the right and the left of a pair of buttons that are simultaneously lit between delays. In DMS, the trial begins with brief presentation of the sample, red or green light, on the upper button; after a delay, both colors appear in the lower buttons, and the animal must press the one matching the sample color; both that color and the positions of the two colors in the lower buttons are changed randomly between trials. In the three task diagrams, white triangles mark the site of the correct response, which is rewarded with a squirt of fruit juice automatically delivered to the monkey's mouth.

its position with respect to the other comparison stimulus or stimuli.

Animals with bilateral lesions of the prefrontal cortex are severely impeded in the learning and performance of delay tasks; that is, they take much longer to learn them than normal animals and, once they have learned them, they perform them well only with much shorter delays between cue and response than normal animals. The deficit has been demonstrated in primates of several species (Jacobsen and Nissen, 1937; Crawford et al., 1948; Lashley, 1948; Pribram et al., 1952; Miles and Blomquist, 1960; Rosvold and Szwarcbart, 1964; Divac and Warren, 1971; Skeen and Masterton, 1976), cats (Lawicka and Konorski, 1961; Warren et al., 1962; Warren, 1964; Divac, 1968, 1972a; Markowitsch and Pritzel, 1976), dogs (Lawicka and Konorski, 1959; Konorski, 1961; Konorski and Lawicka, 1964; Lawicka et al., 1966; Lawicka, 1972), rodents (Wikmark et al., 1973; Johnston et al., 1974; Kolb and Nonneman, 1976; Larsen and Divac, 1978; Markowitsch and Riess, 1981; Sakurai and Sugimoto, 1985), and insectivores (Passingham, 1978; Skeen and Masterton, 1982). The degree of impairment varies considerably, depending on the species and on a number of factors related to the testing method and the cortical areas affected. Next, we attempt to weigh the role of each of those factors.

### Anatomical Factors

Many have tried to delimit subareas of the prefrontal cortex specifically concerned with particular aspects of delay-task performance. For that purpose, numerous variations of the basic delay task have been used, alone or in conjunction with discrimination tasks, and many different types of selective prefrontal ablation have also been used. Most of that work has been conducted on the rhesus monkey and is described here in summary fashion with reference to a picture of the conventional anatomical subdivision of this animal's prefrontal cortex (Figure 4.5).



**FIGURE 4.5** Subdivisions – according to anatomical landmarks – of the lateral and ventral prefrontal cortex in the rhesus monkey, as commonly designated in the ablation literature. (From Rosenkilde, 1979, slightly modified, with permission.)

Contrary to early reports (Jacobsen et al., 1935; Jacobsen, 1936; Finan, 1939; Meyer et al., 1951), unilateral ablation of the prefrontal cortex has been shown to be sufficient to produce a delayed-response deficit, although of less magnitude than that produced by bilateral ablation (Warren et al., 1969a; Warren and Nonneman, 1976). No relationship has been found between hemispheric dominance and the magnitude of the deficit (Warren and Nonneman, 1976). The quantitative nature of the difference between unilateral deficit and bilateral deficit is compatible with the “principle of mass action” (Lashley, 1948, 1950). According to this, the extent of the deficit depends on the quantity of tissue removed as much as, or more than, the site of the removal. This notion has received support from the results of other experiments. For example, some studies have indicated that complete ablation of the lateral prefrontal cortex induces a greater behavioral deficit than does the ablation of any of its parts (Gross, 1963b; Stepien and Stamm, 1970a, 1970b; Stamm and Weber-Levine, 1971; Gentile and Stamm, 1972).

Despite the difficulties inherent in the functional topographic analysis by selective ablation, a reasonably clear picture emerges from the studies reviewed. It shows at least some quantitative differences in the involvement of two broadly defined prefrontal areas in behavior. In the monkey, the picture reveals a functional dissociation between the dorsolateral cortex, including the sulcus principalis, on the one hand, and the ventral cortex, including the orbital cortex and the inferior convexity, on the other (Brutkowski et al., 1963; Mishkin, 1964; Butter, 1969; Mishkin et al., 1969; Passingham and Ettlinger, 1972; Lawicka et al., 1975). The dorsolateral cortex is primarily involved in tasks that require the integration of spatially and temporally discontiguous elements of cognition. Most delay tasks fall into this category. The ventral cortex, on the other hand, appears to be mostly involved in certain aspects of response control, particularly the suppression or inhibition of interfering tendencies. This is the case in reversal tasks and also in delayed alternation, which includes a reversal feature (Mishkin, 1964; Mishkin et al., 1969). In any case, the ventral cortex does not seem to be directly involved in the mnemonic aspect of working memory (Rushworth et al., 1997).

A similar dichotomy has been noted in the dog's prefrontal cortex. Here, the functional homologs of the monkey's dorsolateral and ventral cortex appear to be, respectively, the dorsolateral (proreal) and the medial cortex (Brutkowski, 1964, 1965; Dabrowska, 1971, 1972; Konorski, 1972, 1973). The homology of the dorsolateral cortices of the two species, however, is functionally better established than is the homology of other prefrontal sectors. Selective proreal lesions in the dog induce the same types of deficit in spatial delay tasks as do dorsolateral lesions in the monkey (Lawicka, 1972; Lawicka et al., 1975). On the other hand, there is evidence that at least a part of the canine's medial prefrontal cortex – the pregenual area – is, like the orbital cortex in the

monkey, essential for the inhibition of inappropriate behavioral responses (Brutkowski and Dabrowska, 1963; Brutkowski, 1964; Dabrowska, 1971, 1972). In both primate and dog, the noted functional dichotomy approximately corresponds to the dichotomy of thalamic connections pointed out in Chapter 2.

In the cat, the dorsoventral dichotomy is less evident. Proreal – anterior-lateral – lesions induce deficits in conventional delay tasks, even those with somesthetic cues (Glassman et al., 1981). However, the functional homolog of the monkey's ventral prefrontal cortex is not apparent in the cat. In rodents, because of the relative anatomical and hodological separateness of the two prefrontal sectors, it appears, from the results of lesions produced in one or the other, that the dorsal–ventral dichotomy holds: the medial sector, homologous to the monkey's dorsolateral cortex, enables the bridging of discontiguities in space or time (Kesner, 1990, 1993), and the sulcal sector, homologous to the monkey's ventral cortex, supports behavioral inhibition (Markowitsch and Riess, 1981; De Bruin et al., 1983; Sakurai and Sugimoto, 1985).

Lesions in the posterior border region of the monkey's lateral prefrontal cortex – that is, the arcuate cortex (area 8) – do not substantially impair delay tasks (Pribram, 1955; Goldman and Rosvold, 1970; Goldman et al., 1971) but result in marked impairment of conditional position-response tasks (Goldman and Rosvold, 1970; Stamm, 1973; Milner et al., 1978); in these tasks, the animal is required to execute different positional reactions to different visual or auditory cues. Lesions of the arcuate cortex have also been noted to disrupt a conditional go/no-go task (Petrides, 1986) as well as tactile–visual (Petrides and Iversen, 1976) and auditory–visual (Petrides and Iversen, 1978) matching. The basis for these cross-modal deficits will become clearer in Chapter 6 (Neurophysiology). Also unclear is the role of the monkey's medial prefrontal

cortex in any of the cognitive tasks discussed so far. Some deficits of delay-task performance have been reported after lesions of the cingulate and medial prefrontal cortex in the monkey (Pribram et al., 1962), the cat (Koridze and Oniani, 1972), and the rat (Aggleton et al., 1995; Harrison and Mair, 1996; Mair et al., 1998).

More details of the effects of selective frontal ablations on cognitive tasks, including delay tasks, are presented below in relation to specific issues (also, for more detail in the primate, the reader is referred to Petrides, 1994). The final interpretation of the effects of many published ablation studies must await further experimental evidence. In any event, caution is dictated by the methodological difficulties of those studies, such as the difficulty in dissociating behavioral factors by testing the experimental animal on different tasks. The testing tasks may differ vastly not only with respect to the factors under study, but also with respect to imponderable factors that may complicate the interpretation of results. Because of such complications, the so-called double dissociations, that is, dissociations by task and by cortical area, are of definite value in the quest for functional localization (Teuber, 1955, 1966; Gross and Weiskrantz, 1964). Unfortunately, these dissociations are rare; none has been produced unambiguously in the frontal cortex. All too often and mistakenly, differences in degree of behavioral deficit have been used to support qualitative functional differences between prefrontal regions.

Delay-task deficits have been seen after lesions of some of the subcortical or cortical structures connected to the prefrontal cortex, such as the mediodorsal nucleus of the thalamus (Schulman, 1964; Isseroff et al., 1982), the subthalamus (Adey et al., 1962), the hippocampus (Mishkin and Pribram, 1954; Orbach et al., 1960; Karmos and Grastyan, 1962; Pribram et al., 1962), the cingulate cortex (Pribram et al., 1962; Koridze and Oniani, 1972; Meunier et al., 1997), and the caudate nucleus (Rosvold and Delgado, 1956; Bättig et al., 1960; Divac, 1972b; Dobrossy

et al., 1996). In the monkey, selective lesions of the head of the caudate nucleus have revealed a dissociation of functions within it (Divac et al., 1967): lesions of its anterolateral portion, which is connected to the dorsolateral cortex, markedly impair delayed alternation but not object reversal, whereas opposite effects are produced by lesions of the ventrolateral portion of the nucleus, which is connected to the orbital cortex. On the basis of these and other behavioral findings, and the anatomical evidence, Rosvold postulated two functional systems of interconnected neural structures, one associated with the dorsolateral cortex and the other – mentioned above – with the orbital cortex (Rosvold and Szwarcbart, 1964; Rosvold, 1968, 1972).

Some ablation experiments provide insight into the neural pathways used in a delay task. With the aid of split-brain procedures, Glickstein and collaborators (1963) were able to show that at least some of the sensory information the animal uses for performing delayed responses gains access to the prefrontal cortex by way of corticocortical connections from the posterior areas of the hemisphere. Yamaguchi and Myers (1973) showed that the animal with a commissurotomy can transfer the learning of delayed response and alternation from one hemisphere to the other, even though it is unable to do so with discrimination tasks. The reason, the authors presumed, is that for delay tasks the animal uses proprioceptive cues related to body orientation and movement that, unlike the exteroceptive cues of discrimination tasks, can be processed equally well by the two hemispheres, irrespective of the integrity of the neocortical commissures. The combination of behavioral, electrophysiological, and lesion methods may provide more direct evidence of the mechanisms by which the prefrontal cortex executes its crucial role in delay tasks.

### Sensory Factors

Attempts have been made to reduce the delayed-response deficit to a defect of sensory

function of a particular modality. By varying the kinetic or somesthetic requirements of the task, experimenters have obtained evidence from monkeys with dorsolateral lesions suggesting that their spatial deficits result from a basic difficulty in using proprioceptive cues (Stamm, 1970; Gentile and Stamm, 1972; Manning, 1978). This interpretation parallels Konorski's idea of the prefrontal area as the gnostic area for sensory information of a spatiokinesthetic character (Konorski, 1967). Later experiments have indicated that the proprioceptive interpretation is too restrictive; instead, they support a supramodal role of the dorsolateral prefrontal cortex in egocentric spatial orientation (Pohl, 1973; Mishkin et al., 1977).

Lesions of the inferior cortical convexity have been shown to induce deficits in visual delayed matching-to-sample (Passingham, 1975; Mishkin and Manning, 1978). These have been interpreted as visual non-spatial deficits. This interpretation makes anatomical sense, since the area ablated receives profuse inputs from visual areas of posterior (inferotemporal) cortex (see Chapter 2). The inferotemporal-frontal disconnection leads to visuomotor deficits (Eacott and Gaffan, 1992; Parker and Gaffan, 1998; Bussey et al., 2002). In related experiments, the reversible lesion of inferotemporal cortex, by cooling, impairs the performance of a visual delay task (Fuster et al., 1981) and adversely affects the delay discharge of cells in the inferior prefrontal convexity (Fuster et al., 1985), making that discharge less attuned to the visual memoranda.

Orbital prefrontal ablations impair the rat's performance of olfactory delay tasks (Otto and Eichenbaum, 1992). As we shall see later in this chapter, the cooling of the dorsolateral prefrontal cortex of the monkey causes reversible deficits in visual, auditory, and tactile delay tasks. Temporal factors, however, override sensory factors. The delay of the delay task is all important for the deficit from prefrontal lesion to occur, regardless of the sensory modality of the cue.

### Spatial Factors

It is well established by the results of selective ablations that the integrity of the cortex lining the sulcus principalis of the monkey is especially critical to both delayed response and delayed alternation (Blum, 1952; Mishkin, 1957; Gross and Weiskrantz, 1962, 1964; Butters and Pandya, 1969; Goldman and Rosvold, 1970; Goldman et al., 1971). Suspecting that the delay-performance deficit from lesions of the lateral cortex, including the sulcus principalis, might have to do with the spatial character of the cues in the conventional delay tasks, Mishkin and Pribram postulated a role of that cortex in spatial information processing. They then tested animals with lateral lesions on the performance of several variants of those tasks, some of which did not contain the spatial factor (Mishkin and Pribram, 1955, 1956; Pribram and Mishkin, 1956; Pribram, 1961). The results provided only limited support to their hypothesis. Nonetheless, subsequent investigations, for which other tests and forms of selective lesion were adopted, led to the conclusion that the dorsolateral cortex is indeed important for tasks that require the monkey to use spatially defined information (Mishkin, 1964; Mishkin et al., 1969; Goldman and Rosvold, 1970; Goldman et al., 1971; Pohl, 1973; Mishkin and Manning, 1978). The same seems true for the rat's medial prefrontal cortex (Kesner, 1989; Kesner et al., 1996; De Bruin et al., 2001; Le Marec et al., 2002; Hoh et al., 2003).

Although the region of the sulcus principalis has been identified as most critical for the performance of spatial tasks, it is important to note that those tasks are impaired by principalis lesion only if they have a delay (Goldman and Rosvold, 1970; Goldman et al., 1971; Mishkin and Manning, 1978; Passingham, 1985a). This is clear evidence that there, as elsewhere in the prefrontal cortex, the time factor overrides the space factor. Furthermore, even though the cortex most critical for spatial delay tasks has been localized with remarkable precision in a small

region (the middle third) of the sulcus principalis (Butters and Pandya, 1969; Butters et al., 1971, 1972), ablations of surrounding areas also impair the performance of the same tasks. Those areas, it would appear, can play a surrogate or compensatory role when that small part of cortex is missing. This would explain the partial recovery of performance in animals with principalis lesions, which has been shown to occur most readily when the lesions are made in stages (Butters et al., 1971, 1974; Rosen et al., 1971, 1975; Treichler, 1975; Meyer et al., 1976), although that does not seem to be the case for orbital lesions (Butters et al., 1973). In any event, the notion of a cortical focus critical for a given function and surrounded by a field of marginal or potential involvement in that function (Chow and Hutt, 1953) evidently applies to the prefrontal as well as other regions of cortex.

### Temporal Factors

The intratrial delay is undoubtedly the most important factor, as it operationally defines all delay tasks and the function of working memory that they test. The presence and length of that delay predict whether or not the working-memory deficit will be observable after frontal ablation (Meyer et al., 1951; Meyer and Harlow, 1952; Gross, 1963b; Treichler et al., 1971; Miller and Orbach, 1972). The frontal animal may not make any more errors than the normal animal if that delay is brief (e.g., 1s), but usually makes considerably more errors than does the normal animal when the delay is long (>5s). Consequently, the use of a fixed short delay may not reveal the deficit. Furthermore, the relationship between performance and length of delay varies widely from species to species (Hunter, 1913; Harlow et al., 1932; Maslow and Harlow, 1932; Fletcher, 1965). For these and other reasons it is difficult, on the basis of published reports, to establish interspecies differences regarding the importance of the prefrontal cortex for delay-task performance (Markowitsch and Pritzel, 1977). Nevertheless,

some such differences can be generally deduced from well-controlled experiments. Thus, for example, the delayed-response deficit is smaller in the cat than in the monkey, and smaller in the chimpanzee than in the macaque (Rosvold et al., 1961; Warren et al., 1962, 1972; Warren, 1964).

The essence of a delay task is the mediation of a cross-temporal contingency: the execution of a motor act contingent on an event that has occurred in the recent past. Any single trial of the task is a temporal structure of behavior, a temporal gestalt containing the event, the act, and the delay between them. Furthermore, both the event and the act are part of a repertoire of recurring familiar alternatives whose relevancy to reward changes from trial to trial. Each correct response or choice is contingent on perceiving and remembering the critical event in that particular trial and rejecting inappropriate alternatives. The case for the importance of the time factor in the frontal deficit rests, above all, on the evidence that the deficit depends on the presence of a delay between the event and the act, and that the deficit increases as the delay gets longer.

Research and debate on time factors had an early origin, since time is central to any memory hypothesis of the frontal deficit, including Jacobsen's. He and his colleagues (Jacobsen, 1935; Jacobsen et al., 1935), while entertaining that hypothesis (see below), were the first to express the idea of a broader role of the prefrontal cortex in the temporal organization of behavior. The neuropsychological support we now have for this idea derives not only from the delayed-response deficit of the frontal animal but, more generally, from evidence that the interposition of temporal discontiguities between the events of any task tend to make the task inordinately difficult for that animal (Mishkin and Weiskrantz, 1958; French, 1964; Kolb et al., 1982). Further support has been provided by the results of experiments, such as those by Pribram and collaborators, showing

that the frontal animal has severe difficulties in executing its actions in a given time sequence or otherwise temporally organizing separate events (Pinto-Hamuy and Linck, 1965; Pribram and Tubbs, 1967; Tubbs, 1969; Pribram et al., 1977). These difficulties can be greatly alleviated by experimentally parsing the events of the task (delayed alternation) in such a manner as to make temporal organization easier (Pribram and Tubbs, 1967; Tubbs, 1969; Pribram et al., 1977). Sequencing tasks without temporal discontinuities do not challenge the frontal animal (Passingham, 1985b). In any event, monkeys with lesions of the dorsolateral prefrontal cortex (Brody and Pribram, 1978; Petrides, 1991, 1994, 1995) and rats with lesions of the homologous medial cortex (Kesner, 1990, 1993; Chiba et al., 1994; Granon et al., 1994; Mogensen and Holm, 1994) have been shown to be deficient at tasks in which temporal frequency, temporal order, or temporal sequence is of the essence, in other words, tasks predicated on temporal integration either in the cognitive or in the behavioral domain.

The troubles that the frontal animal seems to experience in bridging temporal discontinuities and in temporally organizing behavior may be expected to be accompanied by impaired performance of tasks that are predicated on the estimation of time. However, the experimental evidence is not uniformly consistent with this expectation. Some studies have shown frontal animals to be deficient at tasks that require timing (Glickstein et al., 1964; Nonneman et al., 1974; Numan and Lubar, 1974; Rosenkilde and Divac, 1975, 1976; Rosenkilde and Lawicka, 1977; Mitchell and Laiacona, 1998). Other studies, however, have failed to show this (Stamm, 1963; Manning, 1973). Perhaps the key to understanding the conflict between outcomes is that the frontal cortex is needed not so much for timing behavior as for the timing of behavior, where the temporal-integration factor is essential.

Thus, in conclusion, on the basis of lesion studies, the dorsolateral prefrontal cortex seems

to be most important for the mediation of cross-temporal contingencies, as required by delay tasks. Nevertheless, orbital and medial cortex, also on the basis of lesion studies discussed in previous and succeeding sections, may also be critical for the broader function of temporal organization, inasmuch as this cortex is essential for inhibitory control of interference, and thus for the suppression of influences that may interfere with the formation of a temporal gestalt.

### **Mnemonic Factors**

It was the relevance of the delay in the prefrontal delayed-response deficit that led to the short-term memory concept of prefrontal function. Jacobsen (1935, 1936), the first to demonstrate that deficit in the frontal monkey, concluded, albeit with some hesitation, that the deficit was one of recent memory. It was a logical *prima facie* interpretation of the phenomenon, an inference readily appealing to anyone who observes that phenomenon. The animal indeed appears unable to retain in short-term memory the event preceding every choice, as it makes an inordinate number of errors. Ostensibly, therefore, the short-term memory of the event is defective. However, there are reasons for questioning that intuitive explanation. In the first place, the frontal animal is not incapable of learning new tasks or discriminations. If some kind of memory is disturbed, it does not seem to be primarily the recent or short-term memory function that conventionally we consider the gateway to long-term storage.

Then there is the evidence that the frontal animal has not completely lost the capacity to retain and retrieve the relevant cue in the delay-task trial. By certain maneuvers the animal can be helped to overcome its apparent memory deficit. For example, the impairment of delayed response can be prevented, at least in part, by making the cue more salient or by somehow ensuring attention to it (Finan, 1942; Meyer et al., 1951; Blake et al., 1966). The same result can be obtained by minimizing distractions

during the delay (Malmo, 1942; Orbach and Fischer, 1959; Konorski and Lawicka, 1964; Bartus and Levere, 1977). Distraction during the delay appears to interfere not only with the cue, retroactively, but also with postural orientation, which animals of some species use as a mnemonic crutch for negotiating the delay. New World monkeys and dogs, for example, tend to orient themselves toward the cue location throughout the delay (French, 1959b; Konorski and Lawicka, 1964). Old World monkeys do not seem to resort to such devices (Gleitman et al., 1963; Fletcher, 1965), except possibly after prefrontal lesions (Kojima et al., 1982).

Other studies show the beneficial effect on delayed response of pharmacologically controlling the hypermotility that is seen frequently as part of the frontal lobe syndrome (Wade, 1947; Pribram, 1950; Mishkin et al., 1953; Weiskrantz et al., 1965). However, some of these studies, like some of those cited in the previous paragraph, lack control measures on the effects of behavioral or pharmacological procedures in non-operated animals. In the absence of such measures, it is difficult to determine how effectively those procedures restore the capabilities that are presumed lost in the frontal ablation.

All these studies taken together, however, challenge the notion that the prefrontal cortex is the storage site for any form of memory. Yet no ablation study disproves a participating role of the prefrontal cortex in a process of provisional or temporary memory. It is not surprising, therefore, that many ablation experts, including some of the most severe critics of Jacobsen's memory hypothesis, felt compelled to reinvoke it in one form or another for at least some portion of the prefrontal cortex (Gross and Weiskrantz, 1964; Pribram et al., 1964; Konorski, 1967; Goldman and Rosvold, 1970; Iversen, 1973; Mishkin and Manning, 1978; Rosenkilde 1983; Passingham, 1985a; Bachevalier and Mishkin, 1986).

Now, thanks in large part to other methodologies, we know that the frontal animal does

have a definite trouble in working memory. Therefore, especially if it has sustained a lesion of dorsolateral prefrontal cortex, the animal has a deficit in the ability to maintain any memory, recent or remote, in the active state for the prospective performance of a goal-directed act. Electrophysiology and neuroimaging of monkeys and humans (see Chapters 6 and 7) have shown that active memories are active neuronal networks that extend over vast cortical regions and that prominently include the dorsolateral prefrontal cortex. In fact, as we shall see, there are plenty of reasons to think that this cortex is what keeps those networks active in anticipation of a motor act. That is part of what we understand as the role of dorsolateral prefrontal cortex in "cognitive control."

Thus, what we have in the prefrontal cortex during working memory is not a transient memory trace but an updated network of short- or long-term memory available and ready to activate others and to keep them active until the behavioral action is executed that that memory calls for. That state, rather than kind, of memory is what frontal-lobe specialists formerly called operant memory, provisional memory (as in previous editions of this book), or simply short-term memory. The dorsolateral prefrontal animal has lost some or all of its ability to maintain that state of working memory toward a goal.

### **Motor Factors**

The frontal animal has trouble learning the procedure of a delay task to begin with, regardless of the length of the delay. Eventually, the animal does learn the task, but after considerably longer time than the normal animal. This fact alone implies that the prefrontal cortex is necessary for acquiring the basic scheme of the task, that is, for establishing the procedure, the motor or executive memory of the task and its rules. As with the learning of certain discrimination tasks, the animal has difficulty learning the essentials of a delay task; only, here, the

difficulty may be greater because the scheme of the task, the motor gestalt, is more complex and contains temporal discontinuities. That the animal does belatedly learn the task indicates that other brain structures (perhaps other cortical areas or premotor cortex) can play a surrogate role in motor memory.

Here, it is helpful to view the prefrontal cortex as part of the frontal lobe at large, because the premotor and motor areas also store motor memory, although of a more concrete character and on smaller timescales. The differences between frontal areas in the kinds of motor memories they store may be only quantitative, not qualitative. Indeed, animals with lesions of premotor cortex also have trouble learning and executing motor sequences, even simple ones, or at least more constrained on the time-scale than delay tasks (Wiesendanger, 1981; Halsband and Passingham, 1985; Petrides, 1986; Chen et al., 1995; Thaler et al., 1995). Needless to say, the primary motor cortex stores the most concrete items of motor memory, the representation of those basic schemes of skeletal action that this author calls phyletic motor memory because they are a part of evolutionary memory, the memory of the species (Fuster, 2003). Consequently, it is useful to introduce here, in the context of animal neuropsychology, the concept of a hierarchical organization of motor memory in the frontal lobe, with the dorsolateral prefrontal cortex on top representing the most complex and temporally extended engrams of action. This concept is amply supported by other methodologies (see Chapters 6 and 7).

Thus, the animal with dorsolateral prefrontal lesion appears to have lost a large part of the executive networks that represent temporally extended gestalts of goal-directed behavior. For this reason, in a delay task, these networks fail to activate other networks (perceptual) in posterior cortical regions and thereby fail to exercise over them the degree of control to keep them active in working memory. As a

result, temporal integration becomes faulty and behavioral gestalts disintegrate.

### Novelty Factors

The animal that has been thoroughly trained on the performance of a delay task, whether the latter is delayed response, delayed alternation, or delayed matching-to-sample, certainly treats each cue, each stimulus, and each response, as old and well rehearsed. They are all part of well-practiced habit and long-term memory. With every trial in the task, that memory is activated and put to use as a part of working memory. Without it the animal cannot perform the task. The new trial, however, updates that long-term memory with new "*ad hoc*" material: a new cue or memorandum and a new response dependent on it. It is likely that this "new" material has recurred repeatedly in previous trials, and therefore is itself part of long-term memory. But for that particular trial, it is new, in the sense that it changes randomly from trial to trial and is thus unpredictable for the animal. In sum, the content of working memory for a particular trial is made of two distinct elements: (1) the memory of the formalities of the task; and (2) the memory of the cue and the appropriate motor response for that trial, which though themselves also in long-term memory are, at that time, *novel* and indispensable for any level of performance above chance.

The reason for dwelling on the issue of the novelty of each delay-task trial is because in any such trial the animal is called to construct a new gestalt of behavior, anchored in long-term memory, but new. Novelty, as will be emphasized later on in this book, is of the essence in the temporal organizing role of the prefrontal cortex. It is somewhat disconcerting that working memory is repeatedly treated in the literature as a form of short-term memory out of its long-term memory context. As we will see repeatedly in the clinical and physiological chapters, by neglecting the built-in novelty of delay tasks, it is easy to forget that

a fundamental function of the prefrontal cortex is to form novel structures of behavior – or language. The prefrontal cortex forms those structures out of old ones, for which working memory and the activation of large expanses of the cortex are necessary.

### C. Inhibitory Control

Another reason for failure at delay tasks, especially after lesions that encroach on orbital prefrontal cortex, is disinhibition from interference. Working memory, like any other form of sustained attention, is notoriously liable to interference and distraction, and, consequently, so are the temporal structures of behavior that working memory mediates. To protect the memory and those structures from interference and distraction, the prefrontal cortex has another function at the service of executive function, this one apparently based in ventral aspects of the frontal lobe: inhibitory control. The effects of ventral prefrontal lesions on delay tasks, as on discrimination tasks, suggest that the critical factor accounting for behavioral deficit after such lesions is the absence of inhibitory control of interference, internal or external.

One form of interference that apparently plays an important role in the frontal animal is the innate or acquired tendency to perseverate in behavioral sets that compete at a given time with the particular response required by the circumstances (Mishkin, 1964). This type of interference explains the perseverative errors of frontal animals, particularly if their lesions involve the orbital or anterior cingulate prefrontal cortex, in delay tasks as well as in discrimination and reversal tasks (Butter, 1969; McEnaney and Butter, 1969; Iversen and Mishkin, 1970, 1973; Jones and Mishkin, 1972; Passingham, 1972a, 1972b; Oscar-Berman, 1975; Kowalska et al., 1991; Otto and Eichenbaum, 1992; Seamans et al., 1995).

Mishkin and his colleagues (Mishkin, 1964; Mishkin et al., 1969) concluded that monkeys

with orbital lesions fail when they perform delayed-alternation and object-alternation tasks because of the reversal factor in these tasks, the same factor that accounts for failure at discrimination and reversal tasks. Therefore, the role of the ventral cortex in delay tasks appears to be related to its role in discrimination. The two may be one and the same inasmuch as any delay task can be considered a special form of discrimination – a concept first proposed by Nissen et al. (1936). According to this view, each delay-task trial is essentially a separate discriminative “learning process” unique to that trial and vulnerable to interference from the incompatible experience of previous trials. Thus, the animal with a ventral prefrontal lesion is basically handicapped by a general deficiency in the learning process. This deficiency may be characterized as the incapacity to withstand the so-called proactive interference of previous experiences, previous learning, and previous trials; in sum, an incapacity to shift set as readily as the circumstances demand. Therefore, the ventral prefrontal cortex, through its role in inhibitory control, appears essential for liberating behavior from established but at the moment inappropriate response modes.

In general, an animal that has been subjected to extensive ablation of its prefrontal cortex – a “frontal animal” by common designation – has little trouble executing a preoperatively learned motor response to a distinct sensory stimulus. The frontal animal can even respond appropriately to elaborate combinations of stimuli, especially if they are highly familiar. It can also learn without difficulty new simple habits that are predicated on the perception of clear and unambiguous cues. The animal may encounter some trouble, however, when it is obliged to learn or to re-enact a discrimination task that demands different responses to different stimuli. If, for instance, two objects or visual stimuli are repeatedly and simultaneously presented for the rewarded choice of

one of them, the trouble is usually minor. The frontal animal is able to learn and retain such a task, although the learning usually takes place at a slower pace than in a normal animal, especially if the stimuli are complex (Jacobsen, 1935, 1936; Harlow and Dagnon, 1943; Harlow and Settlage, 1948; Pribram et al., 1952; Warren and Harlow, 1952a, 1952b; Riopelle and Churukian, 1958).

If, however, the two so-called discriminanda (English and English, 1958), whether visual or of another sensory modality, are presented not simultaneously, but separately in time (successive discrimination), the frontal animal has serious difficulties, either in learning the task anew or in retaining it if it had been learned before the operation (Kalischer, 1911; Allen, 1940; Ettlinger and Wegener, 1958; Weiskrantz and Mishkin, 1958; Rosvold and Mishkin, 1961; Bättig et al., 1962; Brutkowski, 1964; Wegener and Stamm, 1966; Iversen, 1967; Oscar-Berman, 1978). These difficulties are most conspicuous if one of the stimuli demands a given response and the other no response at all: a "go/no-go" task. Indeed, nowhere is the behavioral disinhibition of the frontal animal more evident than in the performance of tasks that involve conditioned inhibition, such as go/no-go. There, where one stimulus demands a given response and another none, the animal shows disinhibition by irrepressibly responding to both (Allen, 1940, 1943; Konorski, 1961; Rosvold and Mishkin, 1961; Brutkowski, 1964; Mishkin, 1964; Gerbner and Pásztor, 1965; Eichenbaum et al., 1983; Sakurai and Sugimoto, 1985). The animal in such a situation shows a marked tendency to make errors of commission, persistently responding to the stimulus that demands no response and emitting responses between presentations, as if unable to inhibit untimely actions. This difficulty in inhibitory response control is at the root of most errors in discrimination tasks.

The frontal animal shows a tendency to react inordinately not only to the stimuli of a

prescribed discrimination task but to unrelated stimuli as well, especially if they are new. The animal is unusually distractible and unusually reactive to novel stimuli (French and Harlow, 1955; Brush et al., 1961; Pribram, 1961; Butter, 1964; Konorski and Lawicka, 1964; Mishkin, 1964; Weiskrantz and Mingay, 1967; Hannon and Kamback, 1972). This hyperreactivity to novelty, however, is curiously accompanied by firmly entrenched responsiveness to old, familiar stimuli that are part of well-established tasks. In fact, once the animal has formed a discrimination habit, which it can readily do if it involves simultaneous, not successive, discriminations, it holds that habit tenaciously, so much so that it is difficult to oblige the animal to reverse the discrimination; in other words, to choose the stimulus-object that heretofore was incorrect and to disregard the other, formerly correct one. That kind of trouble with discrimination reversal is characteristic of the frontal disorder (Harlow and Dagnon, 1943; Settlage et al., 1948; Gross, 1963a; Teitelbaum, 1964; Warren et al., 1969b, 1972; Treichler, 1973; Irle and Markowitsch, 1984; Roberts and Wallis, 2000). The older the habit and the more familiar the discriminanda, the greater the difficulty that the frontal animal ordinarily shows in reversals. Difficulty in reversing is not limited to the discrimination of two discrete stimuli; it also applies to the choice between two different locations in the testing environment, that is, place reversal. The frontal animal continues to approach the previously baited location long after another location has become the site of reward. The animal seems unable to benefit from errors and to adjust to the change in the rules of the game (Settlage et al., 1948; Warren et al., 1962, 1969b, 1972; Mishkin, 1964; Warren, 1964).

Erroneous responses in delay and discrimination tasks may be prompted not only by external sensory stimuli but also by stimuli from the internal environment and by a general tendency to perseverate that appears to

be abnormally enhanced in the frontal animal (Settlage et al., 1948, 1956; Meyer, 1972). This tendency has been construed as a form of proactive interference; namely, the disruptive effect on each trial of competing traces from previous trials and experiences. According to this view, perseverative interference abnormally biases the responses of the animal despite continued errors. Previous responses gain the upper hand, so to speak, and obliterate the response that the specific cue of any given trial requires. To restate Mishkin (1964), the ventral prefrontal cortex plays a major role in the inhibition of that internal interference, which he characterized as "perseveration of central sets." Others, however, view perseveration differently, not as the result of a prepotent tendency but as a regressive strategy that the animal with a prefrontal lesion adopts as a consequence of its difficulties in performing the task (Konorski and Lawicka, 1964). In later chapters, we will see the importance of the anterior cingulate cortex for error correction.

With differences merely of degree, those difficulties in learning and retaining certain forms of behavior, especially those requiring successive differentiations and reversals, appear to be common to frontal animals of all species. Another general consideration is that, regardless of the deficit that follows the operation, the ablated animal shows, with time and retesting, a definite tendency to improve its performance, and in some instances may attain complete recovery (Harlow and Dagnon, 1943; Warren and Harlow, 1952a, 1952b; Warren, 1964; Warren et al., 1972; Treichler, 1973).

It is of singular interest that a deficit in discrimination reversal has also been identified in the pigeon after lesions of the neostriatum caudolaterale (Hartmann and Guntürkun, 1998). On account of its anatomical connections and neurochemical transmission properties, including an exceptionally dense dopaminergic innervation, that brain structure has been considered the avian homolog of the mammalian

prefrontal cortex. Also in accord with that homology at the functional level is the observation that pigeons with those lesions fail in the radial maze (Gagliardo et al., 1997), a task that requires both inhibitory control and spatial working memory.

In some species, the rhesus monkey in particular, efforts have been made to demarcate by selective ablations the areas of the prefrontal cortex that are most involved in sensory discriminations. As a result, it has been determined that monkeys with restricted lesions of the cortex below the sulcus principalis – the so-called inferior convexity – or of the orbital cortex are notoriously liable to deficits in visual (Iversen and Mishkin, 1970; Passingham, 1972a; Stamm, 1973), auditory (Lawicka et al., 1975), tactile (Semmes et al., 1969; Passingham and Ettlinger, 1972), and olfactory (Tanabe et al., 1975) discrimination tasks.

However, there is little evidence of topographic specificity with respect to sensory modality, either within those areas or in the prefrontal cortex at large. It appears, rather, that the critical factors underlying the localization of discrimination deficits are supramodal and related to the formalities of the tasks employed. The tasks that most require the suppression of competing tendencies – for example, successive discrimination, go/no-go, reversal – are generally more disrupted by lesions of the orbital and inferior convexity cortex than by lesions of the dorsolateral cortex (Rosvold and Mishkin, 1961; Mishkin, 1964; Iversen and Mishkin, 1970; Passingham, 1972b; Passingham and Ettlinger, 1972; Deuel and Mishkin, 1977). By manipulating the physical characteristics of the discriminanda and their association with reward, Dias et al. (1996a) show a dissociation of areas controlling interference. Monkeys with inferior convexity lesion exhibit loss of inhibitory attention control, whereas monkeys with orbital lesion cannot overcome response tendencies.

In the dog, the discrimination tasks that depend on inhibitory control are most

disrupted by medial prefrontal lesions (Brutkowski and Dabrowska, 1963; Stepien et al., 1963; Brutkowski, 1964, 1965; Dabrowska, 1971, 1972). In rodents, similar effects can be obtained by lesions of the sulcal cortex (Eichenbaum et al., 1983). Thus, lesions of a prefrontal area that is apparently homologous across species – orbital in the monkey, medial in carnivores, sulcal in rodents – seem to lead to disinhibition and a consequent loss of control, which impedes the appropriate distinction of stimuli and choice of behavioral responses.

We will encounter disinhibition again in humans with prefrontal lesions (see Chapter 5). The principal inference from the findings summarized in this animal section is that the prefrontal cortex of the primate, especially its orbital region, or its homolog in rodents and carnivores, is particularly important for the inhibitory control of attention. It will be remembered (see Chapter 2) that the orbitomedial sector of the prefrontal cortex has distinct connections with the medial thalamus, the hypothalamus, the amygdala, and the basal ganglia. Those structures and their connections constitute the orbital system postulated by Rosvold (1972). It is through that system that the prefrontal cortex executes inhibitory control. Physiological evidence, as we shall see in Chapter 6, also implicates orbitomedial cortex and its related structures in that inhibitory process.

To sum up, experimental observations in this section, as others in previous ones, lead us to conclude that the prefrontal cortex as a whole is an important source of inhibitory control over behavior. The lateral prefrontal cortex, probably through the caudate nucleus, exercises a degree of adaptive inhibition of skeletal and ocular motility. The orbitomedial prefrontal cortex, on the other hand, probably through basal ganglia, hypothalamus, and limbic structures, mediates adaptive inhibition of emotional behavior. Both lateral and orbitomedial cortices may be responsible for the inhibition of sensory events

that at any given time lie outside of the focus of attention. Purposive behavior would thus be served by at least three general categories of adaptive inhibitory control emanating from the prefrontal cortex: control of untimely or inappropriate motor acts, control of drives and internal impulses that tend to release maladaptive emotional behavior, and control of distracting and irrelevant sensory stimuli.

## VI. REVERSIBLE LESIONS

The temporary and reversible inactivation of cortical function has distinct advantages over surgical ablation. For one thing, behavior after ablation is generally subject to alterations not directly attributable to the absence of the cortex removed but due to imponderable changes that the removal induces elsewhere in the brain. With the passage of time, functional readjustments take place that complicate the interpretation of ablation results. One of the manifestations of readjustment is the commonly observed recovery of the animal from some of the behavioral deficits after prefrontal ablation. It appears that, in the absence of the ablated cortex, other structures, cortical or subcortical, assume a vicarious role. A reversible lesion obviates such confounding factors, inasmuch as the temporary disruption of function does not entail those imponderable changes, and inasmuch as the procedure allows the use of the experimental animal repeatedly as its own control. This repeated use of the animal is desirable in the study of certain behavioral effects that, because of their inherent variability, require repeated measurements over long periods.

Electrical stimulation is one way to produce reversible and localized disruption of cortical function. When an electric current of sufficient intensity – yet below the threshold for seizure or motor reactions – is applied to the prefrontal cortex, manifestations of functional ablation

are observed in the performance of delay tasks. [Weiskrantz et al. \(1962, 1965\)](#), using monkeys with implanted electrodes, noted that bilateral pulsating stimulation of the principal sulcus area, but not of the nearby arcuate area, induced a marked deficit of delayed alternation, even though the current applied was insufficient to elicit any detectable motor reaction. Unilateral stimulation had less of a detrimental effect.

In animals that had been subjected to unilateral prefrontal ablation, [Stamm \(1961, 1964\)](#) observed that subconvulsive stimulation of the principal sulcus cortex in the intact hemisphere retarded the learning of delayed alternation, but did not affect the performance of fully trained animals. The mild faradization with currents presumably closer to physiological levels slightly facilitated learning ([Stamm, 1964](#)). Surface anodal polarization had a similar effect ([Rosen and Stamm, 1972](#)).

The reversibility of the effects of disruptive stimulation allowed Stamm and his colleagues to delimit not only the cortical locus that was critical for delay-task performance but also the time within each trial when the functional integrity of the prefrontal cortex was most critical ([Stamm, 1969; Stamm and Rosen, 1969, 1973; Cohen, 1972](#)). A brief stimulus, they found, was maximally disruptive on delayed response if applied to the cortex of the middle third of the sulcus principalis immediately after presentation of the cue, during the first few seconds of the delay. Subconvulsive stimulation at other prefrontal locations – for example, the arcuate and the anterior third of the principal sulcus – did not have any effect on performance, whatever the timing of the stimulation. The detrimental effect of mid-principalis stimulation at the beginning of the delay suggested to those investigators that the cortex affected was essential for a neural process occurring at that time, possibly the encoding of the mnemonic trace of the cue.

Other results of stimulation are in line with ablation results and suggest that the effect is

related to the spatial or kinesthetic character of the delayed-response cue. For instance, although *principalis* stimulation may disrupt the performance of delayed matching (a non-spatial memory task), this effect is much weaker and more inconsistent than the effect on delayed response ([Kovner and Stamm, 1972](#)). Also, stimulation seems to be most effective at producing a delayed-response deficit when applied to the hemisphere contralateral to the monkey's preferred hand ([Stamm and Rosen, 1969, 1973](#)).

Another method to inactivate the prefrontal cortex temporarily is the local application of cold. [Trendelenburg \(1911\)](#) was the first to use hypothermia as a means to induce reversible lesions of cortical areas. More recent studies have shown that, by cooling the cortical surface to subnormal temperatures, one can depress the electrical activity of the underlying cells in a reversible manner, provided that the temperature is not maintained at 0°C or below for any length of time. Between 20°C and 29°C, most cortical cells are depolarized, and the discharge of neurons becomes abnormal in terms of configuration, pattern of occurrence, and frequency of action potentials ([Moseley et al., 1972; Adey, 1974; Reynolds et al., 1975; Brooks, 1983](#)). Those potentials become broad, of small amplitude, grouped in time, and, on average, less frequent than at normal temperature; in extracellular records, some neurons appear to be reduced to complete silence. All these changes are fully reversible, with cellular activity reverting to normal as the normal temperature of the cortex is re-established.

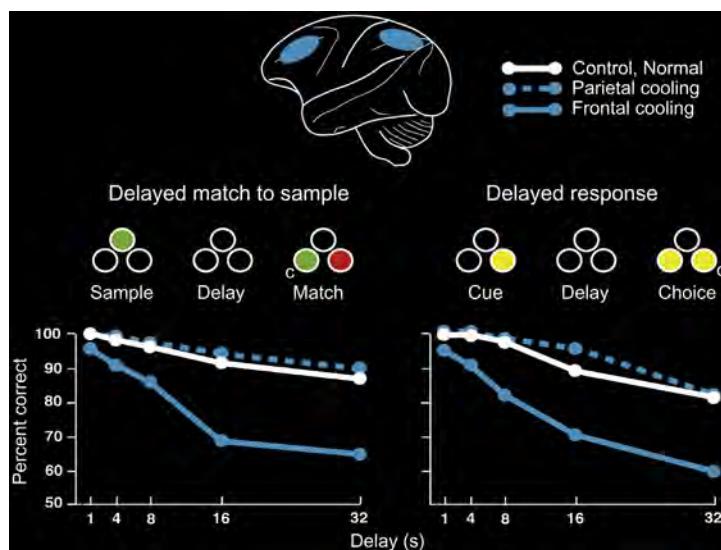
### A. Prefrontal Cooling on Delay Tasks

In monkeys that had been subjected to a frontal lobectomy in one hemisphere and the implantation of a cooling chamber on the lateral prefrontal cortex of the other hemisphere, [Shacter and Schuckman \(1967\)](#) showed a detrimental effect of prefrontal cooling – over the

3–27°C range – on performance of delayed response. Subsequent investigations in our laboratory, using monkeys with bilateral Peltier cooling probes, dealt with the effects of prefrontal cooling on several behavioral variables related to the performance of delay tasks (reviews in Fuster, 1975, 1995). Fuster and Alexander (1970) showed that cooling of the prefrontal cortical convexity induced a marked delayed-response deficit that, in conformity with ablation studies, was greater during bilateral cooling than during unilateral cooling. A relationship was found between laterality of cooling and laterality of errors (more errors were found when the cue was on the side opposite to that of the cooling) but that relationship was not easily attributable to either sensory or motor deficit, since it was apparent only on trials with long delays. No deficit appeared on cooling parietal cortex. The effects of prefrontal cooling, unlike those of ablation, were

completely reversible and could be replicated over many months without evidence of weakening. The brain in which the prefrontal cortex was reversibly and intermittently inactivated did not seem to develop compensatory mechanisms, probably because potential surrogate structures were not given an adequate chance to take over.

The author, in collaboration with Bauer (Fuster and Bauer, 1974; Bauer and Fuster, 1976), showed that the cooling of a large portion of the prefrontal convexity had as much of a deleterious effect on delayed matching-to-sample as on delayed response. Moreover, that effect was delay dependent: it was minimal with brief intratrial delay and increased as a function of the duration of that delay (Figure 4.6). This relationship with delay, which is demonstrated more convincingly by reversible lesions than by ablation, is in good accord with the idea that a prefrontal lesion interferes with



**FIGURE 4.6** Effects of bilaterally cooling (to 20°C) parts of lateral prefrontal cortex or posterior parietal cortex (blue areas) on the performance of two delay tasks. Abbreviation: c, correct response. Cooling was applied throughout blocks of trials (sessions) with delays of varying length. Cooling sessions alternated with control sessions at normal cortical temperature. Note that prefrontal, but not parietal, cooling induces in both tasks deficits in correct response that increase with the length of intratrial delay.

a memory function that has a temporal decay. However, the noted relationship is not by itself conclusive proof of that, because the ceiling at the top of the correct performance scale (100%) may distort what could otherwise be a parallel course of cooling and normal curves. This ceiling effect may enhance, if not completely account for, the statistically demonstrable interaction between cooling and delay. In any event, the correct response data, although not proving the working-memory hypothesis, are fully consistent with it, and so are the reaction time data at the choice, which also show a greater effect of cooling (longer reaction time) as a function of delay. Indeed, under cooling, reaction time at the choice can be expected to be longer after longer delays, as working memory is particularly taxed by those delays.

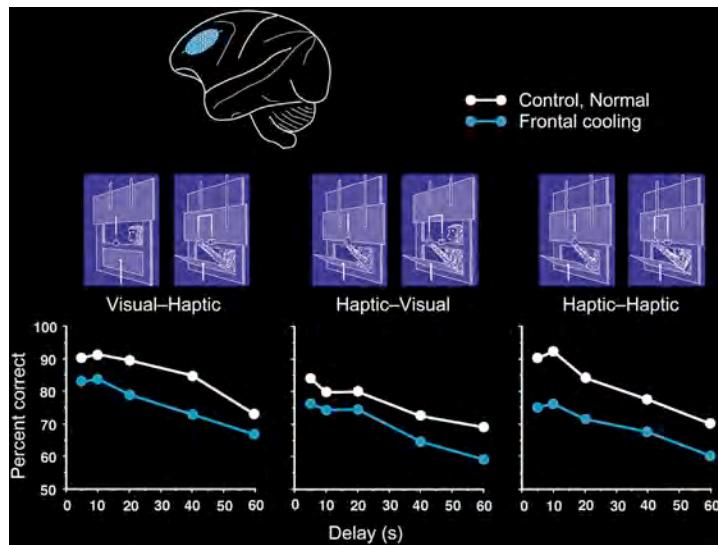
The similarity of cooling effects on spatial delayed response and on a non-spatial delayed-matching task suggests a supramodal role of the lateral prefrontal cortex in working memory ([Bauer and Fuster, 1976](#)). However, a functional dissociation is still possible within the relatively large portion of the prefrontal cortex that is cooled. This dissociation was borne out in selective ablation studies by [Passingham \(1975\)](#) and [Mishkin and Manning \(1978\)](#). They showed that delayed matching was mostly disturbed by lesions of the inferior convexity, whereas delayed response, as previously demonstrated by other ablation experiments, was especially vulnerable to lesions in the sulcus principalis. Both regions were cooled together in our experiments. Yet the dissociation of these regions by certain factors, such as the spatial versus non-spatial nature of the memorandum, does not invalidate the hypothesis of a common function of the two regions in working memory. Although aptly and pointedly amending our conclusions, [Mishkin and Manning \(1978\)](#) explicitly acknowledged the possible mnemonic involvement of the lateral prefrontal cortex as a whole.

That was the main conclusion from our cooling experiments, supported by the parametric

analysis that reversible lesions conveniently allow. However, we cannot ignore the possibility that, in the lesion of the inferior prefrontal convexity, the critical factor is neither the non-spatial character of the memorandum nor memory *per se* but, as those authors pointed out, the lack of control of internal interference, which can result from lesions of ventral prefrontal cortex and could disrupt delay tasks by itself (see above, Inhibitory Control).

A pharmacological study ([Bauer and Fuster, 1978](#)) showed that the behavioral effects of dorsolateral prefrontal cooling could be mimicked or potentiated by amphetamine. A similar interaction has been reported with prefrontal ablations ([Miller, 1976a](#)). The reasons behind that finding are not clear, but catecholamine receptors are so prevalent in the prefrontal cortex, as discussed in Chapter 3, that it is not difficult to understand why a drug that alters or interferes with catecholamine metabolism could significantly affect prefrontal function and its behavioral manifestations.

More recent investigations further support the supramodal nature of the working-memory deficit from cooling the prefrontal cortex. In an auditory-visual delay task, lateral prefrontal cooling interfered reversibly with the memorization of auditory cues ([Sierra-Paredes and Fuster, 2002](#)). In another study ([Shindy et al., 1994](#)), monkeys were trained in haptic and cross-modal (haptic-visual and visual-haptic) delay tasks ([Figure 4.7](#)). One task required that the animal sample an object by sight and then, after a delay, recognize it by touch; another task required tactile sampling and visual recognition; a third task required tactile sampling and tactile recognition. All three tasks were adversely and reversibly affected by bilateral prefrontal cooling. Cooling of a posterior parietal region, away from somatosensory cortex, did not induce deficits in any of the tasks. These results (1) show that the lateral prefrontal cortex takes part in cross-temporal and cross-modal integration of behavior; (2) confirm the



**FIGURE 4.7** *Top:* Diagram of prefrontal area cooled (bilaterally). *Center:* Three delayed matching tasks with visual and tactile stimuli. In the first task (left), the animal visualizes an object, remembers its shape through the delay, and chooses it blindly by touch. In the second task (middle), the animal samples an object by touch and, after the delay, chooses it from two objects presented visually. In the third task (right), the object is sampled and chosen only by touch. *Bottom:* Effects of bilateral prefrontal cooling on the three tasks. (From Shindy et al., 1994, with permission.)

role of this cortex in visual working memory; and (3) show that this cortex is also involved in haptic working memory.

Yet another cooling study (Quintana and Fuster, 1993) confirmed the role of lateral prefrontal cortex in both spatial and non-spatial working memory, while supporting the specific role of posterior parietal cortex in spatial working memory. In this study, one or the other cortex was cooled bilaterally in animals trained to perform two tasks in alternation: (1) a conditional position discrimination task with delay; and (2) delayed matching-to-sample. The cues were visual in both tasks (colors used in the first task as signals for direction of a manual response after a delay, and in the second task as samples for color matching after a delay). Whereas prefrontal cooling impaired both the spatial and the non-spatial task, as in earlier experiments with Bauer, parietal cooling impaired only the spatial task.

In summary, these cooling experiments substantiate the role of the lateral prefrontal cortex in the making of the temporal behavioral structure of the delay-task trial. With the advantages of reversibility and finer parametric analysis than ablation allows, the cooling method gives further credence to the hypothesis of working memory as a critical prefrontal function at the service of the temporal organization of behavior.

## VII. DEVELOPMENT

In the course of ontogeny, the functions of the prefrontal cortex in behavior develop gradually, and therefore this cortical region is not fully committed to them until well after birth. Evidence of this is found in the behavioral effects of prefrontal lesions at various stages of development. The analysis of these effects indicates that, early in life, the integrity of at least

some parts of the prefrontal cortex is more dispensable for certain forms of behavior than it is in the adult animal.

For example, the typical deficit in learning and retaining delay tasks that primates exhibit after prefrontal ablation does not occur if the lesion is made at an early age. Accordingly, if made before the animal is 2 years old, ablations of the lateral prefrontal cortex do not impede the learning and performance of delay tasks, whereas later ablations of the same cortex do (Akert et al., 1960; Harlow et al., 1964; Tucker and Kling, 1967; Kling and Tucker, 1968; Goldman et al., 1970b; Goldman, 1971; Malkova et al., 2000). This finding has been corroborated by reversible functional depression of the prefrontal cortex at different ages: the reversible delay-task deficit from prefrontal cooling is also age dependent (Goldman and Alexander, 1977; Alexander and Goldman, 1978; Alexander, 1982). One study showed that, in the monkey, prefrontal ablation before birth does not subsequently induce an appreciable behavioral deficit (Goldman and Galkin, 1978).

The sparing of delay-task performance after early prefrontal lesions has also been substantiated in the rat. If made before the animal is approximately 25 days old, ablations of the entire prefrontal cortex – or only its dorso-medial aspect – induce no deficits in performance of delay tasks, even though they do so in the adult animal (Kolb and Nonneman, 1978; Nonneman and Kolb, 1979; Kolb and Whishaw, 1981; Nonneman and Corwin, 1981; Kolb et al., 1996). This sparing of delay-task performance in the young rat does not seem to be attributable to a surrogate role of residual anterior neocortex or an intact thalamus after the lesion (Corwin et al., 1982; Vicedomini et al., 1982).

In addition to cognitive defects, other behavioral changes resulting from prefrontal ablations are age dependent. The well-known symptom of hyperactivity has not been observed in young monkeys (less than 2 years old) that have undergone the operation

(Harlow et al., 1964; Franzen and Myers, 1973). In both the rat (Kolb and Whishaw, 1981) and the cat (Villablanca et al., 1978), prefrontal hyperactivity also seems to be age dependent.

The emotional difficulties of the frontal monkey, like its cognitive troubles and hyperactivity, are related to the age at which the lesion is performed. Infant monkeys do not show the emotional and social deficit that adults show (Franzen and Myers, 1973; Bowden and McKinney, 1974). The critical age beyond which frontal ablation results in the appearance of the deficit seems to be, here again, about 24 months. Similarly, in the rat, early prefrontal lesions seem to cause no deficits in conditioned emotional behaviors (Brennan and Wisniewski, 1982). However, these early lesions do not spare the rat from abnormal aggressive and defensive behaviors or from a variety of deficits in other species-typical behaviors, such as feeding, hoarding, and nest building, abnormalities and deficits that the adult prefrontal rat commonly exhibits (Kolb and Nonneman, 1976; Kolb and Whishaw, 1981; De Bruin et al., 1983; Kolb, 1987; Kolb et al., 2004), nor are species-typical behaviors spared in the young hamster with prefrontal ablation (Kolb and Whishaw, 1985).

The reasons behind the early-age immunity from many of the consequences of prefrontal ablation are poorly understood. Presumably, in early life other cerebral structures can and do play the role that the prefrontal cortex later assumes in behavior. In any event, the development of that part of the cortex into an essential substrate for behavior is probably closely dependent on the maturation of its neural elements, including the growth of its intrinsic and extrinsic connections, as well as the maturation of its chemical substrate. Both aspects of maturation have been discussed in previous chapters, but here we shall briefly refer to them again inasmuch as morphological and chemical development has been shown to be correlated with behavioral development, at least in the primate.

As noted in Chapter 2, ontogenetically, as well as phylogenetically, the lateral convexity of the prefrontal cortex of the adult primate has developed morphologically to a greater degree than its orbital region. The orbital cortex seems to have reached full structural development early in life. It is therefore not surprising that orbital lesions induce behavioral impairment at an earlier stage in life than do lesions of the dorsolateral cortex (Goldman et al., 1970a, 1970b; Bowden et al., 1971; Goldman, 1971, 1972; Miller et al., 1973). It appears that the orbital cortex becomes functionally committed before the dorsolateral cortex does.

Prefrontal ablations performed on rhesus monkeys before birth failed in one study to induce the degeneration of neurons in the mediodorsal thalamic nucleus that comparable lesions induce in the adult (Goldman and Galkin, 1978), as if connections between the thalamus and the prefrontal cortex had not yet developed when the lesion was produced. This sparing of the mediodorsal nucleus may have something to do with the sparing of function. Even closer correlations between the development of prefrontal function and the development of prefrontal connections are highlighted by another study, which addressed the maturation of efferent fibers from the prefrontal cortex to the caudate nucleus (Johnson et al., 1976). This study showed that the degree of degeneration of prefrontal–striatal fibers that can be observed after ablation of the prefrontal cortex depends on the age at which the ablation has taken place. In accord with the behavioral findings above, 2-month-old monkeys show little postablation degeneration, whereas 2-year-old monkeys show a large amount of it. This age-dependent difference in fiber degeneration suggests a difference in the degree of maturation of prefrontal–striatal fibers in the two groups of animals. Differences of a similar kind have been observed in the degeneration of intracortical (Kemper et al., 1973) and efferent (Kuypers, 1962) connections of the motor cortex.

For the development of the prefrontal substrate of behavior, the maturation of cortical enzyme systems (Farkas-Bargeron and Diebler, 1978), gonadal hormones (Kolb et al., 2004), and neurotransmitters may be as important as the maturation of neural connections. Especially critical in this respect is probably the maturation of monoaminergic systems, which are well represented in the prefrontal cortex and were discussed in Chapter 3. It is noteworthy that the increase in catecholamine concentration and terminals in the prefrontal cortex seems to parallel the ontogenetic increase in the importance of this cortex for behavior. Two rat studies suggest a possible role of neurotransmitters in the functional sparing and recovery after prefrontal ablation. One shows that the sparing of a spatial learning task in young frontal animals is abolished by norepinephrine depletion (with 6-hydroxydopamine), indicating that such depletion prevents other brain structures, perhaps posterior cortical regions, from compensating for the loss of prefrontal function (Sutherland et al., 1982). The other study, also in frontal animals, reports that the recovery from the delayed alternation deficit is enhanced by transplants of frontal cortical tissue (Kesslak et al., 1986); one of the possible explanations for this phenomenon is the replacement of monoamines, their terminals, or their receptors as a result of the transplant.

Because they are mammals with relatively rapid development and a short lifespan, rodents are exceptionally suitable animals for the study of the anatomical, chemical, and cognitive correlates of prefrontal development and the influences on that development of prenatal as well as postnatal environmental factors. Kolb et al. (2012) reviewed most of the relevant literature on this subject. The thrust of their review is to highlight the evidence that sensory stimulation, stress, hormones, and social experiences all play critical roles in the neurobiology of the prefrontal circuitry. Separate publications emphasize the overriding importance of

stress from parental separation on the development of the prefrontal cortex and the cognitive and social functions that it supports. Of special interest in this respect is the study by

**Mehta and Schmauss (2011)**, who tested the effects of early parental separation on two different inbred strains of mice, one stress resilient and the other stress susceptible. Whereas parental separation did not substantially affect the performance of the former group on a variety of cognitive tests, it did affect adversely the performance of the second group in tasks that test functions especially vulnerable to prefrontal dysfunction, notably working memory and shifts of attentive set.

An earlier review (**Sullivan and Brake, 2003**) surveyed the role of early prefrontal developmental insult, both prenatal and postnatal, on a variety of behavioral manifestations that are typical of attention deficit/hyperactivity disorder (ADHD) in humans, especially hyperactivity, impulsivity and distractibility. As a result of their survey of the rodent data in that respect, the authors conclude that a developmental malfunction of the prefrontal cortex, especially on the right (remarkable laterality in the rodent), could play a key role in the pathogenesis of ADHD. They tie their conclusion to the neurochemical evidence of a lag in the development of frontostriatal dopaminergic systems that are at the center of arousal and attention mechanisms. They, as well as the authors of a subsequent study (**Jezienski et al., 2007**) extend their reasoning to comment on the rationale (or dangers) of using certain drugs, such as methylphenidate, that have been found to be of some benefit in human ADHD.

A study by **Baarendse and colleagues (2013)** provides further evidence of the deleterious effect of early social isolation of the rat (postnatal day 21–42) on the development of prefrontal dopamine systems. Especially vulnerable appear to be the pyramidal neurons of the medial prefrontal cortex. The laggard maturation of their neurochemical connectivity

is accompanied by poor control of impulsivity and other emotional and cognitive disorders reminiscent of human developmental pathology.

## VIII. AGING

As a consequence of the involution of the morphological and chemical substrates of the prefrontal cortex, discussed in Chapters 2 and 3, a gradual deterioration of its behavioral functions occurs with advancing age. The evidence for this deterioration, in animals, comes from three sources: (1) studies showing that older animals cannot perform behaviors dependent on prefrontal cortex (e.g., delay tasks) as efficiently as young animals; (2) studies showing that the behavior of old animals is more vulnerable to prefrontal injury than that of young animals; and (3) studies showing correlations between age-dependent cognitive decline and alterations in the microscopic structure or neurochemistry of the prefrontal cortex.

Old rats learn new tasks more slowly than young rats. This has been shown particularly with spatial tasks, which the animal with prefrontal lesion has trouble learning, whether these tasks have a short-term memory requirement or not (**Gage et al., 1984; Ingram, 1985; Fischer et al., 1987; Rapp et al., 1987**). Furthermore, old rats with lesions of prefrontal cortex show greater deficits than young rats in maze-learning and in performance of spatial delay tasks (**Dunnett et al., 1988; Winocur and Moscovitch, 1990; Winocur, 1992; Menes et al., 1993**).

Comparable phenomena can be observed in the monkey. In this animal, aging has also been shown to lead to poorer performance of working-memory tasks (**Bartus et al., 1978; Presty et al., 1987; Moss et al., 1988; Bachevalier et al., 1991; Rapp and Amaral, 1991**). However, attempts to correlate the behavioral decline with the morphological involution of the

prefrontal cortex or with the appearance of pathological malformations associated with aging (e.g., amyloid deposits) have met with only limited success (Cork, 1993). Plaques and cell losses do develop in the prefrontal cortex as a function of age, but it is difficult to establish a close correlation between their development and the deterioration of behavioral performance. Nonetheless, despite considerable individual variability, it is possible to correlate in general terms the age-related decline of prefrontal functions with the signs of morphological and chemical aging of the prefrontal cortex.

In the recent past, a number of important and rigorous investigations have substantiated the cognitive deficit of older animals and its relationships to alterations in the fine structure and neurobiochemistry of the prefrontal cortex. Most significant in this respect are the contributions of researchers at the Mount Sinai School of Medicine under the direction of John Morrison and at Yale University under Amy Arnsten.

Most prominent among the findings of these investigations is the age-dependent degradation of the minicolumnar structure of the prefrontal cortex. That degradation is accompanied, and to some degree caused, by a dramatic diminution, indeed degeneration, of synaptic dendritic spines, especially in layers II and III (Bloss et al., 2011, 2013). That spine loss is accentuated by stress, and is somewhat reversible in the young adult but not in the old animal (Bloss et al., 2011). This reflects an age-dependent loss of synaptic plasticity (Burke and Barnes, 2006). Nonetheless, animals with successful aging and relatively preserved cognitive functions reveal a preservation of basic electrical synaptic manifestations. By contrast, animals with severe spine loss and cognitive decline show a marked imbalance of inhibitory signals at the synaptic level (Bories et al., 2013).

In the monkey, when the spine loss affects the inferior lateral convexity of area 46, it is more deleterious for cognitive functions,

especially working memory, learning, and memory, than when it affects the dorsal area 46 (Cruz et al., 2004). In any case, as noted in Chapter 2 (Figure 2.12), aging monkeys by and large show a marked depression of sustained working-memory unit activity in their prefrontal cortex (Wang et al., 2011). As noted by Arnsten and her colleagues, and by others (Moore et al., 2005), the electrophysiological manifestations of age-dependent cognitive deficit reflect not only morphological changes at the synaptic level but also deficits in monoamine neurotransmitter systems in the prefrontal cortex (especially norepinephrine and dopamine). Not to be ignored is the possibility that the cognitive decline may be related to trophic factors, such as defects in the regeneration of neurons (Gould et al., 1999) and the availability of gonadal hormones to prefrontal glia (Finley and Kritzer, 1999).

## IX. SUMMARY

Lesions of the prefrontal cortex elicit characteristic behavioral abnormalities. These fall into three major categories: (1) disorders of motility; (2) disorders of emotion and social behavior; and (3) deficits in performance of cognitive tasks, notably delay tasks. Some of the abnormalities are closely interrelated and denote the alteration of common functions, such as attention.

Prefrontal ablations tend to cause hyperactivity. This effect has been most consistently observed in the macaque with orbital lesion. Much of the resulting hyperactivity is attributable to the inordinate reactivity of the animal to external stimuli. Therefore, it is related to and accompanied by distractibility and poor attentive capacity. Hyperactivity reflects the apparent lack of an effective function of inhibitory control based mainly in ventral prefrontal cortex.

Large ablations of the prefrontal cortex generally result in the impoverishment of

emotional life and social isolation of the animal. Certain prefrontal lesions involving medial or orbital prefrontal cortex have been seen to induce, especially in carnivores, behavioral changes suggesting disinhibition of aggression and hunger drives. In the monkey, orbital lesions lead to decreased aggressiveness and a tendency to avoid threatening situations. Dorsolateral lesions, on the other hand, may lead to increased aggressiveness, often accompanied by blunted emotional expression and communication. This deficit may be based largely on a cognitive impairment.

Among the most consistent cognitive impairments of the animal with prefrontal lesion are those of attention. Such impairments permeate and compound the disorders in other cognitive and emotional domains. Basically, the attention deficit is of two kinds: (1) difficulty in concentrating sustained attention or preparatory set (as commonly observed in the performance of tasks that require working memory, i.e., delay tasks); and (2) difficulty in inhibiting external or internal stimuli that interfere with present behavior. In primates, the deficit in sustained attention – and working memory, which is a form of attention – results chiefly from lesions of lateral prefrontal cortex, whereas the deficit in inhibitory control results chiefly from lesions of orbital cortex.

The deficit in discrimination tasks is largely related to task formalities and not the nature of the stimuli to be discriminated (discriminanda). It is most evident in successive discrimination tasks. The deficit reflects the inability of the animal to suppress or inhibit interference from competing tendencies, including internal drives and external stimuli unrelated to the task that the animal is performing. In the monkey, the deficit is most readily induced by lesions of ventral (orbital) cortex and cortex of the inferior prefrontal convexity.

The prefrontal deficit in delay tasks is mainly a deficit in working memory and reflects a more general difficulty in integrating

behavioral acts that are based on temporally separate events – which in large part depends on working memory. The deficit is most consistently induced by lesions of the dorsolateral cortex of the monkey or its homologs in other species. Reversible cryogenic lesions reveal the supramodality of the deficit, which occurs regardless of the sensory modality of the stimulus determining the delayed motor response. Inasmuch as the temporal discontinuity imposed by the intratrial delay is an essential factor for the appearance of the deficit, the prefrontal cortex is implicated in working memory.

In general terms, lesion studies indicate that the cortex of the dorsal and lateral prefrontal surface (medial in the rat, anterior-lateral in carnivores) is primarily involved in cognitive aspects of behavior. The rest of the prefrontal cortex, medial and ventral, appears to be primarily involved in affective and motivational functions. In addition, these orbitomedial regions are implicated in the inhibitory control of external and internal influences that interfere with attention and purposive behavior.

When performed early in the life of the animal, lesions of the prefrontal cortex fail to have the characteristic effects on behavior that they have in the adult. Thus, following early lesions, general motility, emotional behavior, and cognitive tasks (such as delayed response) are spared from deficits and abnormalities. This is true in young primates, carnivores, and rodents. The reason for that early behavioral resistance to prefrontal lesion may be that, in the young organism, the prefrontal cortex has not yet reached functional maturity. Applying similar reasoning to the behavioral results of selective prefrontal lesions in monkeys of various ages, it can be inferred that, in the primate, the orbital cortex matures earlier than the dorsolateral cortex.

The aging of the prefrontal cortex is accompanied by diminishing capacity to learn and perform cognitive tasks that depend on the functional integrity of this cortex, especially

working memory tasks. This has been best demonstrated in rodents and monkeys. Prefrontal aging is accompanied by attrition of dendritic spines and a general deterioration of monoamine transmission systems. These events are responsible for the gradual loss of synaptic plasticity and cognitive support of executive functions that characterize normal aging.

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# Human Neuropsychology

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## I. INTRODUCTION

Lesions of the prefrontal cortex produced by disease or trauma provide helpful insights into the functions of this cortex, even though they occur unpredictably and without investigative logic. Indeed, the arbitrariness of those lesions

aggravates the methodological problems encountered in ablation studies with animals. Nonetheless, clinical research on the prefrontal cortex is of unique value, because only human subjects can contribute phenomenological depth to the cognitive and emotional disorders from prefrontal damage. This research seems

more imperative if we consider that the prefrontal cortex has attained its maximum phylogenetic development in the human brain.

Mainly for heuristic reasons, this chapter will first enumerate the functions that are demonstrably most affected by prefrontal lesion in the human. We will describe the way in which each function is altered, attempting wherever possible to identify the topography of the lesion or lesions most commonly or profoundly leading to the alteration. In a later part of the chapter (Prefrontal Syndromes), we will describe the group of symptoms and manifestations (i.e., the syndrome) most commonly resulting from substantial lesion of each of the major prefrontal regions: orbital, medial, and lateral. In no case will the description be intended to infer a specific function for any prefrontal area. This review of the literature is intended to be factual and data based, and also intended to infer from it the *dominant* – not necessarily exclusive – roles of particular prefrontal areas in particular neuropsychological functions. Finally, the chapter will discuss the principal issues concerning the development and involution of human prefrontal functions, as can be inferred from the effects of prefrontal lesion at different ages.

## II. HISTORICAL BACKGROUND

The history of clinical frontal lobe study is long and rich. An often-cited historical landmark is the case of Phineas Gage, a New England railroad construction worker who, around the mid-nineteenth century, was accidentally struck by a pointed iron bar projected by an explosion. The bar penetrated his face obliquely from below and through the left orbit, traversing the base of the skull and inflicting massive damage to his frontal lobes, apparently destroying completely the left orbitomedial prefrontal cortex (Harlow, 1848; Damasio et al., 1994). Aside from the gruesome aspects

of the accident and the incredible survival of the victim (for 12 years), what made the case unique was Harlow's thorough description of the changes that Gage's personality underwent as a result of the injury (Harlow, 1868; Blumer and Benson, 1975; Damasio et al., 1994). These changes were so remarkable that, in the eyes of his friends, Gage was "no longer Gage." Much changed from what he was before the accident, he now exhibited, among other things, inordinate profanity, vacillation, capriciousness, poor planning, and uncontrolled impulsivity. "A child in his intellectual capacity and manifestations, he has the animal passions of a strong man," Harlow wrote of him many years after the injury (1868).

Unfortunately, the scientific value of that famous case, as of many others, is severely limited because of the irregularities of the lesion, the concomitant damage to brain structures other than the frontal cortex, and the subsequent foci of irritation around the injured area. Generally more instructive are cases of discrete trauma resulting from war injury, as are those studied after both World Wars and the Vietnam War (Choroschko, 1923; Feuchtwanger, 1923; Kleist, 1934; Goldstein, 1942; Luria, 1966, 1980, 1970; Grafman et al., 1986). Also informative are the circumscribed frontal lobe tumors and lobectomies for the removal of tumors and epileptic foci (Brickner, 1934; Rylander, 1939; Angelergues et al., 1955; Milner, 1964). Another source of useful data is a large category of vascular, infectious, and degenerative processes that tend to affect predominantly the frontal lobes. Incipient cases are especially valuable in that they best reveal the characteristic, though subtle, manifestations of discrete prefrontal damage. Also of value are the studies of patients who had undergone psychosurgery of the frontal lobe, which was introduced in the 1930s (Mettler, 1949; Freeman and Watts, 1950; Greenblatt et al., 1950; Greenblatt and Solomon, 1953; Valenstein, 1990). However, the data from those psychosurgery cases can be assessed only

with great difficulty, because most patients submitted to frontal lobotomy or leukotomy suffered from pre-existing personality disorders that were often of long standing and questionably alleviated by the procedure.

Excellent case reports of patients with frontal damage and reviews of the clinical frontal-lobe literature have been written in the past century (e.g., Feuchtwanger, 1923; Brickner, 1934; Rylander, 1939; Denny-Brown, 1951; Ajuriaguerra and Hécaen, 1960; Luria, 1966, 1980; Hécaen and Albert, 1975, 1978; Stuss and Benson, 1986). At the same time, the common inadequacies of sampling, controls, and measurement have received insightful criticism (Hebb, 1945; Reitan, 1964; Teuber, 1964; Kertesz, 1994). Despite the difficulties inherent in clinical research, there is now considerable agreement on the essential symptomatology of prefrontal dysfunctions in the human. Depending to some extent on the location of the frontal damage, its manifestations may be found predominantly in the behavioral sphere, the cognitive sphere, or the affective sphere. Nevertheless, any prefrontal syndrome usually consists of a mixture of symptoms in all three.

Before proceeding with the clinical methodology, it is appropriate to re-emphasize its limits. In the past few decades, formal psychological tests have been added to that methodology. This addition has contributed parametric power to the testing of various psychological functions. Clearly, however, on the basis of lesion studies alone it is impossible to identify any specific function of the prefrontal cortex or any of its parts. The reason for that is because neither the prefrontal cortex as a whole nor any of its parts plays a unique specific function by itself. Cortical function, in general, is determined and defined by functional architecture, that is, by inputs, outputs, and the intrinsic connective substrate. In primary sensory and motor areas, that architecture is to some extent reducible to columns and modules with their discrete inputs and outputs, and so are their

functions. In the cortex of association, including the prefrontal cortex, however, the architecture is made of large, overlapping, distributed, and associative networks with multiple inputs and outputs of distant origin or destination. Most of those networks are "individualized," made by personal experience in accord with Hebbian principles (see Chapter 8).

Thus, in association cortex, including prefrontal cortex, functions are also to some extent "individualized," although within broad anatomical constraints: the prefrontal cortex as a whole is cortex dedicated to action in the widest sense of the word – behavioral, skeletal, ocular, vegetative, and cognitive action. In that broad sense, the prefrontal cortex in its entirety is executive cortex, but its parts can rarely be assigned any particular executive function (area 8 is possibly an exception, for eye movements in executive visual attention). At most, as we shall see, the lateral prefrontal cortex is predominantly, but not exclusively, involved in time integrating and organizing functions, such as working memory. On the other hand, the medial and ventral prefrontal cortices are predominantly involved in such emotional and social functions as the control of impulses, mood, and empathy. However, any attempt to localize any such function, exclusively and specifically in one prefrontal area or another, is implausible. Some published interpretations of the results of prefrontal lesion, in the animal as in the human, are distressingly reminiscent of phrenology.

### III. AFFECT, EMOTION, AND SOCIAL BEHAVIOR

Ever since the publication of the case of Phineas Gage (Harlow, 1868), it has been known that frontal lobe injury can alter not only the cognitive aspects of the personality but its affective and emotional aspects as well. Yet, to date, that knowledge has remained by and

large shrouded in speculation. One reason for this is the difficulty in defining and objectifying abnormalities of affect and emotion (Stuss and Benson, 1986); another is the difficulty in dissociating those abnormalities from cognitive disorders to which they may be secondary. If we add to these problems the vagaries of some published attempts at cerebral localization of certain non-cognitive functions that defy measurement, the sources of the confusion on this issue become glaring.

Many early studies pointed out the variability in the affective manifestations of prefrontal lesions. Some of those studies (Holmes, 1931; Greenblatt et al., 1950), however, emphasized two such manifestations that are most consistently observed in frontal cases, though rarely if ever together: apathy and euphoria. The separate prevalence of these two symptoms provides some support for the distinction of prefrontal syndromes with different disorders of affect, different frontal pathology, or different behavioral manifestations (see Prefrontal Syndromes, below).

### A. Apathy

Apathy usually accompanies the same cluster of symptoms that later will be encountered when dealing with disorders of attention and general motility. It usually results from extensive lesions of the lateral prefrontal convexity (Paradiso et al., 1999) but not necessarily circumscribed to it. It may also be present with medial lesions (see below). The patient shows low awareness, lack of initiative, and hypokinesia. In the affective sphere, the hallmark of the disorder is the generalized blunting of affect, sometimes depression, and weak emotional responses. It is a condition somewhat similar to that which has been described in frontal monkeys (see Chapter 4). The patient's underlying mood is frequently one of profound indifference, and so is his or her attitude toward others (Holmes, 1931; Greenblatt et al., 1950; Stuss and

Benson, 1986; Cummings, 1993). The apathy of the frontal patient can be clinically mistaken for neurotic or psychotic depression, especially because it is accompanied by some of the noted disorders of attention and motility, which are also frequent concomitants of depression. Accordingly, the condition has been called *pseudodepression* (Blumer and Benson, 1975).

Apathy is antithetical not only to depression but also to anxiety. Thus, it is not difficult to understand why the apathy produced by frontal psychosurgery could be used with some practical success for the surgical treatment of severe pain and anxiety (Valenstein, 1990). Apathy is probably at the root of the beneficial effects of leukotomy and lobotomy on psychiatric conditions such as schizophrenia and obsessive-compulsive disorder. Yet, because of the variability in affective changes induced by prefrontal lesion, including leukotomy and lobotomy, the effects of those operations are too unpredictable for their use as standard therapeutic procedures. For this and other reasons, the procedures have been almost completely abandoned, even for the symptomatic treatment of psychiatric conditions.

### B. Depression

Despite the caveat in the previous section, it has become increasingly evident that depression proper, that is, the phenomenological experience of depressed mood, can be a result of prefrontal lesions, especially those involving anterior (Stuss and Benson, 1986; Starkstein and Robinson, 1991) and lateral (Paradiso et al., 1999) aspects of the frontal lobes. A number of studies concluded that left lesions are more likely than right lesions to lead to depression (Gainotti, 1972; Robinson and Benson, 1981; Robinson and Price, 1982; Robinson et al., 1984; Bely, 1985; Rogers et al., 1998; Paradiso et al., 1999). Several of these studies also show a synergistic interaction between prefrontal injury and risk factors for the affective disorder, such

as a family history of endogenous depression. At the same time, the postmortem neuropathology of depressed patients indicates a generalized prefrontal diminution of neuronal size (Cotter et al., 2005). Imaging studies point to a prevalence of subcortical vascular lesions – especially orbitofrontal – in late-onset depressed patients (Macfall et al., 2001) and of abnormal activation in depression accompanied by anxiety (Drevets, 2000, 2003). The role of injured prefrontal, especially orbitofrontal, cortex in depression and bipolar illness is clearly consonant with what we know about the dysregulation of neurotransmitter systems, notably serotonin, in patients with those disorders (see Chapter 3).

In any event, caution should be exercised before assuming that depression due to frontal injury is a primary mood disorder and not secondary to disorders of cognitive functions. Not uncommonly, patients with cortical pathology develop depression secondarily, as they become aware of the deterioration of their mental faculties. This is particularly likely to occur in subjects with a history of intellectual achievement, unless apathy precedes and pre-empts the depression.

### C. Euphoria

Excessive euphoria, an abnormal elevation of mood, is also common in frontal pathology (Holmes, 1931; Kleist, 1934; Rylander, 1939; Greenblatt et al., 1950; Lishman, 1968; Grafman et al., 1986). It is not invariably present in all cases of orbital lesion but is a striking feature of a substantial proportion of them. It, too, seems to have served therapeutic aims; it was a frequent result of orbitofrontal leukotomy (Rylander, 1939) and thus served as a useful measure to treat depression and stupor. The euphoria of the frontal patient, which may meet diagnostic criteria for mania, is neither constant in time nor always characterized by a pure feeling of elation. Rather, it usually occurs

in sporadic or recurrent fashion and resembles the affect of the hypomanic state, with its nervous and irritable, sometimes paranoid, quality. It is usually accompanied by a peculiar kind of compulsive, shallow, and childish humor that has been called moria or *Witzelsucht*. Along with euphoria, irritability, and puerilism, the patient with orbitofrontal damage usually shows the two symptoms discussed below in the context of disorders of attention and motility: distractibility and hyperactivity (or hyperreactivity). Here the parallel is again evident with the consequences of similar lesions in the monkey (see Chapter 4). Nonetheless, the typical manic syndrome of bipolar affective disorders cannot be attributed to orbitofrontal pathology. A thorough investigation of acute manic patients shows clear differences between their neuropsychological profile and that of orbitofrontal patients (Clark et al., 2001).

### D. Motion and Emotion

Lesions of the prefrontal cortex, even if they do not encroach on premotor or motor cortex, can induce disorders of general motility. Two broad categories of prefrontal motor disorders can be distinguished in the human: disorders of general spontaneous motility and disorders of goal-directed motor behavior. The first are essentially of two kinds: hypokinesia and hyperkinesia.

Hypokinesia is characterized by a general diminution of spontaneous motor activity. It is common in patients with large dorsolateral prefrontal lesions. The symptomatology of such patients usually includes apathy and lack of initiative, together with a related diminution of reactivity to external stimuli and events. Frontal hypokinesia (Meador et al., 1986; Heilman and Watson, 1991) may vary greatly in its degree and manifestations, ranging from a certain “aspontaneity” (Kleist, 1934), which affects mainly language and social behavior, to the akinetic-abulic syndrome with mutism

(Luria, 1966, 1980); the latter syndrome, or variations of it, may result not only from extensive dorsolateral injury but from some orbitomedial lesions as well (Benson and Geschwind, 1975; Damasio and Van Hoesen, 1983; Meador et al., 1986; Stuss and Benson, 1986).

In the human, as in the non-human primate, excessive and aimless motility or hyperkinesia is a common consequence of orbitofrontal lesion. Some evidence from lobotomies performed at different frontal planes suggests that hypermotility, or simply restlessness, is caused by involvement of the posterior orbital cortex (Meyer and McLardy, 1948; Fulton, 1951). The symptom is usually accompanied by hyperreactivity and a variety of other symptoms that also commonly result from orbital-cortex damage, such as instinctual disinhibition, distractibility, hypomania, and irritability.

Disorders of goal-directed motor behavior usually coexist with derangements of general motility such as those just described, but are not caused by them. Instead, these disorders are caused by cognitive dysfunctions that impede the initiation and temporal organization of action. Whether as a result of a disorder in general motility or of a cognitive deficit, the patient with even minor prefrontal damage tends to show few deliberate actions. He or she lacks initiative (Penfield and Evans, 1935; Hutton, 1943; Heilman and Watson, 1991). Yet, at the same time, the patient may show an increase in certain automatic behaviors. The frontal patient, like the frontal animal, tends to perseverate – to repeat old patterns of behavior even in circumstances that demand change. Repetitious routine seems to pre-empt what under those circumstances would be more adaptive behavior. In the frontal patient, as in the frontal animal, the presence of perseveration strongly suggests a regression to easy, well-trodden paths of behavior after failing to circumvent a severe, perhaps insurmountable difficulty to adapt to the new. Perseveration in old but inappropriate behavior, despite

repeated and even acknowledged error, is a distinctive trait of the performance of many, though not all, frontal patients in cognitive tasks (Milner, 1964; Luria, 1966, 1980; Konow and Pribram, 1970; Lezak, 1983; Heilman and Watson, 1991).

When not beset by apathy, hypokinesia, depression, or perseveration, the frontal patient is prone to emotional lability and disinhibition. This is again most common in orbitofrontal lesions. Such lesions appear to deprive the patient of the appropriate regulation of emotions and control of basic drives. In the absence of such control, the patient yields to instinctual impulses. Disinhibition from control, however, may not be the only explanation for the behavioral alterations of the orbitofrontal patient. An additional or alternative explanation may lie in the failure of the patient to utilize vegetative or autonomic signals from the body that normally accompany emotional reaction to environmental stimuli. Without such signals, the patient may neglect risk or danger and make erroneous decisions in response to those stimuli. In the eyes of Damasio and his colleagues, this absence of "somatic markers" explains the paradoxical and self-defeating performance of the patient in the Iowa Gambling Task (Damasio et al., 1991; Damasio, 1996; Bechara et al., 1996), a task in which the subject is supposed to balance risk with prospective success. According to them, the patient with ventromedial prefrontal injury is unable to process internal danger signals (conscious or unconscious psychophysiological signals) and consequently makes persistently wrong decisions. That inference became known as the "somatic-marker hypothesis." It attempts to explain the role of the ventromedial cortex in decision-making – by mediating influences from the limbic system. The hypothesis remains plausible, although questionable in several respects, including the physiological mechanisms behind it (Dunn et al., 2006). It seems unquestionable, however, that, as Damasio (1994) has forcefully

argued, decisions are made not only on rational grounds, presumably supported by lateral prefrontal cortex, but also on the basis of affective values probably encoded by limbic structures and influencing those decisions through the orbitofrontal cortex.

### E. “Theory of Mind”: Empathy

“Theory of mind” is the ability of an individual to infer the feelings, motives, opinions, and emotions of another on the basis of that other’s expressions, however fragmentary or incomplete these may be. It is an indispensable ability for meaningful social interaction. Clearly, theory of mind (also designated by the acronym ToM) is closely related to empathy, which ToM can be said to include. Empathy refers specifically, however, to affective understanding (“emotional resonance”), whereas ToM in general extends beyond affect to include cognition. Prefrontal lesions are now well known to commonly impair ToM. Several tests have been developed to assess ToM; most of these tests are founded on the individual’s ability to recognize social errors of ToM, such as *faux pas*, or to recognize the meaning of facial expressions or implicit language. Patients with impaired ToM fail such tests.

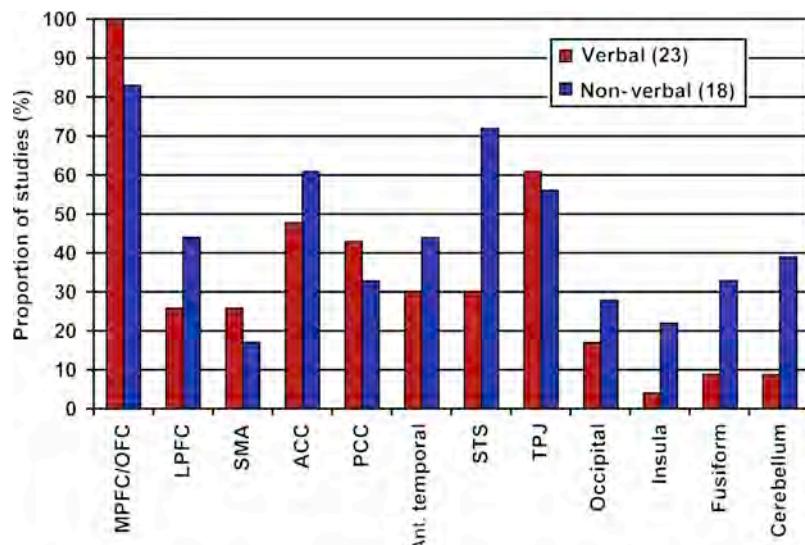
Large prefrontal lesions impair both components of ToM, affective and cognitive, but lesions of orbitofrontal/ventromedial cortex impair mainly the affective, empathic component (Stone et al., 1998; Rowe et al., 2001; Shamay-Tsoory et al., 2004, 2005; Leopold et al., 2012). Lesions of dorsolateral cortex tend to affect mainly the cognitive component as it is most used for language and decision-making (Xi et al., 2011). In the case of the empathic component, a root cause of ToM failure seems to lie in the inability of the orbitofrontal patient to interpret and respond to emotional voice or facial expressions (Hornak et al., 2003; Shaw et al., 2005). That basic lack of empathy, by itself, does not necessarily make the individual

unable to function socially, especially if it is accompanied by the euphoric mood and shallow congeniality that often attend the orbital syndrome. It is often incompatible, however, with normal family life and human relations.

Morphological neuroimaging has shown a correlation between the capacity to “mentalize,” which includes both affective and cognitive components of ToM, and the volume of gray matter in posterior inferior prefrontal cortex and the temporoparietal junction, with some left-leaning lateralization (Lewis et al., 2011).

Functional neuroimaging, on the other hand, and in some accord with lesion studies, demonstrates the activation of ventromedial prefrontal cortex and several other structures in tests of emotional empathy and implicit language (Frith and Frith, 2003; Mar, 2011; Denny et al., 2012; Hervé et al., 2012, 2013; Basnakova et al., 2013), although there are some exceptions (Gupta et al., 2012). Carrington and Bailey (2009), in their thorough meta-analysis, remark on the consistency with which ventromedial and orbital prefrontal cortex is activated in ToM tasks regardless of the nature, verbal or non-verbal, of the material utilized by the subject in any given task (Figure 5.1).

Certain clinical syndromes incipient in early childhood, such as autism, or Asperger’s syndrome – a mild form of autism – are typically characterized by the blunting of emotions and the inability to react to the affective expressions of others, including parents. In the opinion of many observers, children with those syndromes suffer from a severe deficit in ToM, as can be demonstrated by neuropsychological testing. On the basis of the evidence of similarities with the orbitofrontal syndrome with regard to that ToM deficit, it has been argued that autism and Asperger’s are attributable to a possibly genetic dysregulation of limbic–orbitofrontal circuitry (Bachevalier and Loveland, 2006; Schulte-Rüther et al., 2014). Perhaps autism, as for attention deficit/hyperactivity disorder (ADHD), is the result of a laggard or



**FIGURE 5.1** Proportion of verbal and non-verbal tasks that implicate various regions of the brain in theory of mind. The medial prefrontal and orbitofrontal regions are most consistently activated, whether the task is verbal or not. Abbreviations: MPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; LPFC, lateral prefrontal cortex; SMA, supplementary motor area; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; Ant., anterior; STS, superior temporal sulcus; TPJ, temporoparietal gyrus. The numbers in parentheses refer to the number of studies of each task category. (From Carrington and Bailey, 2009, with permission.)

never completed maturation of that circuitry, with the orbital prefrontal cortex at its center.

## F. Social Behavior

All prefrontal lesions alter the patient's social relations in one way or another, usually adversely. Even the most subtle of the cognitive disorders that those lesions can produce tend to change the patient's patterns of behavior. The resulting changes, in turn, tend to constrain his or her social interactions. Commonly, the decline of executive functioning will restrict those interactions, at least as it pertains to other individuals outside the nearest family circle. The higher the functioning before the lesion, the more precipitous will the loss be of normal social relations in the patient's life. The most deleterious changes in social behavior are likely

to be those that accompany the abnormalities of affect reviewed above. The apathetic patient, by the nature of his or her trouble, will shun social contact. The depressed patient will do the same, whether the depression stems directly from the injury or is secondary to the cognitive malfunction produced by the injury.

No prefrontal lesion, however, is likely to have as great an impact on social behavior as the orbitofrontal lesion. The personality changes of orbitofrontal patients, and their effects on social behavior, have been extensively described by many writers, beginning with Harlow (1868) in reference to the case of Phineas Gage (Damasio et al., 1994; Cato et al., 2004). Disinhibition is evidently at the root of the trouble – disinhibition that extends to the cognitive sphere and, as we will see in the next section, is the source of numerous problems

with the focusing and maintenance of attention. As in the animal, orbitofrontal disinhibition leads to faulty extinction and shift of objectives (Rolls et al., 1994). In the presence of disinhibition, instinctual urges are released or exacerbated. Eating is one of them: some patients with orbitofrontal lesions show a tendency to eat excessively, driven to satiate an apparently insatiable hunger (Hofstatter et al., 1945; Kirschbaum, 1951; Erb et al., 1989). Here again, the parallel with the results of some animal studies (see Chapter 4) is obvious. The sexual drive also appears frequently disinhibited by prefrontal, especially orbital, lesions (Jarvie, 1954; Häfner, 1957; Lauber, 1958; Hécaen, 1964; Erb et al., 1989). With such a lesion, the patient may commonly exhibit overt eroticism and hypersexuality. Another manifestation of disinhibition is angry impulsivity (Berlin et al., 2004).

The disinhibition of instinctual drives in the orbitofrontal patient seems fostered by a concomitant loosening of conventional moral restraints and a loss of the capacity to gauge the effects of one's behavior on social interactions with others. Here again, the lack of empathy and the poor evaluation of somatic and emotional signals result in impoverished social perception as well as defective decision-making (Eslinger, 1998; Barrash et al., 2000; Jurado and Junqué, 2000; Clark and Manes, 2004; Mah et al., 2004; Anderson et al., 2006; Boes et al., 2011). Sociopathy is the frequent end-result of orbitofrontal lesion. In fact, the proclivity of the orbitofrontal patient to sociopathy is at the center of the rationale for studies of the anatomical structure of the prefrontal cortex, together with neuropsychological indices, in subjects with antisocial personality disorder (APD). Using magnetic imaging, one such study (Raine et al., 2000) reveals a generalized 11% reduction in prefrontal gray matter in the absence of brain lesion or reduced autonomic stressor-test response. A subsequent critical review (Seguin, 2004) concludes that whatever prefrontal pathology APD individuals may exhibit in morphological or

neuropsychological studies transcends the orbital cortex.

## IV. EXECUTIVE FUNCTION

Executive function is the ability to organize a sequence of actions toward a goal. This simple statement defines also the principal, most general, function of the prefrontal cortex. Slightly modified, the definition can be specifically applied to the human: executive function, the principal function of the prefrontal cortex, is the ability to temporally organize purposive behavior, language, and reasoning. The definition, however, glaringly begs two questions that need to be addressed to avoid tautology: causality and empirical reduction. Both issues have to be dealt with, however briefly, to properly frame the discussion of the effects of prefrontal lesion in the human.

Prior cause is a major problem in any frontal-lobe discourse. That problem, simply stated, is the following: Neuropsychology has unequivocally determined that the prefrontal cortex is *involved* in executive function, but the *assignment* of executive function to the prefrontal cortex inevitably leads to an infinite regress or to the untenable assumption of that cortex as a supreme agent, that is, as the initiator, the organizer, and the executor of action. The infinite regress derives from the need to postulate a prior – “upstream” – agency somewhere in (or outside) the brain that drives and controls the prefrontal cortex, from which the question arises of a still higher agency to drive and control that higher agency, and so on.

The notion of the prefrontal cortex as itself the supreme agent (a kind of “executive homunculus”), the source of volition and decisions, cannot be sustained on either philosophical or neurobiological grounds. As we will see in Chapter 8, both the infinite regress and the superexecutive idea can be avoided by placing the prefrontal cortex at the top of the

perception-action cycle, subject to a multitude of probabilistic inputs from inside and outside the organism, with the capacity to store information, and with access to a variety of effector structures. There is no true origin in that cycle, and thus no true causal agent. As we will see, however, it is legitimate to view the prefrontal cortex as the *enabler* of the cycle at its highest levels, that is, at the levels at which action is organized that is, above all, novel and complex.

The other problem, no less severe, is the methodological difficulty in reducing executive function to discrete and measurable components (attention, working memory, decision-making, etc.) with the aim of identifying for them separate prefrontal areas. The problem basically derives from the functional interrelatedness of all components of executive function. As in all complex systems, no system component can be structurally or functionally segregated from the others without affecting the entire system in more ways than one. Thus, the subtraction of a structural component does not leave the function of the system intact except for the absence of the function of that component. The consequences of that state of affairs for the neuropsychology of the frontal lobe are momentous: (1) no clear-cut double dissociation can be demonstrated of prefrontal areas and executive-function components; (2) after discrete lesion of a prefrontal area, no measurement can be obtained that reflects precisely the contribution of that area to the functional integrity of the executive system; and (3) no prefrontal area can be ascribed to only one executive component.

Nonetheless, it is now undeniable that some prefrontal areas contribute more than others to some components of executive function, again probably by reasons of input, output, and connective substrate. The orbital cortex contributes more to the affective components of decision-making than the lateral cortex; for example, the cortex of area 8 contributes more to the gaze-orientation component of spatial attention than that of area 10; the lateral cortex more to

working memory than the cingulate cortex; and so on. One of the purposes of this chapter is to point to such topographic differences in the functional commitment of prefrontal cortex to executive function.

But another purpose of this chapter is to point to the indivisible commitment of the entire prefrontal cortex to executive function and to dispel the unjustified inferences that abound in the literature on this subject. Above all, in studying the neuropsychology of the human prefrontal cortex, we should never lose sight of the reality that neither the prefrontal cortex, nor any of its parts, does anything in isolation. As we will see in Chapter 6, both the prefrontal cortex and all its parts cooperate with many cortical and subcortical structures in the temporal organization of novel and complex adaptive action.

## A. Attention

The most common cognitive disorders of frontal patients consist of abnormalities of attention, that is, of the capacity to concentrate neural resources in the processing of one given item of information, sensory or motor, to the exclusion of all others. These abnormalities fall into five basic categories, each depending on the aspect of attention most affected as a result of damage to or malfunction of the prefrontal cortex. It is important to note that, given the availability of speech and the capacity to express mental experience (phenomenology), attention in the human lends itself to more descriptive detail than in the animal. Despite the interrelations between them, the following aspects of attention will be considered separately as they are affected by prefrontal disorder: alertness, set, spatial attention, sustained attention, and interference control.

### **Alertness**

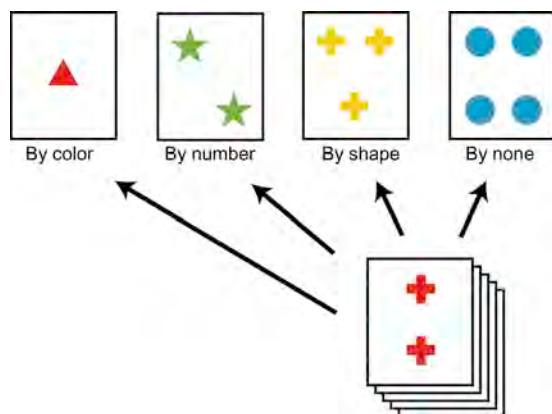
The individual with prefrontal damage is generally less alert and less aware of the world around than the normal individual, especially

if the damage has affected large portions of the lateral prefrontal convexity (Luria, 1966, 1980). A related phenomenon is the patient's having little or no interest in the environment, including the motives and activities of other people. As a result, the patient tends to participate less in society than before the illness or trauma. The root of the abnormality seems to be a basic lack or weakness of drive (*Antriebsschwäche*). This underlying deficit makes the subject not only less spontaneous in his or her actions (Kleist, 1934; Klages, 1954), but also less aware of the surroundings and less responsive to matters of normal concern. A similar condition can result from lesions in certain subcortical structures, such as the reticular formation of the mesencephalon (Goldberg et al., 1989). On the basis of these facts, Stuss et al. (1994b) attribute some of the attention difficulties of the frontal patient to low arousal.

### Set

Set is the preparation of neural resources for expected sensory input or motor response in the course of executive performance. At a given moment, the kind of sensory input or motor response anticipated and to be prepared for is dependent on the temporal and spatial context in which the performance takes place, thus it depends on perception, recent memory, and long-term memory. The preparation of either sensory systems (perceptual set) or motor systems (motor set) is geared to make the performance most efficient in the pursuit of its goal.

One of the most characteristic disorders of individuals with frontal damage is the inability to change attentive set. The disorder is conventionally exposed by testing the afflicted subject on the Wisconsin Card Sorting Test (WCST), a set-shifting task developed by Grant and Berg (1948) after the Category Test that Halstead (1947) used to demonstrate the difficulties of frontal cases in the areas of abstraction and intelligence. Like Halstead's test, the WCST requires the categorization of sensory (visual)



**FIGURE 5.2** The Wisconsin Card Sorting Test (WCST) (see text for description).

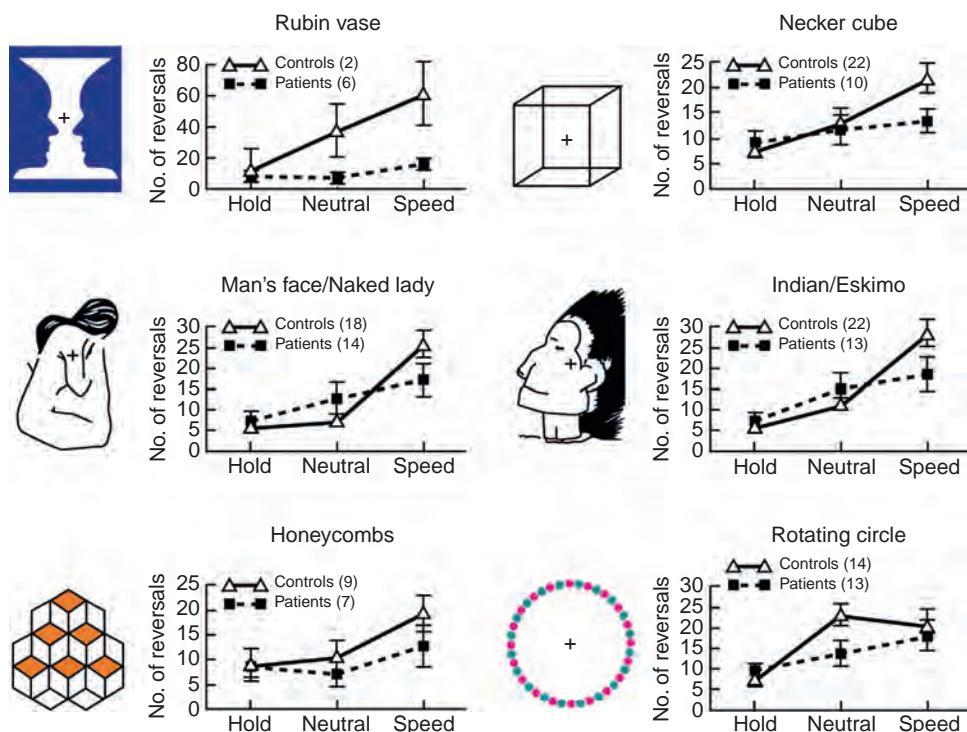
items in accord with a temporally changing principle. Milner (1963, 1964) first showed that frontal patients with lateral lesions are unable to perform the test correctly. Because the test has become the staple of formal neuropsychological testing of the frontal patient, it merits some detailed description (Figure 5.2).

At the start of testing, the subject is shown four "target cards" on a surface, each with a different printed design: one red triangle, two green stars, three yellow crosses, and four blue circles. The subject is then given a deck of cards differing in the number, color, and shape of the figures on them; all the cards match three of the target cards in either the number, the color, or the shape of the items they depict. The subject is then asked to sort the cards and place them, one at a time, under the target cards. After each card placement, the tester simply tells the subject whether the choice is correct or not (according to a tacit matching principle – number, color, or shape – determined by the tester). After 10 correct choices, the tester, again tacitly, changes the matching principle, and the subject must guess that new principle and adjust subsequent choices to it. After 10 more correct trials the principle changes again, and so on. In order to perform the WCST correctly, the subject must

not only retain the current principle but also reject the old one(s). Thus, the WCST tests not only set shifting but also working memory and the ability to withstand interference from inopportune memories. It also tests the ability to plan actions and to get set for them; that is, executive set. All these functions can be impaired in a prefrontal syndrome, and it is probably for this reason that performance on the WCST may be faulty not only as a result of lateral lesions (Milner, 1963, 1964; Drewe, 1974; Nelson, 1976) but also after orbitomedial lesions (Stuss et al., 1982). Furthermore, because it may be impaired also in some patients with non-frontal lesions, some have questioned the WCST's specificity as a test of frontal function (Anderson et al., 1991; Nyhus and Barceló, 2009). In any event, those

non-frontal lesions affect brain structures also involved in attention, and the WCST remains a consistently effective way to test attention-shifting disorder in the frontal-lobe patient. Disorders of this kind have also been substantiated in frontal patients with respect to set shift across behavioral tests (Godefroy et al., 1996; Ravizza and Ciranni, 2002) and temporal context (Meck and Benson, 2002).

Windmann et al. (2006) provide a compelling demonstration of deficit in set shifting from prefrontal damage. For the purpose, they used a test of bistable vision with well-known ambiguous figures (Figure 5.3). At any given time, each figure can evoke one of two different and well-demarcated objects. While fixating their gaze on a central spot, the subjects were asked to



**FIGURE 5.3** Number of reversals per minute of perceptual image reported by patients and control subjects in the three experimental conditions (hold, neutral, speed) for all six bistable figures utilized. Numbers in parentheses are subject-sample sizes. (From Windmann et al., 2006, slightly modified, with permission.)

mentally shift (reverse) from one object to the other and to indicate a shift by a button-press. Three conditions were applied: "hold" (maintaining the dominant view), "neutral" (idle reversal), and "speed" (fast reversal). Especially in the "speed" condition, the patients were not capable of performing as many reversals as control subjects. The patients also showed deficits in performance of another set-shifting test (the Trail Making Test) and working-memory tests.

Probably because of the interference control feature of set-shifting tasks, these tasks have been found to be especially liable after selective lesions of orbital prefrontal cortex (Tsuchida and Fellows, 2013). In this respect, the human attention-shifting deficit from orbital lesion reflects a comparable deficit in the monkey (see Chapter 4).

### **Spatial Attention**

Some of the clearest disorders of sensory attention in frontal patients, especially if Brodmann's area 8 is affected, are those that pertain to spatial vision and the exploratory movements of the eyes. By recording the eye movements of such patients during the scanning of thematic pictures, characteristic abnormalities have been revealed (Luria, 1966; Luria et al., 1966). The most remarkable is the loss of normal logical order in the analysis of pictorial detail; the examination of visual images becomes haphazard, unsystematic, and prone to unnecessary iteration. The patient's gaze at particular areas of the visual field becomes inordinately long at the expense of orderly and integrative scanning of all the pertinent details (Tyler, 1969). Search plans become sluggish, particularly in the hemifield contralateral to a one-sided prefrontal lesion (Teuber et al., 1949; Teuber, 1964). Most peculiar is the inertia of gaze and the failure to correct erroneous or unnecessary eye movements in visual tasks under instructions (Luria, 1966; Guitton et al., 1985).

Spatial neglect is a more specific form of attention deficit encountered in some prefrontal-injury

patients. It is characterized by the subject's lack of full awareness of one side of the body and the stimuli impinging on it (unilateral inattention). The disorder is frequently encountered in patients with unilateral parietal lesions; the sensory neglect applies mainly to the side contralateral to that of the lesion. Sensory neglect may be also observed, although more rarely, with unilateral prefrontal lesions, which also seem to impair awareness of the contralateral side (Heilman et al., 1971; Heilman and Valenstein, 1972; Damasio et al., 1980; Guariglia et al., 1993; Peers et al., 2005).

Taken as a whole, the evidence that spatial neglect (usually contralateral to lesion side) can result from damage to widely separated cortical areas, notably frontal and parietal, indicates that the cause of the disorder is the injury to one or several sites within a widely distributed spatial attention network. This general inference is supported by the findings of modern functional imaging (Coulthard et al., 2006; Urbanski et al., 2008; Correani and Humphreys, 2011; Ptak and Schnider, 2011; Corbetta and Schulman, 2011).

Some frontal patients have been reported to exhibit deficits in the capacity to perceive the spatial relationships between one's self and the environment (Semmes et al., 1963; Teuber, 1964; Butters et al., 1972) or to perform tasks that require the guidance of one's actions by spatial information (Teuber, 1964, 1966; McFie and Thompson, 1972). Left frontal patients are especially liable to deficit when performance relies heavily on verbal instructions; right frontal patients are liable when the guiding information is visual. The deficit of frontal patients in Aubert tasks (Teuber, 1964, 1966) deserves special mention. These tasks require the manual adjustment of a visual display (a lighted rod) to the vertical position in accord with verbal instructions, as well as kinesthetic and visual cues. Frontal patients tend to overcompensate and overdo the adjustment, especially if that adjustment must correct for deviations of the subject from

postural verticality (postural–visual tilt). On the basis of that finding and the results of other perceptual experiments, Teuber argued that the frontal patient suffers from a basic inability to gauge the spatial orientation of his body with respect to the world around and, more important, an inability to anticipate and correct for deviations in that relationship.

Expanding on these inferences, [Teuber \(1964, 1966\)](#) developed his *corollary-discharge* theory. It states that the prefrontal cortex normally sends neural impulses to sensory structures that somehow prepare those structures for anticipated changes in sensory input as a result of an impending movement (attentive set). Perception is thus stably maintained despite movements affecting the relative position of receptors with respect to the environment, movements that would otherwise tend to distort and destabilize perception. The theory has the merit of focusing on the two fundamental elements of prefrontal function: attentive set and the continuous interaction between perception and behavior. Furthermore, the theory supports the critical position of the prefrontal cortex in the neural substrate of the perception–action cycle (see Chapter 8), which enables the organism to adjust its actions to prospective changes.

### **Sustained Attention**

Probably the most consistent and characteristic of all attention disorders from prefrontal damage is the inability to maintain concentration on any given train of action or thought. Especially vulnerable, as a result of that disorder, are all the activities that, for the purpose of reaching a given goal, tax attention in a sustained manner. The patients find most difficult the continued attention to internal representations ([Feuchtwanger, 1923; Rylander, 1939; Robinson, 1946; Luria, 1966; Jetter et al., 1986; Wilkins et al., 1987; Chao and Knight, 1995](#)). The greater the duration and the complexity of the necessary mental operations, the more evident the deficit. That deficit is obvious in

the performance of arithmetic tests without graphic aids. Working memory, as we will see below, is a form of sustained attention focused on an internal representation of a recent event or stimulus for the attainment of a prospective goal. It is almost uniformly impaired in patients with lesions of the lateral prefrontal cortex. Thus, the deficit in sustained attention will be further discussed below, under Working Memory.

### **Interference Control**

In addition to being incapable of concentrating attention in a sustained manner, the subject with prefrontal lesion is incapable of resisting interference with the current set or performance. The patient's attention is abnormally attracted by irrelevant sensory stimuli, the patient unable to resist interference from stimuli that would normally be suppressed or ignored ([Rylander, 1939; Hécaen, 1964; Stuss et al., 1982; Chao and Knight, 1995](#)). As a rule, relevant stimuli are neglected while attention to their background is enhanced. This failure to suppress irrelevant information from the background is reminiscent of the disorder of interference control that animals with orbital prefrontal lesions exhibit in structured tasks (see Chapter 4). It implies the failure of an inhibitory control mechanism, which may be disrupted in both the animal and the human, especially when the frontal lesion involves orbital cortex.

The frontal patient's perceptual attention is vulnerable not only to external interference but also to internal interference, that is, interference from internal representations or impulses. Interference of that kind is at least in part responsible for defective performance of the WCST, in which the subject must keep in mind, and shift when needed, the categorizing principle of a series of visual figures ([Milner, 1963, 1964; Lezak, 1983](#)). Interference may also be responsible for the frontal patient's deficits in short-term memory tasks ([Stuss, 1991; Chao](#)

and Knight, 1995; also see below), in stimulus detection and sequencing tasks (Richer et al., 1993; Décaray and Richer, 1995; Lepage and Richer, 1996; Richer and Lepage, 1996; Tsuchida et al., 2010), in "tests of planning" (Wilkins et al., 1987; Goel and Grafman, 1995), and in the Stroop task (Perret, 1974; Vendrell et al., 1995), which requires the rapid naming of color names written with letters of incongruent color.

## B. Memory

All executive functions discussed in this section operate on, and with, a vast system of cognitive networks (*cognits*) widely distributed throughout the cortex (Fuster, 2003, 2009). These networks are made of connective associations between neuronal assemblies, in some cases widely dispersed from one another, which represent simpler and more concrete items of knowledge and long-term memory. Inasmuch as those networks contain associations with action, they are executive networks and extend into the cortex of the frontal lobe. High-level executive cognits, that is, those that represent goal-directed sequences of actions, especially if these are novel or prospective (plans), extend into the prefrontal cortex. Thus, the prefrontal cortex is the depository of executive memory networks, that is, networks that represent past actions, future actions, or both. It is impossible to construe an executive function without postulating a subjacent executive memory network constituting the neural substrate on which the function will take place. That same network, orderly and timely activated, will be used in attention, in working memory, in planning, and so on. In a word, at a given time, the network will cease to be only representational and will also become operational to serve any or all of those executive functions.

The frontal patient is ordinarily capable of forming and retrieving perceptual long-term memory, that is, memory acquired through the senses. Thus, unlike the Korsakoff patient,

or patients with lesions of the hippocampus or posterior cortex, the subject with frontal damage usually has no difficulty on tests of declarative or episodic memory (Squire, 1986; Tulving, 1987; Janowsky et al., 1989a; Shimamura et al., 1990, 1991). Nonetheless, although the patients are not markedly amnesic, they have difficulties with both free recall and recognition (Hirst and Volpe, 1988; Stuss et al., 1994a; Gershberg and Shimamura, 1995). In any event, whatever problems some frontal patients show in the encoding or retrieval of long-term memory seem attributable to a deficit in the organization and monitoring of mnemonic material (Shimamura et al., 1991; Stuss et al., 1994a; Mangels et al., 1996; Siegert and Warrington, 1996), and thus fall under the category of disorders of executive function and temporal integration. In support of this view is the evidence that the patients have little or no trouble with the recognition of items of either recent or remote memory (Stuss et al., 1994a). Furthermore, recent memory is often found faulty in the frontal patient because, as we have seen, the patient's perceptual attention is impaired and drive is low (Luria, 1966; Barbizet, 1970). For lack of interest, the patient "forgets to remember" (Hécaen and Albert, 1978). Lack of attention and drive may also explain the forgetting of the source of knowledge ("source memory," Janowsky et al., 1989b) and the unawareness of one's memory capability, that is, of so-called metamemory (Shimamura et al., 1991).

Whereas the frontal lobe damage usually does not entail loss of perceptual memory, it does in some cases entail the inability to encode and retrieve serial tasks (Gómez-Beldarrain et al., 1999), stories (Zalla et al., 2001; Gilboa et al., 2006), and verbal material (Floel et al., 2004), especially if the lesion involves the left prefrontal cortex. An interesting side phenomenon, especially if the lesion affects the orbito-olimbic region of the prefrontal cortex, is the presence of spontaneous confabulation and

false recall or recognition (Schnider, 2001, 2003; Gilboa et al., 2006). In such cases, however, the disorder of retrieval is most likely attributable, at least in part, to poor reality testing (monitoring) and to a failure to suppress inappropriate memories, the latter related to faulty inhibitory control on the part of the orbital cortex. These cases illustrate the interrelatedness of executive functions, noted above, and the also mentioned difficulty to dissociate them by neuropsychological study. Again, any inference from lesion study about the functional specificity of a prefrontal area is subject to serious methodological caveats. Any inferred specificity is bound to be *relative*. This is a consequence of the associative, distributed nature of executive memory networks and of their cognitive functions.

Another close relationship between prefrontal executive functions is that between memory and planning. A plan of action is, after all, a memory projected into the future. It is made of associated elements of long-term executive memory bound together into a prefrontal network that contains associations with future time and order. The proverbial difficulty of the frontal patient to formulate and execute plans of action can be properly considered, neurobiologically, as a difficulty to form and retrieve memories – “of the future” (Ingvar, 1985).

### C. Working Memory

Working memory is the ability to retain an item of information for the prospective execution of an action that is dependent on that information. Essentially, it is sustained attention focused on an internal representation. It is a critical cognitive function for the mediation of cross-temporal contingencies in the temporal integration of reasoning, speech, and goal-directed behavior. Like the non-human primate with a frontal lesion, the frontal patient typically exhibits an impairment of working memory, especially if the lesion is of lateral cortex. Working memory, however, can fail in many

pathological conditions of the brain. The reason why its failure is especially evident and consistently found in the frontal patient is because that kind, or rather state, of memory is *necessary for prospective action*, whether the action is a motor act, a mental operation, or a piece of spoken language.

Thus, the patient with frontal damage performs poorly in a large variety of tests of working memory, including delay tasks. However, frontal patients, unlike frontal monkeys, fail delay tests only if those tests meet certain conditions that are related to language. A scaling factor has to be considered here also, for there are large differences between humans and monkeys in the complexity of the memory items and the length of delay they can handle without difficulty. Moreover, language can be easily used by humans to categorize and to retain information, and thus may serve as a source of mnemonic devices to negotiate task delays. Spatial information, for instance, can be readily coded with language. It is probably for such reasons (Milner and Teuber, 1968) that early studies of frontal patients in spatial delay tasks yielded negative results (Ghent et al., 1962; Chorover and Cole, 1966).

Other early studies, however, using delay tasks with complex spatial or non-spatial cues and appropriate delays, clearly demonstrated that frontal patients, unlike patients with posterior cortical lesions, have trouble with the performance of delay tasks. In one of those studies (Milner, 1964), a delayed matching task was used, very similar to one previously developed by Konorski (1959) in animals. Delays were of up to 60s and stimuli were such that verbal rehearsal was extremely difficult. In that non-spatial working-memory task, patients with unilateral frontal damage made significantly more errors than both normal subjects and patients with temporal-lobe damage. Lewinsohn et al. (1972) demonstrated similar deficits with visual, auditory, and kinesthetic stimuli. In their study, frontal patients (with

unilateral right or left lesions) showed poorer performance than both normal subjects and patients with other forms of brain damage. The authors concluded that the frontal deficit was supramodal and reflected both faulty registration and faulty retention. Later, even conventional delay tasks were shown to be impaired after some form of frontal lesion (Milner et al., 1985; Freedman and Oscar-Berman, 1986; Oscar-Berman et al., 1991; Pierrot-Deseilligny et al., 1991; Verin et al., 1993; Dubois et al., 1995; van Asselen et al., 2006; Chase et al., 2008).

Other neuropsychological studies with different methods further substantiate the prefrontal working-memory defect in the human. They show deficits in digit span tests (Vidor, 1951; Hamlin, 1970; Janowsky et al., 1989a; Stuss, 1991), in certain recognition tests (Milner and Teuber, 1968), and in temporal order and recency tests (Milner, 1971, 1982; Milner et al., 1985; Shimamura et al., 1990; Kesner et al., 1994; Jurado et al., 1997, 1998; Marshuetz, 2005). Judging from the effects of prefrontal lesion, working memory of all modalities seems to be distributed throughout lateral cortex, without anatomical compartment for spatial working memory (Müller et al., 2002; Müller and Knight, 2006). However, the reversible transient lesion by transcranial magnetic stimulation (TMS) has been reported to segregate spatial and non-spatial deficits in dorsal and ventral lateral cortex, respectively (Mottaghay et al., 2002). Frontal eye-field (area 8) lesion leads to deficit of working memory for ocular saccades (Ploner et al., 1999). Left-frontal patients have the most difficulty with working memory of verbal items, and right-frontal patients with non-verbal ones. An electrical stimulation study (Ojemann, 1978) suggests a verbal memory focus in the prefrontal cortex adjacent to Broca's area. Frontal patients, unlike temporal patients, have been noted to perform poorly on spatial as well as non-spatial conditional association tests (Petrides, 1985), probably because of the working-memory component that those tests contain.

As noted above, working memory can be characterized as sustained attention to an internal representation. Thus, working memory is subject to distractibility and interference, which are likely after prefrontal damage. In the frontal patient, irrelevant stimuli and irrelevant memories can easily interfere with the currently relevant memory; hence the critical importance of the context in which the relevant memory is tested. In a "rich" environment with plentiful stimuli and distractors, the frontal patient's memory is more likely to fail than in a quiet and simple environment. Just as critically, interference may come from within, that is, from the reservoir of memories and alternatives that the subject has experienced or is likely to experience in that particular context. The greater the similarity between these and the memory currently "on line," the greater the probability that they will interfere with it. We are dealing with the same interference factor that disrupts the frontal animal's memory tasks (see Chapter 4). Interference and the failure to control it clearly play a role in the memory deficit of the frontal patient. This has been demonstrated by the use of memory tasks with proper control of the interference factor (Oscar-Berman et al., 1991; Stuss, 1991; Chao and Knight, 1995; Ptito et al., 1995). Nonetheless, after interference and other relevant factors have been suitably considered and controlled, there remains a population of frontal patients, especially with lateral damage, who exhibit a deficit of working memory not attributable to those factors. Such patients fail a variety of working-memory tests, though, somewhat paradoxically, may not fail others supposed to test recent memory, such as the Wechsler Memory Scale, paired-associates tests, and the Benton Visual Retention Test (Stuss and Benson, 1986).

To sum up, frontal patients show deficits in working memory, especially if their lesions include lateral prefrontal cortex. The magnitude and qualities of such deficit depend on the context of the testing and, most importantly, on the

degree to which the test requires the suppression of interference. Frontal lesion, as we will see below, can adversely affect this interference-controlling function.

## D. Planning

Whereas faulty working memory deprives the frontal patient of the ability to use experience of the recent past, faulty foresight deprives him or her of the ability to plan for the future guided by internal cues. The two deficits are the mirror image of each other: one reflects failure of a temporally retrospective function, the other of a prospective one. These failing functions are two sides of the same coin, two mutually complementary aspects of temporal integration (below). Both tend to be affected together in the frontal patient, especially if the causal lesion is in the lateral prefrontal convexity. The same individual who we have seen lacking memory of the recent past we now see lacking "memory of the future" (Ingvar, 1985) or "prospective memory" (Dobbs and Rule, 1987; Volle et al., 2011).

Perhaps no prefrontal symptom has been reported more consistently than the inability to plan. Harlow (1848) recognized it in Phineas Gage and was probably the first to report it. Innumerable authors have also done it, usually in conjunction with reference to lack of initiative: Penfield and Evans (1935), Brickner (1936), Freeman and Watts (1942), Ackerly and Benton (1947), Lhermitte et al. (1972), Walsh (1978), Eslinger and Damasio (1985), and many others. The failure to formulate plans, especially new plans, is generally accepted as a common feature of prefrontal syndromes. Remarkably, the symptom appears unique to dysfunction of the prefrontal cortex. It is not associated with clinical damage to any other neural structure – in the absence of concomitant dementia or disorder of consciousness.

The lack of foresight or "prospective memory" and the lack of capacity to formulate and

carry out plans are closely related (Meacham and Leiman, 1982; Dobbs and Rule, 1987). The successful execution of a plan necessitates the prior conceptual scheme of the plan, the preparation for each of the steps to implement it, and the anticipation of its consequences. Therefore, it is difficult to dissociate the inability of frontal patients to plan from their poor foresight. The latter is a phenomenological symptom that, as such, is not described in the frontal lobe literature as frequently as its objective consequences in the form of faulty behavioral plans and programs. It is closely related to the temporal concreteness of the patient (see below).

In order to understand how plans are enacted, it is necessary to assume that they are represented in the central nervous system as a form of memory (executive memory), though a memory not yet experienced, an "imaginary" cognit. In the author's view (Fuster, 2003, 2009), the cognits of action are represented in cortical neuronal networks of the frontal lobe, and their representation, as well as their enactment, is impaired in the patient with frontal damage, especially if this damage affects the cortex of the lateral convexity (see Chapter 8). Here again, however, as in the case of defective attention and working memory, apathy and lack of drive probably play a significant role. The absence of active interest and initiative may be the underlying reason, in addition to poor foresight, in what may be appropriately called neglect in the temporal domain. Both memory and planning suffer from that neglect. As a consequence, the patient lapses into temporal concreteness (see next section).

The defective planning is evident on formal neuropsychological testing. It is most apparent in tests that require internal programming of new behavior (Luria, 1966; Shallice, 1982; Karnath et al., 1991; Karnath and Walleesch, 1992; Grafman, 1995; Zalla et al., 2001, 2003). It is in large part from the difficulties of frontal patients under these conditions that Pribram (1973) and others (Lhermitte et al., 1972; Lezak,

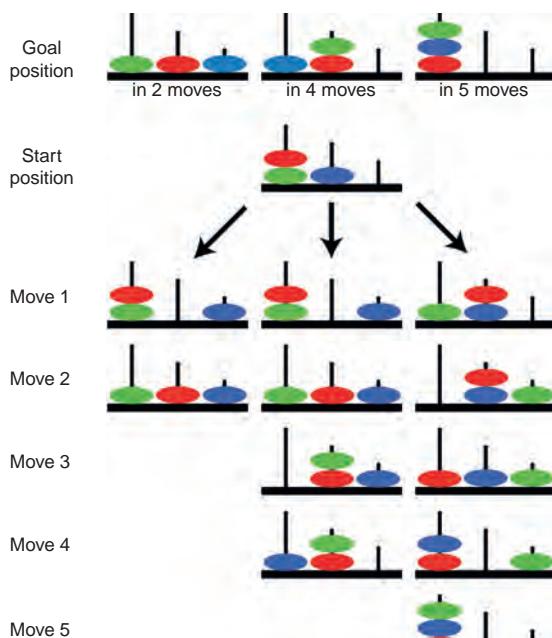
1982; Shallice, 1982) argued for what we now call the executive function of the frontal lobes.

The Tower of London is commonly considered a test of planning and, as such, has been used on frontal patients to substantiate their planning deficit (Shallice, 1982). The test material (Figure 5.4) consists of a board with three vertical sticks planted on it and three wooden rings of different color made to slide up and down on them. The sticks are of different lengths, so that the first can accommodate the three rings on top of one another, the second two rings, and the third just one ring. From an initial position of the rings on the sticks (e.g., red over green on the long stick, blue on the middle stick), the subject is asked to move one ring at a time from stick to stick and, in a prescribed number of moves, achieve a certain order (e.g., green over blue over red on the long stick in five moves). The test requires planning a

series of subgoals to reach the ultimate goal; the subject must anticipate and visualize not only that goal but also the steps to it in the proper sequence. Patients with frontal damage, especially if it is in the left hemisphere, were first found by McCarthy and Shallice to be severely impaired in the performance of the Tower of London (Shallice, 1982), although the results of subsequent experiments turned out to be somewhat inconsistent (Shallice and Burgess, 1991). However, left-frontal patients have been found to exhibit impaired performance in other tasks as well that, as with the Tower of London test, require self-initiated and self-ordered behavior (Messerli et al., 1979; Milner, 1982; Petrides and Milner, 1982; Morris et al., 1997). Most probably, the failure of planning is also the reason for the patients' poor performance in certain maze tests, such as the Porteus maze (Porteus, 1950, 1965; Milner, 1964; Corkin, 1965; Walsh, 1978).

Like working memory, planning and the execution of plans are dependent on attention and thus subject to interference. Especially disruptive may be the internal interference from competing action plans, notably routine plans. More specifically, the enactment of executive sequences requires attention directed to events in the motor or executive sector (Stuss et al., 1995). This kind of attention, which we call *motor* or *executive attention* or *set*, may be defective in the frontal patient in part because of poor inhibitory control of interference. Thus, it is difficult to ascertain the extent to which the failure of frontal patients in formal tests of planning is due to a failure to suppress interference, internal or external (Karnath et al., 1991; Goel and Grafman, 1995; Stuss et al., 1995). The planning deficit of the prefrontal patient is magnified by multitasking, that is, the necessity to execute several plans simultaneously (Dreher et al., 2008; Volle et al., 2011).

In conclusion, the planning and execution of goal-directed schemes of action that are guided by internal cues are markedly vulnerable to frontal lobe lesions, especially if these are in



**FIGURE 5.4** The Tower of London Test (see description in the text).

the left lateral prefrontal cortex. Both the planning and the execution are also vulnerable to defective control of interference, a disorder of attention to which the patient with prefrontal damage is particularly prone.

### E. Temporal Integration

Working memory and planning, the retrospective and prospective aspects of executive function, complement each other to serve the more general function of temporal integration: the ability to carry out new, temporally extended and goal-directed behavior, speech, or reasoning. Virtually all lesions of prefrontal cortex lead to a defect in temporal integration, whereas lesions elsewhere in associative cortex do not. As a rule, the prefrontal patient has no trouble whatsoever executing old and well-rehearsed routines, even if they are temporally extended. The patient encounters trouble, however, when forced to develop a new temporal pattern of behavior, speech, or reasoning, especially if it requires the mediation of cross-temporal contingencies.

The reasons for the difficulty of the prefrontal patient in organizing new integrated sequences can be surmised from what we have already reviewed in this chapter. Indeed, the failure of what has come to be called “executive functioning” (Shallice, 1982; Lezak, 1983; Lhermitte et al., 1986; Stuss and Benson, 1986; Glosser and Goodglass, 1990; Stuss et al., 1992), that is, the “dysexecutive syndrome” (Baddeley, 1986), is the result of failure in one or several of the function domains we have already discussed above, or will discuss below, in our analysis of prefrontal deficits: most prominently attention, working memory, planning, and inhibitory control. Trouble in any or all of them can lead, more or less directly, to inabilities in decision-making and in initiating and carrying out the organizing behavior.

Temporal synthesis or integration, in the present context, is the ability to organize temporally

separate items of perception and action into goal-directed thinking, speech, or behavior. In cognitive terms, this ability derives from the joint and temporally extended operation of attention, memory, and planning. In neural terms, temporal synthesis derives from the cooperation of the prefrontal cortex with other brain structures, cortical and subcortical, in the perception-action cycle (to be discussed in Chapter 8), although the underlying mechanisms are still incompletely understood.

Regardless of the site of the lesion, the frontal patient’s difficulty in temporally integrating behavior is evident only in challenging situations and may not surface in everyday life. That difficulty, which in cases of minor prefrontal damage may be subtle, remains concealed for as long as the cognitive functions that mediate sequential behavior remain unchallenged. To better understand the circumstances under which those functions can be taxed, let us briefly examine further the phenomenology and behavioral manifestations of the deficit.

An inordinate degree of concreteness usually pervades the frontal patient’s perception of the world and of his or her interactions with it. The patient suffers from an overall constriction of the scope and complexity of behavior and of the thinking behind it (Brickner, 1934, 1936; Goldstein, 1944). This concreteness, which affects behavior characteristically, can be appropriately considered *temporal concreteness*; that is, concreteness in the time domain. Behavioral patterns that are not well-established routines appear to be anchored in the present and devoid of temporal perspective, for the past or for the future. Consequently, the behavior of the patient has an air of temporal immediacy, in the sense that it is dominated by present needs and stimuli, the here and now (Ackerly, 1964). Besides spontaneity, behavior seems to have lost its temporality, one action leading to another in more or less stereotyped sequence with little or no regard for either the origins of the sequence or its goal. Temporal concreteness

is one of the signs of incipient dementia with frontal-lobe pathology or the so-called cortico-basal syndrome (Gross et al., 2010).

The severity of the disorder may vary considerably. In some cases it may be so subtle as to escape observation. In many patients, perhaps the majority, the disorder is fully compatible with ordinary life. The patient's life, in fact, may become more ordinary than it would normally be, and troubles may surface only when the patient is confronted with new challenges or changes in the environment. Family and friends, consciously or unconsciously aware of the patient's shortcoming, generally protect the patient from such eventualities. Thus, by all appearances, the patient leads a normal life, albeit constrained by routine and without much display of imagination, let alone creativity.

The temporal-integration deficit can be readily demonstrated by a number of neuropsychological tests. Here, we could mention again many of the tests that challenge attention, memory, planning, or the control of interference. Especially sensitive to the deficit are the tests that require temporal ordering (McFie and Thompson, 1972; Messerli et al., 1979), the learning of new skills (Glosser and Goodglass, 1990; Pascual-Leone et al., 1995), the monitoring of temporal sequences of externally ordered events (Milner, 1971, 1982; Milner et al., 1985), the execution of behavioral programs (Messerli et al., 1979; Shallice, 1982), and the mediation of cross-temporal contingencies (Barceló and Knight, 2007).

In the human frontal case, as in the frontal animal, internal interference can be shown in the performance of behavioral tasks that require not only the activation of pertinent memories and the execution of appropriate responses, but also the suppression of inappropriate alternatives (Malmo and Amsel, 1948; Corkin, 1965; Luria, 1966). As noted above, the failure to suppress these alternatives may account for the poor performance on temporally integrative tasks such as the WCST

(Drewe, 1974; Stuss et al., 1982). However, nowhere is the failure to suppress alternatives so evident as in tasks that critically depend on it, such as go/no-go tasks, the Stroop test, and conditioned differential inhibition (Drewe, 1975b; Stuss et al., 1982; Burgess and Shallice, 1996). These tasks are markedly impaired after orbitomedial lesions. In such cases, the temporal synthesis of behavior is highly susceptible to disruption by external or internal interference. On the other hand, the exclusivity of frontal-lobe involvement in those tasks has been empirically challenged (Andrés, 2003). The alternative has been offered that, as we advance in Chapter 8, the deficits are the expression of pathology in broad dynamic networks in which the prefrontal cortex is a critical participant.

## F. Decision-Making

We lead our daily lives through myriad minor decisions that are determined by habit and the expectation of immediate fulfillment, however minor. Other decisions, less frequent yet more important, are largely the product of logical reasoning and long-term planning; their expected consequences may take time to come to fruition. Occasionally, the opportunity and the expectancy of higher reward – financial gain, social approval, or satisfaction of biological urge – lead us to need to weigh consequential choices in the face of uncertain outcomes. Our decision is then determined by a number of factors, most prominently the amount and timing of potential reward and the degree of potential risk. Because of the indeterminacy of rewards and risks, the decision is then the result of probabilistic estimates of both reward and risk. Those estimates may be unconscious, in which case the choice may be called intuitive, based on so-called gut feeling. The decision is then, most of the time, emotionally biased.

In reality, there is no purely rational or purely emotional decision, as both reason and emotion play a role in all decisions. The

neuropsychological evidence is now substantial that the prefrontal cortex takes part in all decisions, although arguably its lateral regions are mainly involved in rational factors, whereas its medial and orbital regions are mainly involved in emotional factors. Pursuant to previous discussion and without the need to recapitulate the evidence, we may assume that the lateral prefrontal cortex plays a major role in all decisions that are the result of temporal integration, working memory, and planning. Decisions that are not based on these cognitive functions fall largely outside the purview of this cortex, and therefore are not substantially affected by its absence. On the other hand, the orbitomedial prefrontal cortex plays a major role in all decisions that are emotionally determined or biased.

Damasio and his colleagues succeeded in objectifying emotional bias by developing a test, called the Iowa Gambling Task (IGT), in which risk and benefit are titrated against each other in various degrees, whereby the tested subject reveals the level of emotional bias as in real-life decisions. The test ([Bechara et al., 1994](#)) is essentially as follows. The subject, facing the observer, is given \$2000 in play money and four decks of cards upside down to choose cards from. The subject is then asked to turn the cards, one at a time, from any deck. Each choice results in a monetary gain. Unbeknown to the subject ahead of time, although gradually apprehended by him during the course of testing, the cards in two of the decks (A and B) are "disadvantageous" and those in the other two decks (C and D) "advantageous." Turning cards from decks A and B yields relatively high amounts (\$100) but also high penalties (money back to the "house"), whereas turning cards from decks C and D yields lower amounts (\$50) but lower probability of penalty. In the long run, choices from decks C and D lead to positive balance for the subject, whereas choices from decks A and B lead to negative balance.

Normal subjects, after a number of selections, learn the advantage of choosing from C

and D. Subjects with ventromedial prefrontal lesions, however, tend to select cards from the "disadvantageous" decks (A and B), apparently tempted by the higher gains and oblivious to the higher risk. They persist in bad choices despite running into deficit. From such results, Damasio and his collaborators ([Bechara et al., 1994; Damasio et al., 1994, 1996](#)) conclude that the patient with ventromedial prefrontal lesion is incapable of making sound decisions because of insensitivity to future outcomes and willingness to take unwise risks. In a figurative sense, they say that the patient suffers from "myopia of the future" ([Bechara et al., 2000](#)). Here, the reader will recall the temporal concreteness of the lateral prefrontal patient noted in the previous section. In that case, the temporal concreteness was in the cognitive domain; in the ventromedial patient, the temporal concreteness is in the emotional domain. Contrasting further cognition and emotion, [Bechara et al. \(1998\)](#) attempt to establish a double dissociation within the prefrontal cortex: lateral patients have impaired working memory; ventromedial patients have impaired gambling-task performance. Further, during IGT performance the ventromedial patient shows a failure of the psychophysiological response (galvanic skin response) to anticipated risk that normal subjects exhibit before each card selection – after having learned the connotations of the four decks ([Bechara et al., 1996](#)). From this, the authors conclude that "somatic signals" of risk are missing in the patient, wherein they find support for their somatic marker theory of orbitomedial prefrontal cortex, which we visited when discussing the emotional disorders from prefrontal lesion.

There seems to be general agreement about the emotional contribution of orbitomedial prefrontal cortex to decision-making. Yet, the IGT deficit may not be as specific to orbitomedial patients as formerly thought. The deficit appears also in patients with dorsolateral, dorsomedial, or global prefrontal lesions, and may fail to appear in some cases of ventromedial

lesion (Manes et al., 2002; Clark and Manes, 2004; Levine et al., 2005). There is some evidence of laterality in orbitomedial function, with more right-side than left-side involvement in social/emotional functioning and decision-making (Gómez-Balderrain et al., 2004), although that laterality may be less apparent in women than in men (Tranel et al., 2005). In any event, to restate what was said at the beginning of this section, decision-making is the result of the cooperation of all prefrontal areas. The lateral prefrontal cortex would contribute to decision-making the “veridical” (Goldberg and Podell, 2000), multisource (Krawczyk, 2002), “attribute-based” (Fellows, 2006) information within the temporal gestalts of executive sequence, whereas the ventromedial prefrontal cortex would contribute the biologically adaptive, “alternative-based,” value-guided information.

## G. Monitoring

Monitoring is reality testing, whether the reality is external, that is, defined in spatial-temporal coordinates and accessible to the senses, or internal, defined in memory. It is an executive function in that it serves to gauge the effects of our actions on the environment, to match those effects with goals and expectations, and to correct subsequent actions. Without effective monitoring, no executive sequence reaches its goal successfully. Monitoring is essentially based on feedback, that is, on neural re-entry, as such an integral functional component of the perception-action cycle. The prefrontal cortex completes the neural loops at the top of that cycle with afferent and efferent connections between itself and the environment, the limbic system, and the posterior (perceptual) association cortex (see Chapter 8).

Because of its key role in the temporal organization of behavior, monitoring is to some degree affected by practically all lesions of the prefrontal cortex, regardless of location. A monitoring deficit, however, rarely appears

in isolation, as it is usually accompanied by deficits in attention, inhibitory control, planning, and working memory. For these and other reasons, as it occurs with regard to every other executive function reviewed in this section, no prefrontal area has been unmistakably identified as the seat of monitoring on the basis of lesion consequences. Although the anterior cingulate area and the orbital regions have been inferred to be associated with the monitoring of errors (Swick and Turken, 2002) and reward contingencies, respectively, such inferences derive mainly from electrophysiological and imaging studies (see Chapters 6 and 7) rather than from lesion studies.

There is one category of internal monitoring, however, that appears somewhat specifically affected by anterior cingulate and/or orbital lesions. Patients with such lesions have been reported to be incapable of monitoring the authenticity of the spontaneous confabulations to which they are prone (Schnider, 2001, 2003; Gilboa et al., 2006). Here again, however, the monitoring deficit is inextricably related to the deficit in inhibitory control (of false memories in this instance), which we discuss next.

## H. Inhibitory Control

In the prefrontal cortex, as in any other structure of the nervous system, inhibition plays a pivotal role. Like all somatic functions at all levels of the system, executive functions, beginning with attention, make use of inhibition for focus, contrast, suppression of interference, order, and timeliness. Attention has two complementary components or subfunctions: one inclusive and the other exclusionary. The first is the excitatory function of processing the information – sensory, motor, or otherwise – that is within the focus of attention at any given time; it demarcates the content of what is being attended to. The second component of attention, the exclusionary one, inhibits, suppresses, or filters out what is not in the focus of

attention. Both components of attention, inclusive and exclusionary, work in tandem, with the net result of enhancing content and protecting it from interference, thus making the most efficient use of the limited processing resources of the nervous system. Both components are most necessary and efficient when the processing is in series, as in sustained attention and working memory. The neural substrates for both components are intermixed throughout the cortex, where selective processing is accompanied by lateral inhibition to enhance saliency and contrast. Consequently, poor attention focusing and distractibility, the two deficits from failure of the inclusive and exclusionary components, respectively, can accompany the executive deficit resulting from lesion practically anywhere in the prefrontal cortex.

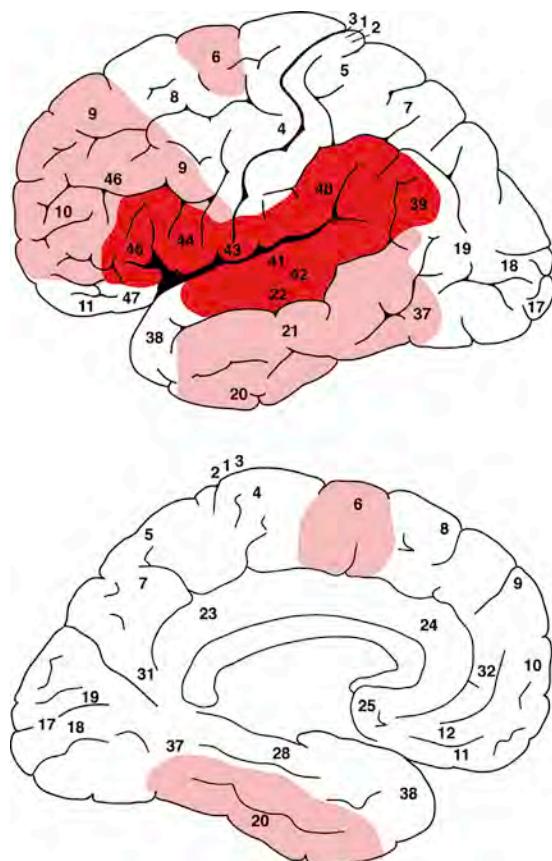
The suppression of untimely actions or memories, however, does seem to depend on the functional integrity of ventral prefrontal cortex. As in animals, lesions of this cortex lead to disinhibition of inappropriate action or memory, in other words, to the intrusion in executive function of well-established, but currently inappropriate, executive and perceptual memories. This is evident in the performance of reversal tasks, go/no-go tasks, and the Stroop task (Hodgson et al., 2002; Thompson-Schill et al., 2002; Fellows and Farah, 2003; Aron et al., 2004). As we have seen in the previous section, the loss of inhibitory control of interference also seems to play a role in spontaneous confabulation, where the patient is unwittingly beset by the intrusion of false memories with an only tenuous relation to past reality. Finally, to restate what was said in the sections on emotional and social behavior, that ventral-prefrontal focus of inhibition appears essential for the control of interference and impulsivity, as well as a wide array of instinctual and acquired drives. In a broad sense, one could reasonably argue that inhibitory control from the prefrontal cortex exerts a stabilizing role over behavior.

## V. LANGUAGE

The spoken language is one form of sequential behavior that is based on the exercise of temporal integration and the cognitive functions that support it. Not surprisingly, language has been found to be adversely affected in a variety of ways by frontal damage (see Meyer, 1974; Stuss and Benson, 1986; Henry and Crawford, 2004; Wilson et al., 2012, for reviews). The nature and severity of the disorder greatly depend on the location and magnitude of the lesion. In any event, the ability to construct original, improvised, and extended speech is particularly vulnerable to any kind of prefrontal injury.

Undoubtedly the best known language disorder resulting from frontal damage is the aphasia from injury to the transitional cortex of the left inferior frontal gyrus (Brodmann's areas 44 and 45), the cortical area named after Broca (Figure 5.5), who was the first to describe the disorder (Broca, 1861). In Broca's aphasia, speech delivery is slow and effortful, lacking normal fluidity and continuity (Geschwind, 1970; Luria, 1970; Passingham, 1981). The articulation of some words may be disturbed. Typically, the patient omits articles and small liaison words, and expresses most verbs in the infinitive form. This distortion of normal speech, with its telegraphic style, has been characterized as "agrammatism." The reversible, temporary lesion – by TMS – of the left inferior prefrontal area, coincident with or overlapping Broca's area, has been shown to interfere with the phonological aspects of semantic processing (Devlin et al., 2003). Lesions immediately anterior or superior to Broca's area often produce what has been called transcortical motor aphasia (TCMA). This type of aphasia is also non-fluent, like Broca's, but with output that is more grammatical, although simplified, repetitive, and delayed (Alexander, 2002).

Lesions of premotor cortex (area 6) including the supplementary motor area (SMA) in



**FIGURE 5.5** Lateral and medial views of the cortex with areas demarcated whose injury may lead to speech disorder (aphasia). Numeration of areas after Brodmann. The more common and severe aphasias result from lesions in red areas, the less common and severe from lesions in pink areas.

the medial surface can cause efferent aphasias somewhat similar to Broca's and TCMA, although less marked (Luria, 1970; Masdeu, 1980; Goldberg et al., 1981; Damasio, 1992; Saygin et al., 2004). In such cases the patient's speech loses its normal smoothness, and becomes hesitant and monotone. In some cases of medial injury, the patient loses his or her speech spontaneity or becomes mute.

More anterior lesions, within what is generally considered the prefrontal cortex proper

(the granular frontal cortex of areas 9, 10, and 46), can produce a certain alteration of speech which, although more subtle and less incapacitating than those mentioned above, is of special interest to us. Goldstein (1948) called it "central motor aphasia." Luria (1970), who studied it extensively, called it "frontal dynamic aphasia." The cardinal features of that disorder, which we may name prefrontal aphasia, are a reduction of spontaneous speech, a curtailment of the amount and range of narrative expression, and a loss of verbal fluency (Benton, 1968). Although the pronunciation of words and sentences remains intact, language is impoverished and shows an apparent diminution of the capacity to "propositionize" (Jackson, 1915). The length and the complexity of sentences are reduced (Lhermitte et al., 1972; Albert et al., 1981). There is a dearth of dependent clauses and, more generally, an underutilization of what Chomsky characterizes as the potential for recursiveness of language (Chomsky, 1965, 1975). Barbizet et al. (1975), in a quantitative study of the disorder, noted that it can result from right as well as from left lesions, although it is most severe in left and bilateral cases. According to them, the degree of deficit is proportional to the extent of the lesion. The disorder can be objectified by use of verbal-fluency and word-production tests (Benton, 1968; Ramier and Hécaen, 1970; Benton and Hamscher, 1978; Bornstein, 1986; Ruff et al., 1997; Baldo and Shimamura, 1998).

All language disorders resulting from damage in the dominant hemisphere are more severe than those from damage in the non-dominant hemisphere. This applies even to subtle word-fluency disorders from anterior frontal lesions (Benton, 1968; Ramier and Hécaen, 1970, 1977; Milner, 1971; Hécaen and Ruel, 1981; Kaczmarek, 1984; Miller, 1984; Ruff et al., 1997). The opposite is true for non-verbal fluency (Design Fluency Test), which seems impaired mainly by lesions of the non-dominant hemisphere (Jones-Gotman and Milner, 1977).

Because of the pervasiveness and subtlety of language disorders from prefrontal injury, neuropsychological tests that depend on the use of language may yield abnormal scores in frontal cases, even though the functions that the tests are intended to test may be normal (Wallesch et al., 1983). For that reason, some frontal patients may do poorly on tests of intelligence, especially tests of verbal intelligence. Probably for the same reason, frontal patients have been noted to perform deficiently on tests of verbal long-term memory (Jetter et al., 1986).

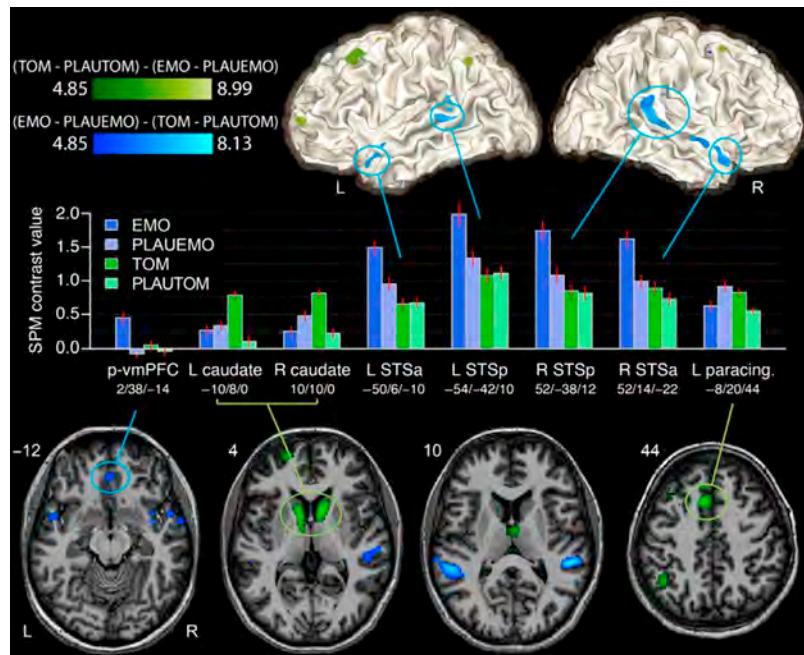
The prefrontal disorders of speech may in part be manifestations of executive disorder, which includes the deficits in attention, working memory, and planning discussed above. Luria, although essentially in agreement with this proposition, additionally postulated that with frontal damage the special position of language in the organization of behavior is compromised. According to him, the prefrontal syndrome is caused to a large extent by the disruption of the normal regulatory role of language on behavior in general (Luria and Homskaya, 1964; Luria, 1966, 1970). Behavior, in his view, suffers from a lack of the internalized linguistic syntheses or schemata that normally precede and guide any purposive action and depend on the integrity of the prefrontal cortex.

The concept of inner antecedent syntheses or schemas of action is plausible. Highly questionable, however, is the role in behavior of those hypothetical syntheses of speech that Luria presumes to reside in the prefrontal cortex (Zangwill, 1966; Drewe, 1975a). Nevertheless, Luria's ideas have the distinct value of emphasizing disorders of synthetic function in prefrontal pathology, disorders of the meaningful sequencing and programming of behavioral acts, such as the spoken language requires. In that sense, any prefrontal disorder of language may be viewed as a special case of a more general disorder of temporal integration, and hence of executive function. Further reinforcing the

relation between executive disorder and verbal disorder is the evidence that the two tend to coexist in left-frontal patients (Glosser and Goodglass, 1990; Stuss et al., 1994a). As a subtle expression of that relationship, there is the intriguing evidence that subjects with frontal lobe injury have more difficulty accessing verbs (action words) than nouns, whereas the converse is true for subjects with postrolandic lesions (Damasio and Tranel, 1993).

In conclusion, there seems to be some uniformity behind the diversity of speech and language disorders resulting from prefrontal damage. All of them may be interpreted as impairments of the synthetic or syntagmatic (Pei and Gaynor, 1954) properties of language (Von Stockert and Bader, 1976; Zurif and Caramazza, 1976; Caramazza and Berndt, 1978). The various prefrontal deficits of language suggest a gradient of increasing complexity of temporally synthetic function: from Broca's area, which is essential for the most elementary combinations of morphemes, to the more anterior prefrontal cortex, which mediates elaborate structures of spoken language. Thus, whereas a basic syntagmatic function seems localized in a relatively circumscribed cortical area of the dominant hemisphere, the more complex construction of language seems to depend, in addition, on the less localized and less lateralized functions of the prefrontal cortex above and in front of that area.

Finally, a note is in order to attempt to separate the relative contributions of prefrontal regions into the cognitive versus the emotional or affective components of language. Earlier in this chapter, in the context of theory of mind (ToM), we remarked on the consistent activation of ventromedial prefrontal cortex by the emotional aspects of ToM. Here, we have to complement that statement with the apparent evidence that the contributions of emotion and cognition of language comprehension to brain activation largely overlap. This is the



**FIGURE 5.6** Difference scores of activation by emotional (EMO) and linguistic (TOM) aspects of sentence comprehension. Plausible but emotionally neutral sentences (PLAUEMO and PLAUTOM) were used to control for effects of syntactic differences. Blue lines and histogram bars mark emotional activations greater than linguistic (TOM) activations; green lines and histogram bars mark the reverse effects. Abbreviations: p-vmPFC, posterior ventromedial prefrontal cortex; L, left; R, right; STS, superior temporal sulcus; paracing., paracingulate. (From Hervé et al., 2013, with permission.)

conclusion of a functional magnetic resonance imaging study aimed at demarcating that separation (Hervé et al., 2013). In this study, activations by ToM and emotional speech overlapped in posterior cortex, in dorsomedial prefrontal cortex, and in the left orbital prefrontal cortex (Figure 5.6). In agreement with prior studies (see meta-analysis by Carrington and Bailey, 2009), the ventromedial prefrontal cortex was more active during the emotional than the linguistic aspects of sentence processing. Taken as a whole, these imaging studies clearly indicate that language processing engages widely distributed networks that involve cortical and subcortical regions, with a dominant node in ventromedial prefrontal cortex for the affective aspects of that processing.

## VI. INTELLIGENCE

Intelligence may be defined as “the ability to adjust by reasoning to new changes, to solve new problems, and to create valued new forms of action and expression” (Fuster, 2003). From early on in the history of frontal-lobe research, human intelligence has been thought to be served by that vast region of cortex, which reaches its greatest expansion in the most intelligent animal organism. It is indeed tempting to assume that the cortex of the frontal lobes constitutes the neural substrate of the intellect. Also from early on (Munk, 1882), however, that assumption has been challenged on the basis of numerous experimental and clinical observations. Most patients with frontal lesions do

not exhibit intellectual deficits when properly tested for such deficits. They have a normal intelligence quotient (IQ), and some are capable of notable intellectual achievement (Hebb, 1939; Stuss and Benson, 1986).

Nevertheless, intelligence being the complex function that it is, the issue remains unsettled, for certain aspects of that function are frequently compromised by prefrontal damage. Prominent among these are attention, reasoning, problem-solving, verbal expression, memory, abstraction, and the ability to formulate behavioral plans and to pursue them to their goal. All these capabilities are components of intelligence, and any of them may be deficient in the frontal patient, as many early studies concluded (Brickner, 1936; Rylander, 1939; Goldstein, 1944; Halstead, 1947; Milner, 1963, 1964; Hamlin, 1970; Drewe, 1974), and as we have seen in previous sections. All the executive capabilities discussed above, in fact, are needed for the intelligent temporal integration of behavior, most certainly when that behavior is complex, original, and creative.

Thus, on close analysis it turns out that even standard tests of intelligence can expose deficits of this function in some frontal patients, especially if their damage is to the left hemisphere (Tow, 1955; Milner, 1964; Smith, 1966). For that purpose, the Wechsler Adult Intelligence Scale (WAIS) is more sensitive than the Stanford-Binet Test. Even more sensitive to frontal-lobe damage is the Spearman's Test which, with its "g-factor," tests what has been named "fluid intelligence," which includes the capacity to solve new problems (Duncan et al., 1995; Roca et al., 2010). The test is also particularly sensitive to *goal neglect* (Duncan et al., 1996), a disorder of temporally extended goal-directed behavior and therefore of temporal integration. In any case, there is usually a striking discrepancy between intelligence-test scores, which may even be in the high range (Blumer and Benson, 1975; Damasio, 1985), and the degree of impairment, often severe, of the cognitive

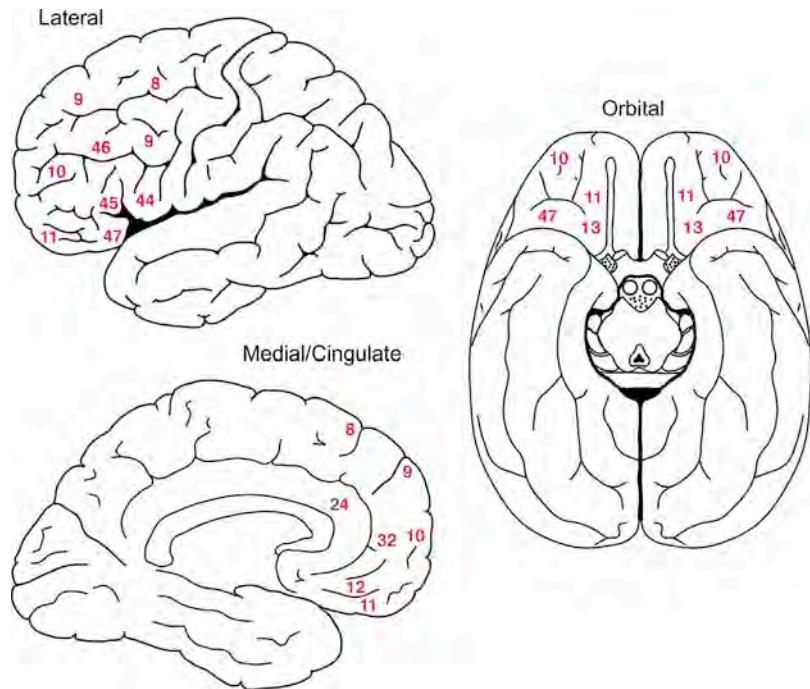
functions that we have been discussing and that unquestionably support intelligence.

Almost by its definition, there is one form of intelligence that is bound to suffer from frontal lobe damage: creative intelligence. Creative intelligence is the capacity to create new goals, projects and plans; indeed, we might say, "to invent the future." To the extent that prefrontal damage compromises such executive functions as planning, creative intelligence must be compromised. Yet there is a dearth of neuropsychological studies dealing specifically with the effects of prefrontal damage on creative intelligence. A few of these studies (Luria and Simernitskaya, 1977; Cook, 1986; Lezak, 1995) point to the contribution of the right hemisphere in general, and the right frontal cortex in particular, to creative intelligence. The issue will be further discussed in Chapter 8.

## VII. PREFRONTAL SYNDROMES

It seems questionable to expect *a priori* that lesions – however well defined anatomically – of such a heterogeneous brain structure as the human prefrontal cortex should result in uniform and well-identifiable syndromes. By simply considering the large diversity of connections of prefrontal areas (see Chapter 2), it is difficult to conceive that the lesion of any area, singly or in combination, should result in a clinical picture that we could call unique for all cases with anatomically identical lesions. The problem with any attempt to define any such clinical entity is compounded by individual variability in the connective makeup of prefrontal networks. That variability derives from the fact that these networks, prior to lesion, have become differentiated through imponderable synaptic changes that are the result of individual development and experience.

There are, however, certain groups of symptoms that tend to occur together after prefrontal lesion and that differ depending on the



**FIGURE 5.7** Lateral, orbital, and medial views of the cortex to illustrate the prefrontal regions (areas numbered after Brodmann's cytoarchitectonic map) within which lesions lead to the three major prefrontal syndromes.

location and magnitude of that lesion. Lesions in the three major regions of the prefrontal cortex, as defined by gross anatomy – lateral, orbital, and medial – tend to yield three different syndromes or clusters of symptoms, which are described below. Thus, what follows is a brief recapitulation of observations previously discussed in this chapter, now grouped by prefrontal region and with added emphasis on interhemispheric differences and on the relationships between symptoms.

### A. Lateral

The lateral prefrontal cortex is the prefrontal cortex of the lateral convexity of the frontal lobe (Figure 5.7). It comprises part or the entirety of areas 8, 9, 10, and 46. Lesion in any or all of these areas leads to the lateral syndrome. The

lesion may be caused by trauma, tumor, vascular accident, or other disease processes.

An attention disorder is usually at the foreground of the lateral syndrome. This disorder, however, has certain features deriving from the particular aspect of attention disturbed by the frontal injury, and to some extent from the area injured. As noted above, attention has two major aspects. One may be called *inclusive* or *selective*; it is the attention directed to, focused on, a particular item of sensorium or inner experience. The other may be called *exclusionary*; it is the capacity to suppress from sensorium or inner experience items that can interfere with what is currently on focus.

It is the first aspect of attention, the selective one, which is commonly disturbed in the lateral syndrome, especially if the lesion is large. At its foundation seems to be the lack of drive

and awareness. Patients are generally apathetic, uninterested in themselves and the world around them. Many manifestations of frontal neglect derive from this, including possibly visuospatial neglect, along with gaze abnormalities, if the lesion encroaches on area 8. The apathy seems present to some degree in all lateral-damage conditions, in the right or the left hemisphere, and is most apparent after large bilateral lesions of the frontal convexity. The absence of a driving interest makes the patient vulnerable to interference, and this leads among other things to perseveration, which is another frequent lateral symptom.

The attention disorder permeates all other frontal cognitive functions, especially those that support executive functioning. The "dysexecutive syndrome," with the attention, working-memory, and planning disorders at the core, is basically the lateral syndrome. Patients are incapacitated not only in initiating spontaneous and deliberate action, but also in pursuing to their goal those actions that they have been able to initiate.

The difficulties in planning and working memory, which are frequent manifestations of lateral damage and the cause of the faulty temporal integration of behavior, reflect to some extent the difficulty in sustaining attention on internal representations. Both are more common in left than right lesions, with the possible exception of visual, non-verbal, working memory, which seems more prevalent after right lesions.

The lateral prefrontal syndrome is also characterized by disorders of the spoken language. These are partly secondary to the mentioned deficits in drive and attention. Language disorders, however, are most directly attributable to failure of temporal integration, with adverse consequences on speech fluency and often leading to prefrontal aphasia (Luria's frontal dynamic aphasia or TCMA). These language disorders are especially common in left prefrontal lesions.

Finally, a substantial proportion of patients with lateral prefrontal damage suffer from depression. In some patients the depression is secondary to cognitive disorder; in others it seems to be primary and indistinguishable from endogenous depression. It appears to be especially common in left-hemisphere lesions.

## B. Orbital

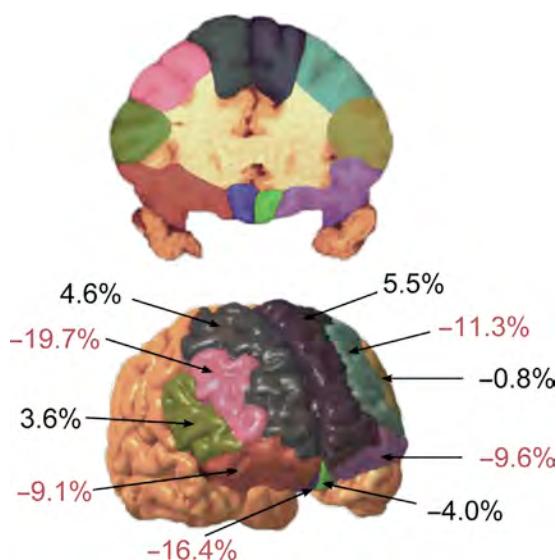
The orbitofrontal cortex is the cortex of the ventral, inferior, aspect of the frontal lobe ([Figure 5.7](#)). It comprises mainly areas 11 and 13. The orbital prefrontal syndrome can ensue from a variety of disease processes, including tumors and aneurysms of the anterior communicating artery.

Attention is disturbed mainly in its exclusionary aspect. The patient is unable to suppress interference from external stimuli or internal tendencies. Imitation of others and utilization behavior – the compulsion to utilize objects or tools prompted simply by their presence – may be symptoms related to that lack of interference control ([Lhermitte et al., 1986](#)). Another symptom is perseveration, which occurs in some patients, but not the majority. Orbitofrontal hypermotility is the opposite of the hypomotility and aspontaneity of the apathetic syndrome from lateral or medial lesions. Instead of too little drive, the patient has too much of it, and as a result seems driven by ceaseless energy and impulsivity, which may even interfere with normal physiological functions such as sleep. In a substantial number of patients the prevalent affect is euphoria, often accompanied by irritability and a contentious, paranoid stance ([Cummings, 1985](#)). Instincts are disinhibited and moral judgment impaired. Orbitofrontal patients may show by their behavior a blatant disregard for even the most elementary ethical principles. All in all, the orbitofrontal syndrome is often indistinguishable from mania.

Criminal sociopathy is another psychiatric condition analogous in some respects to the

orbitofrontal syndrome. Because of the similarities between the orbital patient's social behavior and that of the psychopath or sociopath, several studies have been conducted of neuropsychological indices of prefrontal function in psychopaths with the aim of finding prefrontal abnormalities in such individuals. At least two of the studies (Gorenstein, 1982; Lapierre et al., 1995) show deficits in test performance compatible with orbitofrontal pathology. An imaging study (Raine et al., 2011) found subnormal volumes of gray matter in several prefrontal regions, including orbital cortex, in people with APD (Figure 5.8).

Yet another clinical parallel is the one between the orbital syndrome and ADHD in the hyperactive child. This is discussed below, under Development.



**FIGURE 5.8** Top: Coronal view of the frontal cortex illustrating segmentation into major regions. Bottom: Three-dimensional view illustrating the percentage volume reduction (or increase) in subjects with antisocial personality disorder compared to normal controls. Significant volume reductions are coded in red. (From Raine et al., 2011, slightly modified, with permission.)

The emotional and instinctual disorders that color the orbital patient's personality and psychosocial behavior have been extensively studied and described by Damasios and colleagues (Damasio et al., 1991; Damasio, 1995). In their studies, they refer to the results of damage to the ventromedial prefrontal cortex, that is, orbital damage encroaching on medial cortex, or *vice versa*. What they describe, however, is in almost every respect the typical orbitofrontal syndrome outlined above.

### C. Medial/Anterior Cingulate

The medial prefrontal cortex comprises parts of areas 8–10, and areas 12, 24, and 32 (Figure 5.7). The latter two areas constitute the anterior cingulate cortex.

Most of the medial frontal cortex is involved in attention and somatic motility in ways that are not completely understood. Because of this, the disorders resulting from medial lesions are poorly defined, except in the case of large lesion (Cummings, 1985, 1993). Lesions in the medial aspects of areas 6 (SMA) and 8 frequently lead to difficulties in the initiation and performance of limb, eye, or speech movements. Lesions of the anterior cingulate region generally lead to hypokinesia or akinesia, depending on their size (Meador et al., 1986; Verfaellie and Heilman, 1987). They are also frequently accompanied by defective self-monitoring of behavior and of the ability to correct errors (Rollnik et al., 2004; Di Pellegrino et al., 2007). Akinetic mutism often results from massive bilateral lesions. It is usually accompanied by severe neurovegetative deterioration.

Some patients with lesions of the anterior cingulate region have been noted to suffer from cataplexy (Ethelberg, 1950), that is, the paroxysmal and general loss of muscle tonus commonly induced by strong emotion (Levin, 1953). It happens in the fully conscious state; for example, a patient, in a tense moment of a televised sports event, may fall to the floor in a

cataplectic fit and be unable to reach the burning cigarette that he sees smoldering on the carpet. This writer once postulated that the global adynamia of anterior-cingulate cataplexy results from irritation of area 24 (Fuster, 1955). Area 24 is at the crossroads of pathways linking the limbic system with the frontal lobe (see Chapter 2) and, at the same time, is one of the so-called suppressor areas, which upon stimulation induce general muscular hypotonia (Smith, 1945). To this day, however, the pathogenesis of frontal cataplexy remains obscure.

Apathy is the most prevalent disorder of affect from medial frontal damage, again especially if that damage is large. In this respect, medial patients may resemble lateral patients. As with regard to everything and everybody else, subjects with large medial lesion appear characteristically unaware of their own condition (Nielsen and Jacobs, 1951; Barris and Schuman, 1953).

## VIII. DEVELOPMENT

As we have seen in Chapter 2, the prefrontal cortex is structurally one of the last cortical regions to reach full development in the course of ontogeny, as in the course of evolution. By certain criteria (e.g., myelogenesis), its complete structural maturation does not occur until the third decade of life. The available evidence indicates that the development of prefrontal functions generally takes place *pari passu* with that structural development. This evidence is reviewed in this section.

A central theme of this monograph is that the prefrontal cortex is critically involved in the temporal organization of goal-directed actions in the behavioral, linguistic, and cognitive domains. This supraordinate function of temporal organization, mainly with a base in lateral cortex, is supported by the executive functions that, as we have seen earlier in this chapter, are impaired after prefrontal lesion: above all,

attention, working memory, planning, decision-making, and inhibitory control. The latter function, with a base in orbital cortex, serves also social and emotional functions. All these functions are interrelated and widely distributed, hence *per se* non-localizable anywhere in the brain. All, however, have a prefrontal support that serves the temporal organization of actions toward prospective goals. This prospective, telological, attribute of executive functions is, as we argue in Chapter 8, the hallmark of that prefrontal contribution to them. Next, we review what is known about their development.

Before proceeding with the normative functional development of the prefrontal cortex, and in accord with the general subject of this chapter, it is appropriate to consider what happens when frontal damage in early childhood somehow impedes that development. Here, two principles seem in conflict with each other. One is the general rule that cortical damage in the adult is more deleterious and leaves longer lasting sequelae than in the child. This is a well-known principle that, as we have seen in Chapter 4, applies also to frontal animals. Accordingly, large lesions of the left hemisphere (hemidecortication) before the age of 6 years have been seen to induce minimal or no deficit in the development of language (Lenneberg, 1967; Dennis and Whitaker, 1976; Hertz-Pannier et al., 2002). The clear, substantiated implication is that the right hemisphere takes over the plasticity of the missing hemisphere.

On the other hand, there is the seemingly conflicting evidence that early frontal lesions, however discrete, can leave deficits that are not immediately apparent but later lead to developmental problems. Those problems include attention deficits, learning disabilities, impaired reasoning, impulsivity, emotional instability, lack of moral judgment, and criminal behavior (Welsh and Pennington, 1988; Price et al., 1990; Marlowe, 1992; Anderson et al., 2000, 2006; Christ et al., 2003; Eslinger et al., 2004;

Max et al., 2005). It would appear that some functions are more vulnerable to early injury than others, which suggests that, in childhood, different functions develop at different times. The longitudinal use of various psychological tests at different ages strengthens this suspicion (reviewed by Anderson et al., 2002).

What, then, is the developmental timetable for the different prefrontal functions? The answer to this question should logically lie in the testing of cognitive functions at different ages. Probably no one did this earlier, and in many respects better, than Piaget (1952, 1954), although his intent was not especially to explore the functions of the frontal lobe. His published work is full of valuable insights and unique observations on the development in the child of the very functions that interest us, such as attention and short-term memory. However, perhaps because his primary interest was not in these functions but in perception, reasoning, and abstraction, his work has not received the attention it deserves from neuropsychologists of the frontal lobe (with one exception; see below). One of the many things we have learned from Piaget is that logical reasoning, which in turn depends on basic cognitive functions of the prefrontal cortex, does not attain full development until the age of about 12 years.

Both components of attention, selective and exclusionary, seem also to develop gradually toward full maturity at about 12 years, with maximum development between 6 and 9 (Humphrey, 1982; Passler et al., 1985; Miller and Weiss, 1981, 1982; Tipper et al., 1989; Crone et al., 2006; Ghosh et al., 2010; Gandhi et al., 2011; Vuontela et al., 2013). The maturation of exclusionary attention, that is, the inhibition of interference (distraction), proceeds along with the acquisition of perceptual and motor skills that heavily depend on attention (Chadwick and Rutter, 1983; Becker et al., 1987).

Because the maturation of perceptual and motor attention, both selective and exclusionary, is eminently dependent on prefrontal

development, it is reasonable to suppose that their failure in childhood is attributable to a deficit in that development. Consequently, many have entertained the hypothesis that ADHD, with the hyperactivity (or hyperreactivity) that is usually part of it, is due to a lag of neural development, more specifically a lag in the development of the prefrontal cortex (Kinsbourne, 1973; Satterfield et al., 1974; Stamm and Kreder, 1979; Rosenthal and Allen, 1978; Mattes, 1980; Chelune et al., 1986; Barkley, 1997; Sullivan and Brake, 2003; Shaw et al., 2013). Several studies directly tested this hypothesis by submitting inattentive-overactive children to a battery of tests of prefrontal function, including the WCST, memory tests, reversal tests, and the Stroop test (Gorenstein et al., 1989; Aron and Poldrack, 2005; Mercadillo et al., 2012; Sun and Buys, 2012). As predicted, the subjects showed deficits in all of them.

In the light of the well-known role of the prefrontal cortex in working memory, it is reasonable to explore in the child the development of the ability to perform delay tasks. Because of the abundant data from non-human primates on this issue, the first question is how infant humans compare to infant monkeys in delay tasks. Diamond (1990) addressed this question by using on children a test that is virtually identical to delayed response. The test was originally devised by Piaget and designated the *A-not-B task*. Essentially, it requires retaining in memory – for 0–10s – the observed position of a reward (right or left), which the tester changes from one trial to another. Infants have the tendency to repeat responses to a position once rewarded, despite the need for change (the “A-not-B error”). Beginning at about 7 months of age, they can tolerate a 1s delay without error. Tolerance of longer delays increases as a function of age. Thus, it turns out that human infants develop between 7½ and 12 months of age the ability that monkeys develop between 1½ and 4 months of age (Diamond and Goldman-Rakic, 1989). The same is true

for other delay tasks (Diamond and Doar, 1989; Crone et al., 2010; Vuontela et al., 2013). Nonetheless, the length of the delay is just one parameter of delay tasks. Others include the complexity of the cue, its verbal load, and its saliency. If these parameters were tracked, it would probably reveal a longer timetable for the full development of the ability to perform the tasks.

Kaldy and Sigala (2004) show that 9-month-old infants can integrate the visual features of an object with its location as part of the content of working memory in delay tasks. On the basis of this and other evidence, they argue for the early development of the *what–where* integration in working memory and against the segregation of working-memory components in prefrontal cortex.

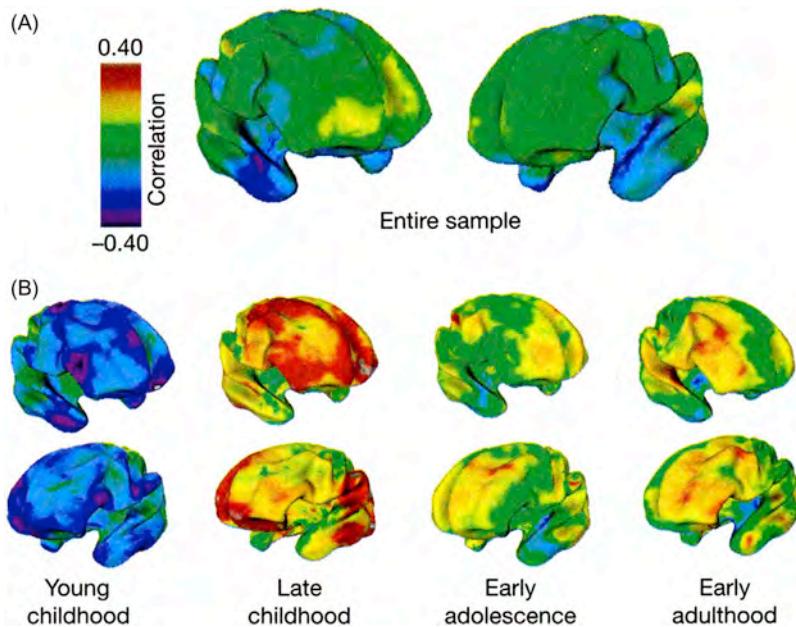
In addition to testing working memory, delay tasks test the capacity to suppress internal interference. Thus, the development of the ability to perform those tasks reflects also the development of this inhibitory-control function. The same can be said for the development of performance in several other tasks presumed to test working memory or, more generally, executive function, such as the WCST (Chelune and Baer, 1986; Welsh et al., 1991), the Tower of Hanoi (Welsh et al., 1991), temporal ordering (Becker et al., 1987), and arithmetic competency (Espy et al., 2004). In all of them, the child reaches the mature level of performance by age 10–12 years, relatively independent of IQ.

Planning and executive memory appear to have a similar timetable, possibly also with rapid development between the ages of 6 and 9 years. An interesting question in this regard is how early children develop the capacity to form inner representations of complex sequential action. Here, the work of Meltzoff and colleagues is revealing. It shows that 6-week-old infants can imitate the actions of adults on re-encounter after 24 hours (Meltzoff and Moore, 1994). This clearly indicates the formation and retention of motor patterns at that

age. The capacity to form and retain complex motor memories, as that of complex perceptual memories, undoubtedly increases subsequently with age. Eighteen-month-old children can not only re-enact complex series that they have witnessed adults perform, but also anticipate and create the serial acts needed to fulfill the adult's intentions as the children intuit them (Meltzoff, 1995). If the goals are made clear, by age 6 years children can construct elaborate plans (Klahr and Robinson, 1981).

Reading is one of the activities of temporal integration with the highest hierarchical position; even silent reading demands attention, working memory, and the re-enactment of complex motor memory. Thus, we can reasonably assume a prefrontal development disorder in reading disabilities. A study by Kelly et al. (1989) supports this assumption. Twelve-year-old children with dyslexia show a higher incidence of temporal-integrative dysfunction (i.e., measured deficits in selective attention, interference control, phonemic production, etc.) than children of the same age without a reading disability. A neuroimaging study of dyslexics (Hoeft et al., 2011) shows that greater activation of right prefrontal cortex predicts greater improvement in the acquisition of reading skills, indicating that that cortex is of fundamental importance in the functional reorganization of neural networks in dyslexia.

The development of executive functions does not end at age 12, any more than the structural maturation of the prefrontal cortex reaches completion at that age. True, the basic capability to exercise those functions may have been reached before puberty, but the proficiency, range, cognitive content, and resilience of each one of them certainly expand beyond that time. Well into adulthood, attention span increases, plans become more elaborate, goals include increasing numbers of subgoals, decision-making is more dependent on deliberation, and the capacity increases to use both inductive and deductive reasoning. Impulsivity



**FIGURE 5.9** (A) In a sample of 307 children and adolescents, a low positive correlation was found overall between intelligence quotient (IQ) and cortical thickness. (B) By separating the subjects by age group, significant negative correlations were found in young children (age 7–9), which denoted higher IQ with thinner cortex. That correlation reversed in late childhood, when the correlation became positive and stayed positive into early adulthood (higher IQ with thicker cortex), especially in prefrontal areas. (From *Shaw et al., 2006*, with permission.)

also becomes more restrained, as does risk-taking. Accordingly, the performance on gambling tasks (e.g., IGT) steadily improves from the sixth grade to adulthood (Overman et al., 2004). Brain imaging shows that prefrontal structural maturation progresses into the third decade of life (Sowell et al., 1999, 2002). Imaging also shows that, in adolescence, this maturation goes hand in hand with the development of intelligence: Shaw et al. (2006) demonstrate a significant correlation between IQ and the increase in cortical thickness, notably in prefrontal regions (Figure 5.9).

To sum up, the review of the developmental literature (see also Stuss, 1992, Anderson et al., 2002, and Spencer-Smith and Anderson, 2009) indicates that, indeed, the temporal-integrative functions of the prefrontal cortex – attention, memory, planning – develop *pari passu* with its

structural maturation. Those functions develop gradually, with spurts between 5 and 10 years of age, to reach completion at about age 12. Nevertheless, executive functions continue to develop beyond that age, along with cognitive ability and prefrontal maturation.

## IX. AGING

Both phylogenetically and ontogenetically, the prefrontal cortex is one of the last neocortical regions to develop structurally, yet it seems to be one of the first to deteriorate with senescence. The timetable and consequences of prefrontal senescence, however, are much more difficult to define than those of prefrontal development. The reasons are fairly obvious. In the first place, the manifestations of cortical

involution are subject to greater individual variability than those of cortical development. Second, they are subject to certain psychosocial factors that are specifically related to advancing age. Third, they are subject to medical illness, which is more common in the aging than in the growing organism. Despite those difficulties, it is possible to discern the general characteristics of the cognitive impairment of normal aging and the role of prefrontal involution in it. After discussing normal aging, we shall deal briefly with nervous diseases of the aged that more or less selectively affect the frontal lobes.

The age-dependent decline in executive functions has been well documented (see, for example, earlier and comprehensive reviews by [Hasher and Zachs, 1988](#), and [Kausler, 1991](#)). The decline has been substantiated by use of a number of neuropsychological tests described in detail by [Weintraub and Mazour \(2000\)](#).

After an extensive review of the literature, [West \(1996\)](#) concluded that cognitive aging is to a large degree consistent with the involution of the prefrontal cortex. In agreement with several aspects of the neuropsychological model of prefrontal functions presented in Chapter 8, he emphasized the overall age-dependent decline in the general function of temporal integration and its supportive processes of working memory (both prospective and retrospective) and inhibitory control. As did many others, he argued for a representation of the latter function in dorsolateral prefrontal cortex, in addition to orbital cortex.

Those views are now borne out by structural imaging. Elderly individuals show high degrees of white matter hyperintensity, a magnetic-resonance sign of white matter degeneration, especially under lateral prefrontal cortex and other cortices connected with it ([Gunning-Dixon and Raz, 2003](#); [Taylor et al., 2003](#); [Elderkin-Thompson et al., 2008](#); [Hinman and Abraham, 2007](#)). Given the essential role of connectivity in the integrative functions of the prefrontal cortex, that evidence apparently

constitutes an important correlate of aging and of the cognitive deficits that accompany it.

Among the executive functions subject to aging decline, attention occupies a central position. In general, normal aging is accompanied by a gradual diminution of attentive functions, the interest in the self and the world, and the capacity to focus the mind on limited aspects of them. That broad decline of attention is minimal in some individuals, marked in others. The onset of the decline varies considerably from one person to another, usually appearing in the seventh or eighth decade of life. Its progression is largely independent of the generally minor mood swings of normal existence.

Is that decline of selective attention specifically a sign of prefrontal involution? The argument for this rests on two points: (1) the attention deficit resembles phenomenologically those that result from prefrontal injury (see above), although it may be more subtle than them; and (2) that deficit correlates with decline in other executive, temporal-integration functions. That correlation may reflect, in fact, a causal relationship, for many of those functions depend on attention, beginning with working memory – attention directed to an internal representation.

Indeed, the decline of the intensive, selective aspects of attention probably plays a major role in the working-memory decline of elderly people, exemplified by deficits in performance of tasks of temporal ordering ([Kinsbourne, 1973](#); [Daigneault and Braun, 1993](#); [Parkin et al., 1995](#); [Szymaszek et al., 2009](#); [Blachstein et al., 2012](#); [Fogerty et al., 2012](#)), free recall ([Craik and Byrd, 1982](#); [Craik, 1986](#); [Parkin and Lawrence, 1994](#)), and recency judgment ([McCormack, 1982](#)). Difficulties with the inhibitory control of interference also play a role in that working-memory decline, as indicated by deficits in tasks where that control is essential, such as the WCST ([Benton et al., 1981](#)), the Stroop test ([Comalli et al., 1962](#); [Cohn et al., 1984](#)), or a conditional associative learning test ([Levine et al., 1997](#)). In sum, attention deficits account in part for the cognitive disorders of

elderly people, as they undoubtedly account for disorders in planning, set shifting, and decision-making, which are other prefrontal functions that support the temporal organization of actions. These functions also deteriorate with advancing age, although their deterioration is less well documented.

In the elderly person, long-term memory and its retrieval are less affected than short-term memory (for a comprehensive review see [Moscovitch and Winocur, 1995](#)), except in the presence of pathological aging that affects brain structures besides the prefrontal cortex. Nor is performance impaired on tests that depend on established memory ([Moscovitch, 1982](#); [Light and Singh, 1987](#); [Light and Albertson, 1989](#); [Mitchell, 1989](#)).

Analysis of the interactions of psychosocial factors with involutional factors emphasizes the central role of the attention deficit in cognitive disorders of elderly people. That analysis substantiates the decisive influence of the environment in maintaining drive and attention, and thus forestalling the cognitive decline of the elderly individual ([Arbuckle et al., 1986](#)). Winocur and his colleagues ([Winocur et al., 1987](#); [Winocur and Moscovitch, 1990](#)) compared the cognitive functioning of institutionalized with that of community-dwelling old people. Subjects in the two groups were matched for age, health, and IQ, and given tests of frontal function, including working memory. Consistently, the community-dwelling elders outperformed the institutionalized ones. The results show that an environment promoting interests and self-reliance, thus countering the attention deficit, leads to higher cognitive functioning than one without incentives in which the individual loses control of their circumstances.

Because the cognitive decline of old age is so critically dependent on the decline of executive functions with a prefrontal base, notably attention and working memory, special care should be taken with the administration of certain drugs that impact adversely on those

functions and are widely used in elderly people for medical or psychiatric reasons. In a study of 500 cases, accompanied by an extensive review of the literature, [Robles Bayón and Gude Sampedro \(2012\)](#) amply document the abuse of those drugs and their iatrogenic ill-effects on the cognitive faculties of elderly individuals. They recognize the appropriateness of using benzodiazepines to treat anxiety, statins to treat excessive blood cholesterol, anticholinergic drugs to treat memory loss in dementia, as well as antihypertensive drugs to treat high blood pressure. At the same time, they caution that all of them have untoward effects on cognition and behavior, especially in elderly people. For that reason, the authors advise the judicious choice of every drug, as well as the dosage and the length of treatment in accord with the special clinical needs of each patient.

Finally, there are degenerative diseases of old age that prominently affect the prefrontal cortex, sometimes first and foremost. One is Pick's disease, which usually affects both frontal and temporal lobes, and is distinguished neuropathologically by the presence of cortical neurons with certain characteristic inclusion bodies, called Pick cells ([Constantinidis et al., 1974](#); [Brun, 1987](#); [Gustafson, 1987](#); [Neary et al., 1988, 2005](#); [Neary and Snowden, 1991](#); [Kertesz, 2005](#)). Now known as frontotemporal dementia (FTD), Pick's is one of the dementias originally described by [Alzheimer \(1911\)](#).

Considerable progress has been made in determining the genetics of FTD: a strong linkage to chromosome 17 among others, especially around the so-called *tau* locus ([Foster et al., 1997](#); [Bronner et al., 2006](#); [Pan and Chen, 2013](#); [Rademakers and van Blitterswijk, 2013](#)). The ratio of the incidence of FTD to that of Alzheimer's disease is about 1 to 4 and its onset is usually between 45 and 65 years of age. The clinical picture of FTD varies somewhat from case to case ([Neary et al., 2005](#); [Ghosh and Lippa, 2013](#)). Some of the symptoms are non-specific and of a general nature, such as

lack of spontaneity, lack of concern, personality changes, and loss of social graces. Others seem to depend on the prefrontal region most affected. These symptoms tend to cluster in syndromes resembling those described in the previous section: (1) apathy, blunt affect, inertia, perseveration, impoverishment of speech, lack of foresight, and poor short-term memory; (2) euphoria, hyperkinesia, irritability, impulsivity, distractibility, inappropriateness, poor self-monitoring, and insomnia; and (3) lethargy, akinesia, and mutism. Most cases present mixtures of these symptoms because ordinarily their pathology is not circumscribed to any one anatomically defined prefrontal region.

Alzheimer's disease has yet broader pathology. In addition to the prefrontal cortex, it affects the cortex of the entorhinal, temporal, and parietal regions. The prefrontal cortex may not be the first to be involved in the course of the illness. Thus, the symptomatology of Alzheimer's is ordinarily broader and less characteristically frontal than that of FTD (Neary and Snowden, 1991). The patient with Alzheimer's disease typically has disorders of attention and memory that are usually more severe than in FTD. In late stages of Alzheimer's, the patient is disoriented in space and time, and amnesic. The patient's mood and affect are highly labile. Both frontal and posterior types of aphasia are common in Alzheimer's. Frontal symptoms like those enumerated in the previous paragraph (with regard to FTD) may appear as the disease advances and affects the prefrontal cortex. That pathological progression toward the prefrontal cortex is substantiated by structural neuroimaging (Thompson et al., 2003; Hua et al., 2009; Verdoorn et al., 2011).

## X. SUMMARY

The main sources of empirical data on the effects of prefrontal damage in the human are diseases and traumatic lesions of the frontal

lobe. Also contributory are cases of frontal psychosurgery, which is no longer carried out. The neuropsychological effects of prefrontal damage vary greatly depending on the location and the extent of that damage. This chapter deals with those effects, which are first discussed by separate altered functions and then by syndrome; that is, by group of symptoms from damage to each of the major prefrontal regions.

Apathy and a general lack of interest are common results of large prefrontal lesion, especially if it involves lateral or medial cortex. Depression is the most common affective symptom from more circumscribed prefrontal lesions, especially if they involve the left lateral and polar cortex, although some affective disorders can result from orbital damage as well. Large lateral or medial lesions, in addition to inducing apathy or depression, lead to low general motility, whereas orbital lesions frequently lead to hyperactivity. Orbital lesions are also accompanied by hyperreactivity to extraneous or irrelevant sensory stimuli, yet low reactivity to emotional stimuli. They also lead to the weakening of autonomic or visceral signals that are normally concomitant to emotion. Low emotional response is a reflection – or the cause – of low empathy, the emotional component of *theory of mind*, which is the ability to infer someone else's state of mind, including feelings and thoughts.

All prefrontal lesions, by reason of the emotional and cognitive changes they produce, tend to affect adversely the social life of the patient, usually constricting it. Orbital lesions, however, generally induce the most dramatic changes in social behavior, and these changes are usually opposite to social restraint. The most immediate reasons for those changes are five, acting singly or in combination: euphoric mood, disinhibition, faulty empathy, risky decision-making, and blunted moral judgment.

In the cognitive sphere, disorders of attention are the most common disorders of executive function from prefrontal damage. Those

abnormalities of the control of attention may take several forms: loss of general alertness, sensory – notably spatial – neglect, excessive distractibility, set-shifting deficit, disorder of ocular control, difficulty in sustaining attention, internal interference, and faulty executive set (executive attention). Attention disorders can be grouped into two major categories: (1) deficits in focusing or concentrating attention; and (2) deficits in suppressing external or internal interference (inhibitory control). The two kinds of deficit can coexist and strengthen each other. However, the first is especially common in damage to the lateral or medial prefrontal region, the second in damage to the orbital region. Both deficits may be partly responsible for deficits in other executive functions (e.g., working memory, action planning) and in the performance of tasks that test them.

Although prefrontal damage does not usually impair long-term declarative memory, many prefrontal patients have difficulties in encoding new memories as well as in retrieving and manipulating old ones. Some of these difficulties are reducible to deficits in attention, especially in interference control, and in monitoring or reality-testing, which are primarily affected in frontal injury and which, when not properly functioning, may give rise to false memory and confabulation.

The deficit in working memory, that is, in the ability to retain an item of information for a prospective action, is arguably the most characteristic executive deficit from prefrontal damage. It can occur as a result of any prefrontal lesion, but it occurs most consistently as a result of lateral damage. The working memory of verbal material is particularly vulnerable to left damage. The working-memory deficit can be exposed by the use of a large variety of tests, including delay tasks and the WCST. However, the performance of any of these tests is liable to certain deficits of attention, notably the inhibitory control of interference, which are themselves the result of frontal injury. The disruptive

effect of interference is most prevalent in orbital damage.

Patients with prefrontal damage, again especially if the damage is in lateral cortex, also commonly show a deficit in the ability to construct and execute plans of action. This deficit can be objectified with several neuropsychological tests. In the prefrontal patient, prospective action plans and motor attention are as vulnerable to interference as are perceptual memory and attention. Thus, the lack of inhibitory interference control, a common prefrontal disorder, contributes to the failure to formulate and execute plans.

Because of the failure of both the retrospective and the prospective aspects of executive functioning, the subject with substantial prefrontal lesion manifests a deficit in the ability to integrate actions in time. This deficit in temporal integration pervades all activities and prevents the patient (who lives "here and now") from constructing new sequences of behavior, speech, and reasoning. The resulting temporal concreteness is at the core of the executive deficit of the individual with prefrontal damage. Like all other defects of executive function, the temporal-synthesis defect may be compounded by the deficit in inhibitory control.

In the prefrontal patient, decision-making is impaired or distorted for one of two reasons (or both): failure of temporal integration – from working-memory and planning deficits – or emotional bias. Lateral-lesion patients make poor decisions mainly on account of their failure to integrate information across time; orbital-lesion patients do so mainly on account of emotional bias or reckless risk-taking. Poor decisions are usually accompanied by poor monitoring of their consequences, another common deficit from prefrontal lesion.

Using appropriate instruments, intelligence can be shown to be impaired in some individuals with frontal lesion. That impairment, which occurs mainly after a left lesion, is usually minor and disproportionate to the impairment of other

cognitive functions. Nonetheless, because intelligence depends to some degree on those functions, their failure, singly or in combination, may lead to lowering of IQ with accompanying deficits in general intelligence, abstraction, and creativity.

Lateral and medial frontal injuries, especially on the left or dominant hemisphere, commonly lead to difficulties in the spoken language. The prefrontal aphasia is characterized by a lack of spontaneous speech, impoverished verbal expression, and loss of verbal fluency. All the language disorders from damage to the frontal lobe reflect deficits in the temporal synthesis of language (syntagmatic properties of language). The language-integrating deficit from lesion of Broca's area is severe, whereas the one from lesion of more anterior prefrontal areas is more subtle.

Damage to each of the three major prefrontal regions results in a different syndrome or cluster of symptoms. The lateral syndrome is characterized mainly by difficulties in focusing and sustaining attention, lack of initiative and decision-making, inability to make plans and to execute them, poor working memory, and low verbal fluency; apathy and depression are the most common disorders of affect from lateral lesion. Almost all disorders are more conspicuous if the left lateral cortex is involved than if the right cortex is involved. The orbital syndrome is chiefly marked by impulsivity, hypermotility, distractibility, instinctual disinhibition, irritability, euphoria, perseveration, and lack of moral restraint. The medial/anterior cingulate syndrome is mainly distinguished by lack of initiative and spontaneity, hypokinesia or akinesia, and apathy. Also commonly impaired are the monitoring and correction of errors.

In the child, the cognitive and emotional functions of the prefrontal cortex develop in apparent synchrony with its structural maturation. All seem to reach a relative plateau of maturity at about the age of 12 years. Both aspects of attention, selective (focus) and exclusionary (inhibitory), also reach maturity at about age 12, after a period of relative acceleration

between the ages of 6 and 9. Working memory and planning (along with executive memory) seem to develop at the same pace and toward the same plateau (about 12 years). The same can be said for temporal integration, which depends on both working memory and planning. However, higher cognitive functions such as language and intelligence continue to develop into the third decade of life supported by the lateral prefrontal cortex, which does not reach full maturity until that time.

The prefrontal cortex is one of the first neocortical regions to undergo involution in normal aging. Attention is the first cognitive function to suffer from that involution. At an age that varies greatly from one individual to another, the elderly person usually becomes less interested in, and less attentive to, their environment than before. That loss of interest and attention is markedly sensitive to psychosocial factors, and has much to do with the rate of deterioration of other prefrontal cognitive functions that depend on attention. Working memory and planning are two of the functions that gradually deteriorate in normal aging with the advance of prefrontal involution.

All the cognitive declines of prefrontal aging are compounded and accelerated by pathological processes that affect the prefrontal cortex of the elderly person. This is most evident in FTD, a degenerative disorder characterized by premature atrophy of frontal and temporal lobes, and in Alzheimer's disease. Patients affected by these conditions exhibit personality changes, cognitive disorders, and affective disorders that are common consequences of prefrontal damage.

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# Neurophysiology

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## I. INTRODUCTION

It is by the use of electrical stimulation and recording methods that the prefrontal cortex has been shown to fulfill the basic rule first enunciated by [Hughlings Jackson \(1882\)](#) for motor cortex: the very same cortical area that represents an action is responsible for its coordination. In the prefrontal cortex, however, the action takes the form of complex behavior, and consequently it is more difficult here to correlate discrete sensory or motor events with electrical events; in fact, it is not possible to ascribe strictly sensory or motor properties to prefrontal cells. Any attempt to do so usually comes

into conflict with the associative, indeed integrative, nature of this cortex and its elements. Thus, the behavior of a cell is inextricable from its role in the cell assembly or network, which is distributed and has been formed in life experience by both sensory and motor associations. From motor to prefrontal cortex, the assemblies and networks of the frontal lobe are hierarchically organized to represent, and thus to coordinate, actions of increasing complexity. The most complex behaviors, especially if they are novel, temporally extended, and dependent on the resolution of ambiguities and uncertainties, are represented and coordinated in the prefrontal cortex.

Many uncertainties remain concerning the physiological functions of the prefrontal cortex, but it is unquestionably through neuroelectrical research that we have come to understand some of the basic functions by which it contributes to complex behavior. Field-potential and single-unit studies, and to some extent stimulation studies, have shown the importance of certain prefrontal areas in the neural processes that support certain sensory, motor, and visceral functions. Much beyond that, however, those studies have put us on the path to understanding the fundamentally integrative functions of the prefrontal cortex as a whole, and its role in the organization of goal-directed sequences of behavior. In that respect, single-unit studies have contributed in no small measure to the understanding of the role of prefrontal executive networks in working memory, in prospective planning, in temporal integration, and in the implementation of rules. In a word, electrophysiology – especially behavioral electrophysiology – has been critical to our query into the prefrontal mechanisms at the root of the cognitive control of goal-directed action. Before dealing with those issues, however, this chapter will discuss the involvement of certain prefrontal areas in the collection of sensory inputs, the generation of motor outputs, and their visceral and emotional functions, all of which undoubtedly serve the eminently integrative executive functions of the frontal lobe. These functions, as we shall see, can be best explored in the behaving animal.

## II. HISTORICAL BACKGROUND

For the neurophysiologists of the nineteenth century, the frontal association cortex was, by definition, electrically unexcitable. The localizationist explorations initiated by [Fritsch and Hitzig \(1870\)](#), using the technique of electrical stimulation, led to the mapping of the motor fields of the frontal cortex and, by exclusion, to

the demarcation of the vast “silent” region anterior to them, a region already some psychologists at the time presumed to be involved in associative functions ([Wundt, 1910](#)). It was soon recognized, however, that the border between electrically excitable cortex and unexcitable cortex could not be sharply drawn, in part because of some unexplained variability of stimulation effects, a so-called instability of motor points ([Grünbaum and Sherrington, 1903; Penfield and Welch, 1949](#)), and in part because of difficulties inherent in the use of electrical stimulation as an investigative tool. For example, it is difficult to determine the parameters that should be given to the artificial stimulus for eliciting physiologically meaningful effects. Indeed, given certain parameters (especially enough current), no part of the cortex is silent. Motor reactions can be elicited by stimulating practically any cortical area, including prefrontal areas ([Lilly, 1958](#)).

Since the mid-1990s, a great deal of research has been devoted to the effects of the application of electrical stimulation to the prefrontal cortex. Although the brain is essentially an electrically excitable organ, it has long been known that current exceeding certain physiological limits has a disruptive effect on it. In fact, the direct electrical stimulation of certain points of the human cortex has been shown to block the recall or articulation of certain words. Further, in humans and animals, electrical stimulation has been used to produce reversible functional lesion of brain areas, the prefrontal cortex among others. However, the mild direct current or the repetitive magnetic stimulation of this cortex has been shown to enhance or potentiate its physiological cognitive functions ([Pascual-Leone et al., 1999; Gazzaley, 2011; Cho et al., 2012; Coffman et al., 2012; Manenti et al., 2012; Balconi, 2013; Brunoni and Vanderhasselt, 2014](#)). Furthermore, the transcranial stimulation of the dorsolateral prefrontal cortex has a therapeutic effect on depression ([Padberg and George, 2009; Aleman et al., 2013; Allan et al., 2012](#)).

Recording techniques were not developed until the 1930s. Then, many of the connections of the prefrontal cortex were electrically demonstrated by combined use of stimulation and recording. In the same decade, chemical neuronography came into use. Introduced by Dusser de Barenne, the procedure was at one time extensively utilized for tracing cortical connections (Dusser de Barenne and McCulloch, 1938). Now it has little more than historical significance, having been largely superseded by more precise anatomical methods. Here, it should suffice to point out that strychnine neuronography provided evidence of some of the most important connective links of the prefrontal cortex before silver-stain and axon transport methods defined them with greater accuracy. Basically, the same reciprocal connections between prefrontal and other cortical regions that the newer methods have revealed in detail were previously outlined on the monkey's brain by neuronography (Bailey et al., 1944, 1950; Ward et al., 1946; McCulloch, 1948; Sugar et al., 1948, 1950). Prefrontal efferents to the thalamus (Bailey et al., 1950) were also demonstrated by the same method.

The evoked-potential method also contributed toward confirming the anatomical connections of the prefrontal cortex with other cortical regions (Bignall, 1969; Bignall and Imbert, 1969; Desiraju, 1975, 1976), the thalamus (Jasper et al., 1952; Felix, 1969; Desiraju, 1973, 1975), the hypothalamus (Kazakov et al., 1976), and the caudate nucleus (Liles, 1973). By using that same method and by applying appropriate parameters of stimulation, it was shown that the prefrontal cortex is one of the prime projection areas of the non-specific midline thalamic system (Starzl and Magoun, 1951; Starzl and Whitlock, 1952; Jasper, 1954; Nelson and Bignall, 1973). By the joint application of electrical stimulation and single-unit recording, evidence was obtained of the physiological relationships between the prefrontal cortex and limbic structures (Edinger et al., 1975; Canedo, 1982).

Also by use of the evoked-potential method, corticocortical connections between posterior and prefrontal cortices have been demonstrated in the human (Matsumoto et al., 2007). Those connections, previously demonstrated by anatomy – in the monkey – undoubtedly serve the perception-action cycle at higher levels of its organization (see Chapter 8).

### III. SENSORY FUNCTION

In the early 1960s, a number of investigations provided electrophysiological evidence for a role of the prefrontal cortex in the integration of inputs from various sectors of the sensorium. Some of that evidence was based on the analysis of sensory evoked potentials. Grey Walter (1964b) showed that electrical responses elicited by visual, auditory, and somatic stimuli can be recorded from humans over large and overlapping frontal areas. Subsequently, animal studies have more clearly defined the distribution of evoked responses on the cortical surface and provided clues about the routes that sensory inputs follow to reach the frontal cortex. Monkey studies (Bignall and Singer, 1967; Bignall and Imbert, 1969) showed that stimuli of three modalities elicited evoked responses in frontal areas, with considerable overlap in the prefrontal region. The ablation of primary sensory areas did not abolish sensory evoked potentials in the prefrontal cortex, an observation suggesting that those potentials are mediated, at least in part, by thalamic pathways possibly involving non-specific midline nuclei. On the other hand, electrical stimulation of primary areas, or areas in their vicinity, elicited potentials in the prefrontal cortex even after thalamectomy, suggesting that polysynaptic corticocortical pathways intervene in the transmission of sensory input to the prefrontal cortex. In the cat, connections from sensory areas to the frontal cortex have been traced electrophysiologically as far forward as the anterior

sigmoid and the orbital gyri (Imbert et al., 1966; Buser and Bignall, 1968) but not the prefrontal (proreal) cortex itself, although one evoked-potential study (Narikashvili et al., 1970) indicates some sensory convergence on that cortex.

Those early evoked-potential studies were not so much significant for their contribution to our understanding of the physiology of the prefrontal cortex as they were pointers to the sensory-integrative role of this cortex in cognition and behavior. Much more relevant to prefrontal physiological mechanisms has been single-cell recording in behaving animals, especially primates.

Neurons in the prefrontal cortex of the monkey react to visual stimuli (Mohler et al., 1973; Nelson and Bignall, 1973; Kubota et al., 1974; Schechter and Murphy, 1975; Benevento et al., 1977; Pigarev et al., 1979; Goldberg and Bushnell, 1981; Rizzolatti et al., 1981; Suzuki and Azuma, 1983; Thorpe et al., 1983; Bruce and Goldberg, 1985; Joseph and Barone, 1987; Romanski, 2007), auditory stimuli (Nelson and Bignall, 1973; Schechter and Murphy, 1975; Newman and Lindsley, 1976; Benevento et al., 1977; Azuma and Suzuki, 1984; Joseph and Barone, 1987; Romanski and Goldman-Rakic, 2002; Cadoret and Petrides, 2007), somatic stimuli (Nelson and Bignall, 1973; Schechter and Murphy, 1975; Romanski, 2007), olfactory stimuli (Tanabe et al., 1974, 1975; Critchley and Rolls, 1996a, 1996b; Zou and Buck, 2006), and gustatory stimuli (Thorpe et al., 1983; Scott et al., 1986). Some of the neuronal reactions exhibit substantial selectivity with regard to stimulus parameters. Although considerable variability has been observed in the topographic distribution of units as it pertains to the modality of the stimuli to which they respond, there seems to be a degree of specificity in that distribution; it is particularly evident in visual, olfactory, and gustatory cells. Units reactive to visual stimuli are especially common in the prearcuate region (area 8) and the inferior lateral prefrontal convexity. In the latter region,

units have been noted to respond to complex stimuli, such as faces (Scalaidhe et al., 1997). Olfactory and gustatory units, on the other hand, have been found in the posterior orbital and opercular (orbitotemporal) regions, respectively. In the orbitofrontal cortex of the rat, olfactory units have also been found which seem to engage in ensemble encoding of odors (Schoenbaum and Eichenbaum, 1995a, 1995b).

Whereas some studies reveal prefrontal units that respond to stimuli of only one modality, others show bimodal and trimodal responsiveness (Nelson and Bignall, 1973; Schechter and Murphy, 1975; Benevento et al., 1977; Ito, 1982). Benevento et al. (1977) report the interaction of auditory and visual inputs on units of the ventrolateral prefrontal cortex. By intracellular recording, they determined that some of those interactions could occur in the prefrontal units themselves and not at some previous synaptic step. Several forms of interaction were observed, some of them the result of opposite effects from auditory and visual stimuli on one and the same prefrontal cell; for example, inhibition from auditory stimuli and excitation from visual stimuli. Auditory–visual interactions were also observed at the unit level in the cortex of the superior temporal sulcus, another region that on the basis of anatomical connectivity could be expected to show multisensory convergence.

The presence in the prefrontal cortex of cells reactive to stimuli of every one of the sensory modalities, and most particularly of cells with multimodal properties, confirms the multisensory character of the prefrontal cortex that studies of connectivity and evoked potentials have suggested. Indeed, on both anatomical and physiological grounds, the prefrontal cortex is evidently cortex of sensory association. Its associational character is further highlighted by massive evidence, to be reviewed below, of its involvement in the animal's performance of motor actions contingent on exposure to behaviorally significant stimuli. Units of the frontal eye

field (area 8) epitomize the conditional stimulus-movement linkage, a form of association that requires the prefrontal cortex if and when a time lapse separates the stimulus from the action.

Another characteristic of prefrontal cells, also exemplified by area 8 units, is their involvement in selective sensorial attention. Many of those cells are demonstrably reactive to sensory stimuli, especially visual, if and insofar as such stimuli are motivationally or behaviorally significant (Fuster, 1973; Pigarev et al., 1979; Suzuki et al., 1979; Kojima, 1980; Kubota et al., 1980; Thorpe et al., 1983; Bruce and Goldberg, 1985; Watanabe, 1986, 1992; Joseph and Barone, 1987; Yamatani et al., 1990). This kind of conditional reactivity indicates that the sensory input to prefrontal units is subject to modulation by neural influences related to prior experience, motivation, or internal state. The mechanisms of such modulation of afferent input are unclear, although they probably involve limbic and diencephalic structures, as well as other regions of association cortex that project to the prefrontal cortex. In any case, the prefrontal cortex participates in controlling selective attention, that is, in suppressing the irrelevant, and enhancing the relevant, sensory information. Lesion studies, as we have seen, implicate the prefrontal cortex, especially the orbital and prearcuate areas, in these two aspects of attentive control. Next, let us briefly consider the experimental evidence bearing on some of the mechanisms underlying sensory attention and the role of the prefrontal cortex in them.

In the cat, some data suggest that the prefrontal – orbitofrontal – cortex and the midline thalamic nuclei projecting to it constitute a functional system regulating the activity of wide regions of the cerebral cortex. Experimental lesion or functional blockade of that system abolishes spindle bursts, recruiting responses, and other forms of synchronous electrographic activity associated with cortical inhibition (Lindsley et al., 1949; Velasco and Lindsley, 1965; Weinberger et al., 1965; Velasco

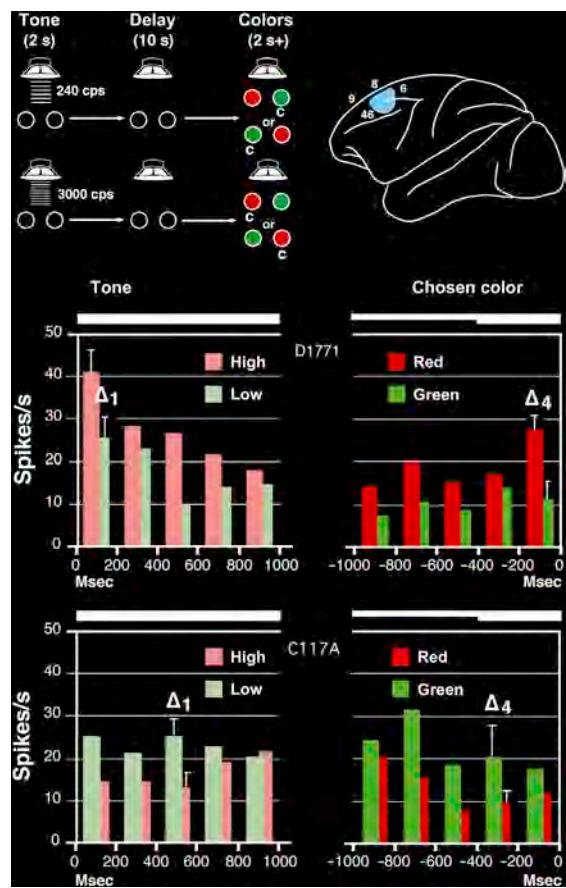
et al., 1968; Robertson and Lynch, 1971; Skinner, 1971b). Such procedures have also been reported to increase the amplitude of sensory evoked potentials (Skinner and Lindsley, 1967, 1971) and to abolish a slow negative potential on the frontal cortical surface that normally accompanies states of vigilance or expectancy (Skinner, 1971a). Furthermore, the cryogenic blockade of the inferior thalamic peduncle, which links the orbitofrontal cortex with the medial thalamus, has been shown to interfere with behavioral performance of simple alternation (Skinner and Lindsley, 1967). Skinner and Lindsley (1973) interpreted all these experimental observations as evidence for an orbitothalamic system that normally exerts inhibitory or suppressive influences over sensory inputs and is thereby essential for regulating sensory attention. Such influences may be mediated by other thalamic nuclei, notably the nucleus reticularis (Waszak et al., 1970; Yingling and Skinner, 1975; Skinner and Yingling, 1976). Crick (1984) made the hypothetical regulation of sensory input by the thalamic reticular complex a central element of his “searchlight” theory of attention.

Other studies, in both cats and monkeys, provide evidence of influences from the prefrontal cortex on the excitability of neurons in sensory systems, possibly channeled through the suggested corticothalamic system. For example, prefrontal stimulation has been noted to modify visual single-cell responses in the lateral geniculate body and to enhance recovery function after photic evoked potentials in the visual cortex (Spinelli and Pribram, 1967). In another study, interactions of prefrontal input with auditory input were observed in neurons of the superior temporal gyrus of the squirrel monkey (Alexander et al., 1976). Knight and collaborators, in humans, have been able to substantiate the influences of prefrontal cortex upon sensory cortices. In comparison with controls, patients with prefrontal damage show a relative increase (disinhibition) of auditory (Knight et al., 1989) and somatosensory (Yamaguchi and Knight,

1990) short-latency (25–35 ms) evoked potentials in cortical sensory areas.

The empirical evidence mentioned in the last three paragraphs points to a general role of the prefrontal cortex in the top-down regulation of central sensory mechanisms and, by implication, in perceptual attention. More specifically, the prefrontal cortex is implicated in spatial attention by evidence of its control of eye and head movement. In particular, the prearcuate prefrontal region (area 8), in the primate, is known to play a critical role in peripheral aspects of visual and possibly also auditory attention (Schiller et al., 1980; Goldberg and Bushnell, 1981; Azuma and Suzuki, 1984; Bruce and Goldberg, 1985; Bruce et al., 1985; Goldberg and Bruce, 1986; Vaadia et al., 1986). That cortical region controls those movements that adjust the spatial orientation of two important sectors of the sensory apparatus; those movements have the effect of optimizing the acquisition of sensory information coming through telereceptors.

In recent years, microelectrode studies in the behaving monkey have provided evidence of the associative, hence integrative, functions of the prefrontal cortex in long-term memory. The majority of these studies have been carried out in delay tasks, thus dealing with the capacity of prefrontal units to integrate sensory information across time. Numerous such studies of temporal integration at the single-cell level will be detailed below, in connection with delay tasks and working memory. Here, to conclude this section, we will only mention one of ours (Fuster et al., 2000) that illustrates the capacity of those units to integrate not only across time but also across sensory modalities. In this study, single-cell activity was recorded from the lateral prefrontal cortex of animals that had been previously and thoroughly trained to perform a task in which auditory stimuli were behaviorally associated with visual stimuli. On each trial of the task, the animal was presented with a brief tone (Figure 6.1) (Fuster et al., 2000). Depending on the pitch of that tone,



**FIGURE 6.1** Cross-temporal integration of sound and color in prefrontal cells. *Top left:* Event sequence in a trial: (1) brief tone; (2) 10 s delay; (3) two colors simultaneously presented; (4) animal rewarded for choosing the color (c) that matches the tone – green if low-pitch tone, red if high-pitch tone. (Tone and color position change at random from trial to trial.) *Top right:* Diagram of monkey's cortex, with numbers indicating Brodmann's areas; in blue, frontal region from which tone- and color-responsive cells were recorded. *Bottom:* Firing-frequency histograms from two cells, one, on top, selective for high-tone and red, and the other, below, for low-tone and green. The histograms are from a 1 s period beginning with tone onset (left), and from a 1 s period immediately preceding choice of color (right). Cellular discrimination:  $\Delta_1$  marks the 200 ms bin of maximal discrimination of tones, and  $\Delta_4$  of colors. Note the correlation of cell responses to tones and colors in accord with the rule of the task. (From Fuster et al., 2000, with permission.)

animal had to choose one or another of two different colors presented simultaneously a few seconds later (low tone signaled green choice; high tone signaled red choice). Cells in lateral prefrontal cortex responded to both tones and colors successively in the course of any given trial. Computational analysis showed that their responses to the tones were correlated in magnitude with their responses to the colors, in accord with the rules of the task. In short, the cells associated sounds with colors just as the monkey had learned to associate them during previous learning of the task. This finding highlights the cross-modal associative property of prefrontal neurons in long-term memory.

#### IV. MOTOR FUNCTION

Electrophysiological experiments have implicated certain parts of the prefrontal cortex in the execution or inhibition of certain specific categories of movements (e.g., eye movements from area 8). As in the case of sensory functions, the involvement of the prefrontal cortex in motor functions is most apparent in the awake and behaving animal. Outside the behavioral situation, the movements that can be elicited by electrical stimulation of prefrontal areas, with the exception of area 8, are variable and unpredictable, and generally have a high stimulation threshold; in some instances those movements appear to be fragments of larger motor action or to depend on conditions that are inadequately met in the acute experiment. Thus, the neuroelectrical manifestations of prefrontal function in movement can be studied best where, by design, discrete movements are conditioned to a stimulus or combination of stimuli. These phenomena are discussed in detail later in this chapter. First, however, we will discuss some issues concerning the functional connectivity of the prefrontal cortex with motor structures and the involvement of prefrontal areas, especially the frontal eye fields, in motor control.

The prefrontal cortex has been shown to modulate neuronal activity in subcortical motor structures. In the cat, the corticostriatal projection is demonstrated by stimulation and evoked-potential methods (Liles, 1973). The discharge of cells in the caudate nucleus is reportedly modulated by prefrontal input, which apparently interacts within the nucleus with input from the substantia nigra and the entopeduncular nucleus (Liles, 1974). Also in the cat, an inhibitory pathway has been traced from the prefrontal cortex to the ventromedial nucleus of the hypothalamus (Ohta and Oomura, 1979b). Conversely, an ascending facilitatory monosynaptic pathway connects that nucleus to the prefrontal cortex (Ohta and Oomura, 1979a). Both these pathways are presumably involved in the prefrontal control of feeding behavior (see Visceral and Emotional Functions, below). As some lesion studies suggest, the prefrontal cortex also exerts some control over aggressive behavior; the electrical stimulation of its medial surface in the cat is reported to suppress that kind of behavior (Siegel et al., 1974). Electrical stimulation studies provide evidence of the inhibitory control that the prefrontal cortex exerts over other aspects of motor behavior as well. Motor inhibition has been induced, in the cat, not only by orbitofrontal stimulation but also by stimulation of more posterior areas of the basal forebrain (Brutkowski, 1965; Sterman and Fairchild, 1966; Sauerland et al., 1967; Siegel and Wang, 1974), as if the orbital prefrontal cortex were the most anterior part of a vast basal compound of cortical areas adjacent to, or part of, the limbic system exerting inhibitory control of general motility. A related finding is that the stimulation of certain points within that basal cortical region can also induce sleep (Kaada, 1951; Clemente and Sterman, 1967; Alnaes et al., 1973).

The most consistent and extensively investigated motor effects arising from stimulation of the prefrontal cortex are the conjugated movements of the eyes that can be induced by

electrical stimulation of the so-called frontal eye fields, whose existence has been known for more than a century (Ferrier, 1874; Hitzig, 1874). These are discrete parcels of cortex, identified in both primates and carnivores and situated, depending on the species, somewhere between the frontal pole and the electrically delimited motor cortex of the precentral or precruciate region. Largely for reasons of methodology, the published descriptions of those "frontal eye fields" differ somewhat. Parameters of stimulation and certain experimental conditions (e.g., level of anesthesia) are known to be critical in that respect (Robinson and Fuchs, 1969). However, it has been established that the frontal eye field of the primate is a relatively circumscribed area in the dorsolateral frontal convexity, approximately corresponding to Brodmann's cytoarchitectonic area 8 (Penfield and Boldrey, 1937; Schiller et al., 1979; Schiller and Sandell, 1983; Bruce et al., 1985). This cortical field can be functionally subdivided into different sectors depending on the direction of the eye movements that can be elicited from it. Transcranial magnetic stimulation (TMS) in the human has permitted the delimitation of the frontal eye field within an area that comprises portions of dorsolateral prefrontal and premotor cortex (Chouinard et al., 2003; Pierrot-Deseilligny et al., 2004).

In the monkey, by stimulation and single-unit recording, a second eye field has been identified, straddling the upper edge of the prefrontal cortex (Schlag and Schlag-Rey, 1987). Because of its location and properties, this dorsomedial sector of prefrontal cortex has been called the *supplementary eye field* (SEF), a supplementary motor area (SMA) for the eyes. It appears, on the basis of the results of a large number of studies (for review see Tehovnik, 1995), that this cortical region is involved, among other things, in the integration of sequences of eye movements.

In the cat, also two separate and discontiguous eye fields have been identified. One is

in the region of the presylvian fissure and the other in the medial cortex (Schlag and Schlag-Rey, 1970); the latter is the SEF. All frontal eye fields are cytoarchitectonically of transitional character and receive projections from the mediodorsal nucleus of the thalamus, thereby qualifying as prefrontal cortex by our definition (see Chapter 2).

Under certain conditions, electrical stimuli applied to area 8 elicit not only eye movements but also other physiological changes indicative of more general action. For example, stimulation of this area can induce eyelid movements, pupillary dilatation, rotation of the head, and other phenomena, some of which resemble fragments of attentive behavior (Levinsohn, 1909; Smith, 1949; Penfield and Rasmussen, 1950; Bender, 1955; Segundo et al., 1955; Wagman et al., 1961; Wagman and Mehler, 1972). All these phenomena, eye movements included, implicate the frontal eye fields in anticipatory and goal-directed actions, of which ocular motility is an essential component. It is reasonable to suppose that the eye fields constitute an integral part of an assembly of neural structures, called by Hess (1943) the *teleokinetic system*, that serves ethological defense and adaptation. Orientation, fixation, centering, and pursuit movements of the eyes would be coordinated with the functional contributions of the other components of such a system. In this light, the relations of the optokinetic centers – including those in area 8 – with the visual system, with extrapyramidal structures, and with the vestibular apparatus would appear to be of clear biological significance.

Similarly, limb movements can be elicited by stimulation of some of the points of the supplementary area for the eye, which to some extent overlaps the SMA in area 6a (Macpherson et al., 1982; Alexander and Crutcher, 1990b; Lupino et al., 1991). Furthermore, single-unit studies show that cells in the SMA and premotor cortex of the monkey are modulated by visually guided forelimb movements (Okano and Tanji, 1987; Romo and Schultz, 1987; Kurata

and Wise, 1988; Rizzolatti et al., 1990; Mushiake et al., 1991). It is reasonable to conclude that this is also a teleokinetic area involved in the coordination of eye and hand toward attainable goals. Functionally, therefore, the SMA appears to be a microcosm of the prefrontal cortex at large (Tanji, 1994) for the temporal organization of goal-directed behavior (see Chapter 8).

Although the frontal eye fields evidently participate in the coordination of eye movements, they constitute more than a command post for initiating and executing such movements. This was evinced early on by the outcome of research by Bizzi and Schiller on the discharge of units in the monkey's arcuate eye field during movements of the eyes and the head (Bizzi, 1968; Bizzi and Schiller, 1970). They found two basic types of cells: cells that only exhibited firing during voluntary saccades and cells that discharged continuously during smooth pursuit or orientation in a given direction. Some cells have been shown to discharge before the initiation of movement, as in the precentral motor cortex (Evarts, 1966). Eye field (area 8) cells encode eye position, but the kind of input by which they do it is not clear. Apparently, that input is neither exclusively proprioceptive nor exclusively visual, although some of the cells have visual receptive fields (Mohler et al., 1973; Wurtz and Mohler, 1976; Goldberg and Bushnell, 1981; Suzuki and Azuma, 1983). In the dorsolateral prefrontal cortex, cells have also been found that encode sequences of eye movements (Barone and Joseph, 1989a).

Prefrontal neurons take part not only in the execution but also in the preparation of movement in general, not just eye movement (Boch and Goldberg, 1989; Sawaguchi et al., 1989; Requin et al., 1990; Funahashi et al., 1991; Sakagami and Niki, 1994; Iba and Sawaguchi, 2002). Sawaguchi et al. (1989) report evidence that movement-preparation cells have a certain distribution that marks the progression of preparatory cell activity in dorsolateral prefrontal cortex. They conclude that such activity

begins in layer IV, expands upward to layers II and III (note, the source of corticocortical connections), and subsequently involves layers V and VI, which throughout the cerebral cortex are the "effector layers" inasmuch as they are the source of output to effector subcortical structures.

Bizzi's observations, above, were the beginning of a long series of studies that were to modify the long-held assumption that the prefrontal cortex is a kind of "supramotor" cortex from which decision and voluntary command emerge. This assumption is a variation on the old notion that the cortex in front of the central fissure is motor, and that behind it, sensory (Betz, 1874). It is the extension to the cerebral cortex of the anterior-posterior (motor-sensory) dichotomy of functions that prevails in lower levels of the neuraxis. As we shall see (below, and in Chapter 8), this basic idea has considerable merit but needs the qualification that the prefrontal cortex is essentially integrative cortex, where sensory and other inputs determine and guide commands and decisions.

Thus, defying a clearly motor or sensory explanation, the electrophysiology of eye fields highlights the integrative character of the prefrontal cortex at large. It is cortex that is both sensory and motor at the same time, inasmuch as the kinds of purposive behavior for which it is essential require the continuous integration of sensory input with motor command. A theoretical elaboration of this idea is the proposition that eye-field cortex integrates afferent input on eye and head position (and, in the case of the SMA, limb position) with some form of input related to the anticipated consequences of movements that alter that position: a running blend of current sensory input with prospective information by which the eye field continuously adjusts the motor apparatus and sensory mechanisms to ensure coherence in both perception and movement. The resulting output to sensory systems would constitute what Teuber (1964, 1972) called *corollary discharge*.

He postulated that the prefrontal cortex is a source of such output to all sensory systems involved in voluntary movement. The output from eye fields would be a special case of his theory.

So far, the corollary-discharge theory has received only limited support; at most, it can be said that the electrophysiological eye-field data are fully consistent with it. [Wurtz and Sommer \(2004\)](#) persuasively argue that the signals from the superior colliculus to the frontal eye field, which are copies of saccadic motor commands, qualify as the conveyors of corollary discharge to prefrontal cortex. As such, these efferent-copy signals serve to prepare the frontal eye field for consequent eye movements.

One important general concept derives from the corollary-discharge theory and the empirical evidence for it: the concept of a cortical mechanism for anticipating events and preparing the organism in such a manner that, when those events occur, they are immediately incorporated into a perceptual or behavioral whole without disturbing the stability and continuity of either perception or action. This prospective aspect of prefrontal function is essential to the participation of the prefrontal cortex in the perception–action cycle and to the role of this cortex in the temporal organization of behavior, especially novel behavior (see Chapter 8).

Any action organized by frontal cortex, however, implies a pre-existing representation of that action in the same cortex, much as Jackson postulated long ago for motor cortex. Thus, we would expect that there should be, in the prefrontal cortex, cell assemblies representing sequences or temporal *gestalts* of goal-directed actions. Microelectrode studies in the monkey show that this is indeed the case. [Averbeck et al. \(2003a, 2003b\)](#) trained monkeys to draw – in space, by manipulating a joystick – copies of visually displayed geometrical shapes (triangles, squares, etc.). In the lateral prefrontal cortex, they found cell populations that encoded shape, segment of shape, trajectory, and sequence.

One of their most remarkable findings was that of cells that simultaneously encoded shape, sequence, and segment. Those findings are clearly in accord with the “broadly tuned” and distributed coding of temporal sequences of actions by a substantial proportion of prefrontal cell assemblies. This conclusion was reinforced by use of an oculomotor paradigm of action-sequence representation ([Averbeck et al., 2006](#)).

More recently, [Shima et al. \(2007\)](#) obtained clear evidence that prefrontal neurons encode complex sequences of actions at an abstract level. Their monkeys were trained to perform sequences of three hand movements (push, pull, and turn) in various combinations: (1) “paired” (one movement repeated, followed by another repeated; e.g., turn–turn–pull–pull); (2) “alternate” (repeated alternation of two movements; e.g., push–turn–push–turn); and (3) “four-repeat” (e.g., pull–pull–pull–pull). By the use of auditory and visual signals, the animals learned to memorize and to perform the three categories of sequences. Microelectrode records were taken from lateral prefrontal cortex before (in preparation for performance) and during each of the sequences. Some cells were attuned to a particular movement or sequence of movements. Remarkably, a substantial number of cells showed increased firing in preparation for all the sequences of one given sequence category and not the other two. Thus, some cells abstracted “paired action,” others “alternate action,” and still others “four-repeat action,” regardless of the particular combination of movements that each category included. It is reasonable to conclude that the cells were capable of planning abstract action. It is also reasonable that, in agreement with findings of neuropsychology (see Chapters 4 and 5), the prefrontal cortex and its elements take part in the representation in memory and the execution of complex plans of behavior. [Averbeck and Lee \(2007\)](#) provide another example of the cellular representation of behavioral sequences in the prefrontal cortex.

## V. VISCERAL AND EMOTIONAL FUNCTIONS

As has become evident in previous chapters, certain parts of the prefrontal cortex, notably its medial and orbital aspects, are critically involved in the integration of visceral, somatic, affective, and instinctual inputs. It is also evident that those regions of the prefrontal cortex send substantial controlling outputs to hypothalamic and limbic structures that modulate emotional behavior, instincts, and drives. It is erroneous, however, as Damasio (1994) has persuasively argued, to dissociate the function of these prefrontal regions from those of lateral prefrontal cortex; both are anatomically and physiologically intertwined. Equally erroneous is to dissociate cognitive functions, especially executive functions, from the powerful role of those internal inputs and drives. Indeed, those inputs and drives are to some degree determinant of any decision and course of action, however exclusively cognitive those may appear. Strictly speaking, there is no cognition without some affect and emotion.

Since the latter part of the nineteenth century (Schiff, 1875; Munk, 1882), it has been known that faradization of certain areas of the frontal cortical surface can induce a variety of visceral changes. This has been observed in dogs, cats, monkeys, and humans. Most of these changes can be elicited at the lowest thresholds from the posterior orbital area: in primates, area 13 of Walker or area FF of Bonin and Bailey. This is a transitional area that may be considered limbic by virtue of its development, architecture, and connections, yet also prefrontal by virtue of its relationships with the mediodorsal nucleus of the thalamus.

The most prominent effects of stimulating the orbitofrontal cortex have been noted in the cardiovascular system and include changes in blood pressure, heart rate, cardiac dynamics, and skin temperature (Bailey and Sweet, 1940; Livingston et al., 1948; Sachs et al., 1949; Kaada,

1951; Delgado, 1960; Hall et al., 1977). Effects on respiration (Smith, 1938; Bailey and Sweet, 1940; Kaada, 1951), epinephrine release (Euler and Folkow, 1958), and plasma cortisol (Hall and Marr, 1975) have also been observed. The majority of autonomic effects seem to be parasympathetic or the result of inhibitory influences on the sympathetic system (Hoff et al., 1963). This is in accord with the conclusion, derived from studies of visceral afferents to the cortex, that the posterior orbital area constitutes the cortical representation of the vagus (Bailey and Bremer, 1938; Dell and Olson, 1951; Encabo and Ruarte, 1967). As noted above, stimulation of that area can induce sleep (Kaada, 1951; Clemente and Sterman, 1967; Alnaes et al., 1973); in physiological sleep, the vagal tone predominates.

In rodents, judging from the effects of lesions and stimulation, both the medial and the lateral prefrontal cortex appear to be involved in autonomic control and in stress response (for reviews, see Neafsey, 1990; Critchley, 2005). Especially remarkable, though not yet precisely defined, seems to be the role of medial cortex in the regulation of the visceral and humoral concomitants of stress and defense (Thierry et al., 1976; Henke, 1982; Verberne et al., 1987; Maskati and Zbrozyna, 1989; Diorio et al., 1993; Critchley, 2005; Rodrigues et al., 2009; McEwen and Morrison, 2013). Whereas in the rat the medial cortex is obviously involved in the efferent ("motor") aspects of visceral function, the lateral and orbital cortices appear to be substrates of visceral representation.

A particular aspect of visceral representation is visceral pain, which is transmitted via the spinothalamic tract and, through the nucleus submedius of the thalamus, to the orbital and medial prefrontal cortex (Craig et al., 1982; Price and Slotnick, 1983; Shackman et al., 2011). The severance of this pathway may explain the efficacy of prefrontal lobotomy in the treatment of intractable pain (Falconer, 1948; Freeman and Watts, 1948). Conversely, as part

of the reward structures yielding self-stimulation (Routtenberg, 1971; Goeders et al., 1986), the orbital prefrontal cortex also has neuronal enclaves apparently representing pleasure. For a fuller discussion of the issue, as it bears on dopaminergic neurotransmission, the reader is referred to Chapter 3.

The endocrine and autonomic effects from stimulating orbital prefrontal cortex are probably mediated by the efferent fibers from this cortex to the hypothalamus, the amygdala, and other limbic structures (see Chapter 2) involved in visceral function and emotion (LeDoux, 1993). Furthermore, the prefrontal outflow to the hypothalamus plays a role in the inhibitory control of instinctual and emotional behaviors that are accompanied by endocrine and autonomic changes. This, as we see next, has been substantiated electrophysiologically with regard to both feeding behavior and aggressive behavior.

As mentioned in Chapters 4 and 5, lesions of the orbital prefrontal cortex, in animals and in humans, frequently induce hyperphagia. This phenomenon can be inferred to result from the disinhibitory release of hypothalamic centers mediating feeding behavior, especially the lateral hypothalamic area and the ventromedial nucleus, which are known to be involved in satiety and regulation of eating (Hetherington and Ranson, 1940; Brobeck et al., 1943; Anand and Brobeck, 1951). Excessive eating would be the consequence of liberating those centers from prefrontal control. In accord with this interpretation, electrical orbitofrontal stimulation in the cat has been shown to inhibit eating behavior (Siegel and Wang, 1974). Furthermore, inhibitory prefrontal projections have been electrically demonstrated to the lateral hypothalamus (Kita, 1978) and to the ventromedial nucleus (Ohta and Oomura, 1979b). It is reasonable to conclude that those parts of the hypothalamus, which are known to be sensitive to glucose levels in the blood (Oomura et al., 1969, 1974), normally signal satiety to the prefrontal

cortex, apparently through excitatory fibers (Ohta and Oomura, 1979a), and thus elicit descending inhibitory feedback from the prefrontal cortex, which has the effect of arresting food intake.

Somewhat parallel phenomena and mechanisms have been revealed experimentally with respect to aggression. Here, however, the effects of prefrontal lesions (see Chapter 4) are less clear and predictable. They seem to vary considerably from species to species and in relation to the extent and location of the lesion: in carnivores, large prefrontal lesions tend to increase aggressive behavior, but in monkeys this is not the case, except possibly as a result of dorsolateral lesions, and then only because, as noted above (see Chapter 4), such lesions induce cognitive deficits indirectly conducive to aggressive acts. In the cat and the rat, orbitofrontal lesions lower the threshold for attack behavior, either spontaneous or induced by stimulation of the lateral hypothalamus (Sato, 1971; Sato et al., 1971; De Bruin et al., 1983; De Bruin, 1990), whereas direct orbitofrontal stimulation arrests that kind of behavior (Siegel et al., 1974, 1977; Kruk et al., 1979). Such observations support the hypothesis that aggressive behavior is controlled from the prefrontal cortex by inhibitory influences upon the hypothalamic centers mediating or integrating that behavior. Regarding sexual behavior, no directly pertinent electrophysiological evidence is available, but there are good reasons to suspect, from lesion studies, that the prefrontal cortex plays an inhibitory role comparable to the one it plays in eating and aggression, and possibly also mediated by hypothalamic and limbic structures. On this subject, however, whereas the animal lesion literature is scarce and anecdotal (e.g., Brutkowski, 1964), the clinical literature is more substantial (see Chapter 5).

Mostly based on stimulation and lesion studies, the literature thus far cited in this section leads to three general inferences about the involvement of the prefrontal cortex in visceral

representation and emotional response: (1) certain areas of medial and orbital prefrontal cortex represent various forms of visceral sensation; (2) these same areas give rise to efferent outputs to somatic and autonomic systems that modulate instinctual and emotional behavior; and (3) some of these outputs are channeled through the hypothalamus and the limbic system and have the net effect of exerting inhibitory control over those forms of behavior.

## VI. VALUE AND REWARD

More recent literature on the results of electrophysiological recording not only confirms but also further substantiates those inferences. In the context of behavior, electrical data confirm the involvement of medial and ventral prefrontal regions in the attribution of value and rewarding properties to external stimuli. Those data, complemented by imaging data (see Chapter 7), lend support to the concept, already advanced by neuropsychological studies (see Chapter 4), that those prefrontal regions not only are “evaluators” of sensory stimuli in terms of drive and motivation, but also take part in eliciting rewarding behavior. At the same time, reward is the operational definition of value, and thus it is not surprising that the orbital and medial prefrontal cortex should be involved in both value attribution and value-reinforced behavior.

In the monkey and in the rat, the evidence is extensive that neurons in the orbital prefrontal cortex encode information about values, rewards, and reinforcement, which are the instinctual and emotional motivators of behavior (Niki and Watanabe, 1976b; Thorpe et al., 1983; Rosenkilde et al., 1981; Schultz, 1998; Schoenbaum et al., 1998, 2003, 2006; Ichihara-Takeda and Funahashi, 2006; Asaad and Eskandar, 2011; Kennerley and Walton, 2011). Also involved in the encoding of those qualities are cells in anterior cingulate cortex (Amiez

et al., 2005; Seo and Lee, 2009) and the amygdala (Schoenbaum et al., 1998). A single-unit investigation in the human shows cells in anterior cingulate and orbital prefrontal cortex that respond to visual displays of emotional scenes (Kawasaki et al., 2005). Thus, in summary of the electrophysiological studies reviewed, it would appear that the ventromedial prefrontal cortex, together with the amygdala (notably its basolateral nucleus), contain critical neuronal circuitry for the encoding of motivational significance and “value.” This circuitry intervenes in the evaluation of the emotional connotations of sensory stimuli.

Now it is known that “reward cells” not only respond to an available reward but may anticipate it, in other words, prospectively code that reward and its value before the animal’s action to obtain it. This prospective evaluation of reward in its behavioral pursuit is in agreement with the role of orbitomedial prefrontal cortex in the emotional perception-action cycle, which is parallel to and interactive with the cognitive perception-action cycle that circulates through the dorsolateral prefrontal cortex. Both have temporal perspectives and both serve the cognitive and emotional interactions of the organism with its environment in goal-directed behavior. Because they operate in tandem in practically all forms of goal-directed behavior, their roles are difficult to analyze separately (see further discussion in Chapter 8).

Neurons that anticipate reward or “motivational context” by activated discharge can be found in dorsolateral and orbitomedial areas of the prefrontal cortex of the monkey in a variety of behavioral paradigms (Watanabe, 1996; Leon and Shadlen, 1999; Amador et al., 2000; Tremblay and Shultz, 1999, 2000; Hikosaka and Watanabe, 2000; Kobayashi et al., 2002; Wallis and Miller, 2003; Roesch and Olson, 2004, 2005; Amiez et al., 2005; Watanabe et al., 2005; Ichihara-Takeda and Funahashi, 2006; Watanabe and Sakagami, 2007; Seo et al., 2007; Seo and Lee, 2009; Abe and Lee, 2011;

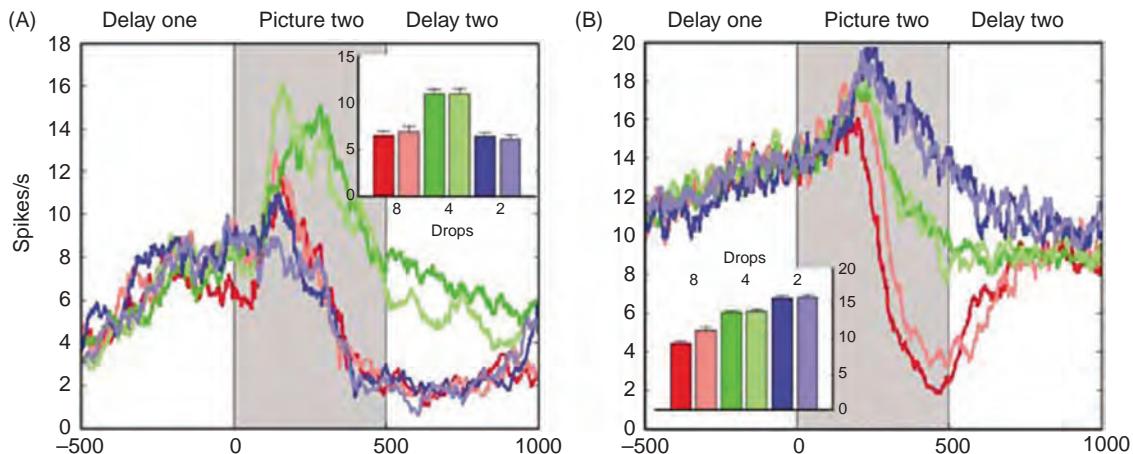
[Asaad and Eskandar, 2011](#)). In general, however, “reward cells” are more commonly found in orbital than lateral areas of the monkey’s prefrontal cortex. In the rat, they have been described in orbitofrontal cortex ([Schoenbaum et al., 1998; Roesch et al., 2006](#)). Their concentration in orbital prefrontal cortex makes them candidate components of the dopamine circuitry of that part of cortex that is critical in encoding reward (see Chapter 3).

By their frequency of discharge, reward-anticipating cells encode not only the quantity but also the quality of the expected reward ([Tremblay and Schultz, 1999, 2000; Wallis and Miller, 2003; Roesch and Olson, 2004, 2005; Abe and Lee, 2011](#)). In the experiment by Wallis and Miller, the monkey had to fixate its eyes on a central spot. Then, two pictures, one on one side of the spot and the other on the other, were presented in succession with a 1000ms delay between the two. A second delay followed the second picture. At the end of that second delay, the animal had to choose one of the two pictures by directing an eye saccade to the location where it had appeared. The monkey knew

that each picture was associated with a given amount of juice reward, varying between zero and eight drops. Some neurons predicted with different firing rate, although not necessarily parametrically, the amount of juice to be delivered after the choice (Figure 6.2) ([Wallis and Miller, 2003](#)).

One of the most remarkable features of reward-anticipating cells is their apparent ability to predict reward as well as the spatial direction of the motor action required to obtain it ([Kobayashi et al., 2002; Wallis and Miller, 2003; Watanabe et al., 2005; Roesch et al., 2006; Watanabe and Funahashi, 2007](#)) (Figures 6.3 and 6.4). Moreover, in some of the just cited experiments, reward expectation enhances the differential, direction-specific firing of some units in preparation for the motor action, while that of other units is depressed. These relationships between spatial direction and reward at the single-unit level are further manifestations of the associative and integrative capacity of the prefrontal cortex.

Another extrinsic parameter of reward value that affects prefrontal – especially orbitofrontal –



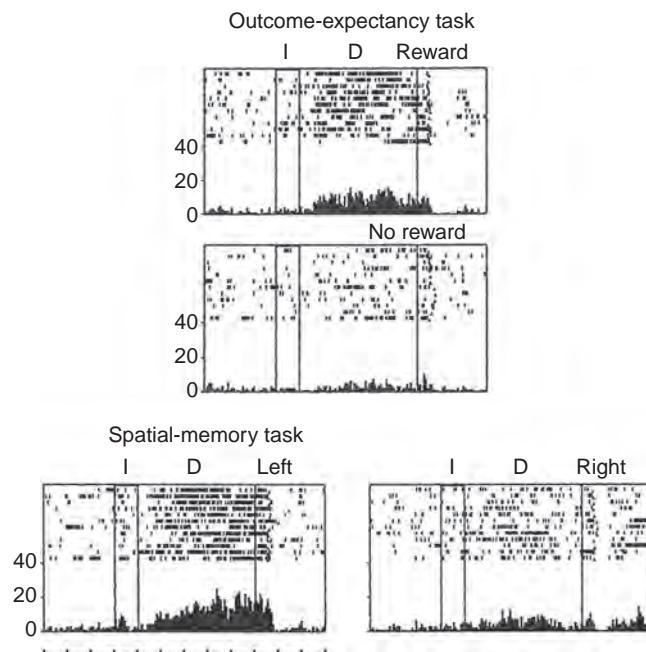
**FIGURE 6.2** Two orbitofrontal units predicting reward in the task described in the text. Records begin in the middle of the first delay and terminate at the choice saccade. Unit A shows higher firing if the chosen picture predicts four drops, versus eight or two. Unit B predicts reward with an excitation followed by a parametrically graded inhibition that is largest for eight drops and progressively weaker for smaller amounts. (From [Wallis and Miller, 2003](#), with permission.)

units is the amount of time that the animal must wait to obtain the reward. Those units, apparently reflecting the animal's preference for immediate gratification and aversion to delayed gratification, generally fire more in anticipation of a short delay than of a long one (Roesch and Olson, 2004, 2005; Roesch et al., 2006; Ichihara-Takeda and Funahashi, 2006). Thus, those cells would reflect the greater perceived value of short- over long-delayed rewards (Montague and Berns, 2002). Further, as Figure 6.4 illustrates, the "deferral penalty" or "delay discount" interacts with, and attenuates, the spatial preference – right or left – of the cells in expectation of the reward.

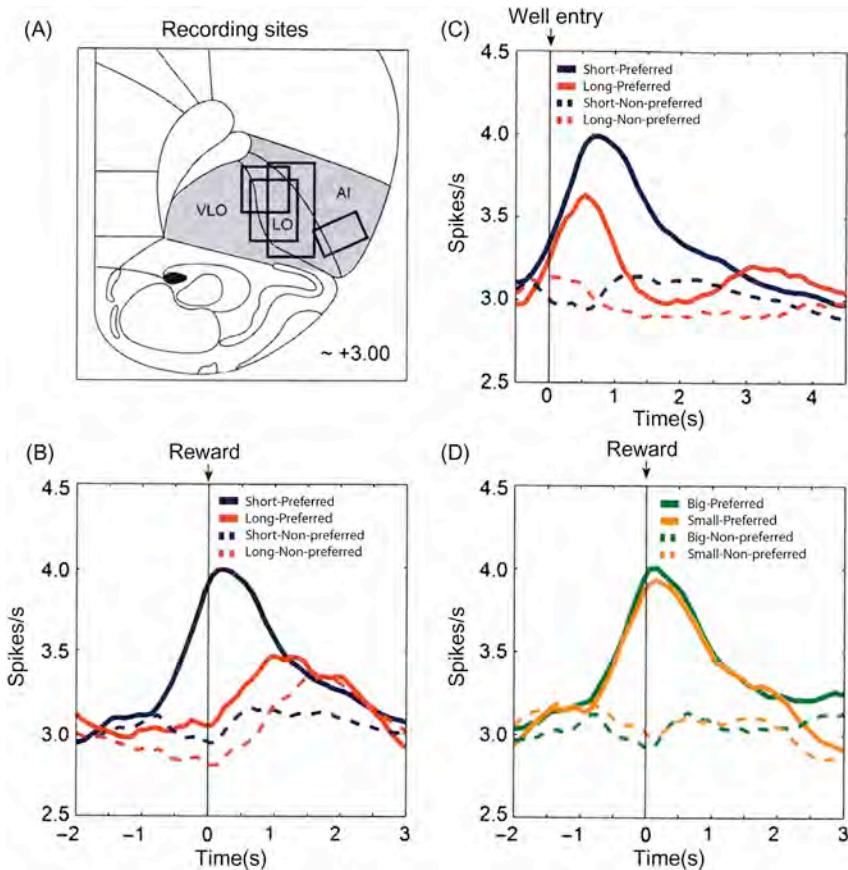
The value of a reward, and the utility of decisions based on it (Glimcher, 2002), is a function of many factors, some internal and others external. The two most prominent internal factors

are biological need and biological want, namely, the determinants of drive and motivation. Among the external factors are those that have been seen to excite prefrontal neurons in anticipation of a reward: the quality, quantity, and timing of that reward. Other external factors are risk and cost. As we have seen, the first group of external factors have been noted to interact with one another in the discharge of some prefrontal cells (Roesch and Olson, 2004, 2005), in some cases with trade-offs between them, giving the experimenter the ability to "titrate" one against another. Thus, for example, quantity and quality can be changed in opposite ways to obtain the same behavioral effect or neuronal firing level (Padoa-Schioppa and Assad, 2006).

The interactions between reward variables on prefrontal cells are compatible with a cardinal scale of reward value representing the



**FIGURE 6.3** Prefrontal cell showing reward-anticipating and spatial-selective activity. *Top:* In a delay task with and without reward, the cell is activated only in trials in which reward is expected. *Bottom:* In a spatial delay task, the unit is more active during delays in anticipation of left-side choice than right-side choice. (From Watanabe et al., 2005, with permission.)



**FIGURE 6.4** Impact of delay and size of reward on a population of reward-related orbitofrontal neurons in the rat. The animal, departing from a central position, was forced to choose one of two wells, right or left, for food reward. An odor in the departure port signaled to the animal the position and amount of reward for that trial. The cells showed preferential (higher) firing for one of the two directions. A delay, short (0.5s) or long (1–7s), was interposed between reaching the chosen well and delivery of the reward. (A) Location of recording sites on coronal section. (B) Average discharge of cells sorted for length of forced delay of reward and cells' preferred direction (records time-locked with reward delivery). (C) Same records, sorted in the same manner as in B (records time-locked with well entry). (D) Records from a population of cells in free choice trials, sorted by reward size and cell-direction preference (records time-locked with reward). (From Roesch *et al.*, 2006, with permission.)

aggregate incentive from all sources of reward. According to this neuroeconomic view, decisions in the brain would not be made by the winner-takes-all preference of one reward over others on an ordinal scale; rather, they would be made after additive and subtractive computations of potential gains and risks weighed by probability estimates that are based on prior

experience. Because the information about each component value is incomplete or uncertain, or both, the executive system of the brain, of which the prefrontal cortex is an essential part, would work somewhat like a marketplace, where prices are determined by the decisions of many individuals acting on incomplete and uncertain information (Ainslie and Monterosso, 2004).

## VII. EXECUTIVE FUNCTIONS

As we will see in Chapter 8, the most general, overarching function of the prefrontal cortex is the conception and execution of *new* sequences of goal-directed actions. This, naturally, includes the formulation and execution of all novel plans with goal and purpose. Excluded from the main prefrontal agenda are habits and old behaviors, however complex, overlearned actions, familiar rules and their implementation, as well as routine and unimaginative language. That does not mean that the prefrontal cortex is not involved at some time in these old activities. It is definitely involved in their original learning and also in their re-enactment when they contain uncertainties or ambiguities that make them “new for the occasion” (e.g., an individual trial in a delayed-response task). But once established, those old activities become the physiological purview of motor and premotor cortex, the thalamus, the basal ganglia, and the cerebellum.

Novel action sequences, however, require the functional integrity of the prefrontal cortex, especially, in the primate, the dorsolateral prefrontal cortex. This is because only this cortex can provide the neural basis for creative imagination, prediction, preadaptation to future change, pursuit of distant goals, and the mediation of cross-temporal contingencies. The prefrontal cortex contributes these attributes to some degree to any new purposeful action in the exercise of its cardinal executive functions. These functions, which the prefrontal cortex performs in cooperation with the rest of the cortex and subcortical structures, are the subject of this section.

It is through the analysis of neuroelectrical phenomena in behavior that cognitive neuroscience has exposed the roles of the prefrontal cortex in executive cognitive functions. As we will see, the electrophysiological methodology has made it possible to study the neural dynamics behind the temporal integration of sensory,

motor, and motivational functions toward goals and rewards. Thus, having reviewed the prefrontal physiology of those categories of function, in addition to value and reward, we will now turn to the prefrontal electrophysiology of their temporal integration, which is at the root of the organization of new behavior and language.

All behavioral structures and sequences, however simple, demand a degree of sensory-motor integration. Much of this integration consists of the continuous circular processing of information between sensory input and motor output, through the environment and the nervous system, that we have termed the perception-action cycle (see Chapter 8). Behavioral sequences of goal-directed acts depend on the proper operation of that cycle. One important aspect of sensory-motor integration is the bridging of time at the top of the perception-action cycle, in the cortex of association. In that time-bridging process, motor acts are coordinated with sensory inputs that for whatever reason are not contemporaneous with them; in other words, inputs that have occurred in the past or are expected to occur in the future. Electrical signals show that for this form of cross-temporal integration – the integration of temporally separate acts and percepts – the prefrontal cortex is essential, especially if the behavioral configuration is new.

Cross-temporal integration can be suitably tested and investigated in delay tasks and other similar behavioral paradigms where signals are temporally detached from consequent actions. This has been extensively done in the human as well as the non-human primate. By the use of those behavioral methods, the electrophysiological correlates of cross-temporal integration have been revealed in the prefrontal cortex. Two basic methods of electrical recording have made it possible: (1) the recording of field potentials; and (2) the recording of action potentials from single units.

## A. Attentional Set

Attention is a basic and ubiquitous cognitive function. Its primary role is the physiological allocation of limited brain resources to neural processes for maximum efficiency of all other cognitive functions: perception, memory, language, and intelligence. It has two major components: one is inclusionary and the other exclusionary. The first consists of the focus in neural processing on the elements of cognition that are relevant to present or impending goal-directed behavior or language. Its cognitive content, frequently sensory, coincides with what is commonly designated the *focus of attention*. The exclusionary component of attention consists, as the adjective implies, of the exclusion, limitation or inhibition of everything that is irrelevant at that time; in a word, potential or actual *distraction*.

The prefrontal cortex is heavily involved in both aspects of attentional set. Its dorsolateral region is mainly involved in the first, namely the concentration of attention on the relevant aspects of novel goal-directed action sequences. Its ventromedial region, on the other hand, is involved in the suppression of extraneous cognitive material or impulses that might interfere with ongoing behavior or language. Extensive studies now support the original tenet (Miller, 2000; Miller and Cohen, 2001) that the prefrontal cortex, at the top of the executive cortical hierarchy, flexibly controls those two components of attention. It sends top-down influences over sensory and motor systems to adjust them to the changing demands of the organism and its environment in goal-directed behavior. The aggregate of those top-down attentional influences has been named *cognitive control*.

A most important qualification of prefrontal attentional set or cognitive control is its prospective or future aspect. In that sense, prefrontal attention is inseparable from expectancy, prediction, and preadaptation. In a more

concrete neurobiological sense, attentional set consists of the priming of the sensory and motor apparatus for expected stimuli and the actions they are supposed to elicit.

The first recordings of prefrontal potentials related to sensory and motor expectation in behavioral performance were obtained from humans. Having established, by evoked-potential study, that the frontal cortical region is accessible to a variety of sensory inputs (Walter, 1964a), Walter and associates discovered that practically any sensory stimulus can elicit a protracted surface-negative potential over the same region if, by training or verbal instruction, the stimulus has acquired behavioral significance; more specifically, if that stimulus has become a precursor signal for a second stimulus, to follow a short time later, which in turn will call for a motor response (Walter, 1964b, 1973; Walter et al., 1964). The future tense is used here advisedly, for the prospective, predictive significance of the first stimulus is a critical factor.

Because of the cross-temporal contingency linking the "conditional" stimulus with the "imperative" stimulus and the motor response, the frontal potential that develops in the interval between the two stimuli was named the *contingent negative variation* (CNV). Whether picked up with electrodes on the scalp or on the cortex itself, the CNV is of relatively low amplitude (20–40 µV) and can be recorded only by direct coupling or with minimal filtering in the low-frequency range. The CNV was first discovered in humans, where control of certain relevant variables is easier than in animals. However, with the help of instrumental conditioning, it was subsequently detected also in monkeys (Low et al., 1966; Borda, 1970; Donchin et al., 1971; Rebert, 1972; Gemba and Sasaki, 1990).

The investigation of stimulus conditions shows that neither sensory modality nor intensity is an essential factor for either the appearance or the amplitude of the CNV. It can be

elicited by semantic, pictorial, or verbal signals, provided those signals are followed by an event that triggers an action or a decision (Walter, 1967; McCallum, 1979). Within broad limits, the length of the interval between the signal and the event is also relatively unimportant. A fixed interval of about 1 s, as used in early experiments, is demonstrably adequate, but the interval need not be fixed and may exceed that duration by 15 s or more. An inverse relationship has been found between the amplitude of the CNV and the subject's reaction time (Hillyard, 1969).

Walter viewed the CNV as a bioelectrical wave sweeping the frontal cortex in an anterior-posterior direction and intimately related to expectancy (Walter, 1964b, 1967, 1973); that is, related to attention directed to an expected event in the proximate future (Tecce and Scheff, 1969). The phenomenon has been conceptually and experimentally ascribed also to motivation (Irwin et al., 1966; Low and McSherry, 1968) and conation (Low et al., 1966). The obvious interdependence of these functions makes the argument somewhat abstruse and inconclusive. Let us keep in mind, nonetheless, the anticipatory, prospective, predictive character of the phenomenon, which for that reason has been dubbed the *expectancy wave*.

Several questions were raised from the beginning regarding the neural substrate of the expectancy wave. It is now apparent that the wave is most easily detectable in the simple sensory-motor paradigm introduced by Walter. Furthermore, it is most probably a composite of waves of different cortical origins and significance (Kutas and Donchin, 1980). At least two components have been identified in it (Borda, 1970; Järvilehto and Fruhstorfer, 1970; Loveless and Sanford, 1974; Brunia et al., 1985). One component is a negative potential that develops over the central area immediately before movement, is maximal at the vertex on scalp recording, and has been characterized as the so-called readiness potential (*Bereitschaftspotential*)

(Kornhuber and Deecke, 1965; Deecke et al., 1969; Libet et al., 1982, 1983a, 1983b); it is clearly related to the volitional initiation of movement. A similar potential, related to voluntary eye movements, has been recorded from the human scalp (Kurtzberg and Vaughan, 1982) above the region originally identified by Penfield and Boldrey (1937) as the frontal eye field.

The other, earlier, component is a slower potential, also negative, which develops over a more anterior frontal area after a stimulus calling for a subsequent decision – not necessarily to execute a motor act – and connoting a degree of effort or uncertainty; the decision may be based on the comparison between two stimuli separate in time (Järvilehto and Fruhstorfer, 1970), an operation closely resembling delayed matching-to-sample (see below, Working Memory). An apparent equivalent of this second potential, which by its distribution seems to be limited to the dorsolateral prefrontal cortex and may be considered the CNV proper, can also be observed in the planning or programming of organized movement (Deecke et al., 1985; Singh and Knight, 1990).

Thus, the anterior (prefrontal) potential seems to be related to the anticipatory preparation for movement, whereas the more posterior readiness potential seems to be related to the actual execution of the movement. Nevertheless, it is possible that the two potentials are manifestations of a spatial and temporal continuum of frontal activation in motor control. Both may be part of a gradient of surface negativity, which begins in the prefrontal cortex with the conceptualization of the broad scheme of the action and progresses in cascade fashion through the premotor cortex to the motor cortex, where the action is organized and executed in its more concrete aspects.

Remarkably, in the course of the learning of a hand movement in response to a light flash or a tone, the amplitude of premovement potentials follows, in the monkey, that same progression (Sasaki and Gembä, 1982; Gembä and

([Sasaki, 1984](#); [Gemba et al., 1995](#)): it appears and increases first in the prefrontal cortex, then in the premotor cortex, and lastly in the motor cortex, where it is the largest in the fully trained animal. The electrical correlates of learning to perform a movement seem to develop over the cortical surface in the same order as the potentials that precede a movement conceived and executed in response to a prior signal. As will be discussed in Chapters 7 and 8, that anterior-posterior progression of neuronal activation reflects the successive engagement of hierarchically organized frontal cortices toward the action.

It is practically impossible to dissociate the concept of anticipatory preparation for movement from that of motor attention or set. Motor attention, like sensory attention, consists of the timely selection of a sector of the nervous system for maximum gain and efficiency in the face of limited resources. That selection of a certain sector of the motor apparatus is accompanied by the suppression or inhibition of other sectors of that apparatus that are irrelevant or a source of interference.

In any case, it is in that selected sector of the motor apparatus that the action will be "initiated," although we will see that the action, even voluntary action, is always couched in a mesh of sensory-motor arcs where it is futile to search for the origin. By a clever method of field-potential recording at the start of self-initiated movements in humans, [Libet et al. \(1983b\)](#) studied the temporal relationship between the frontal "readiness potential" and the decision to execute a motor movement. The investigators found that invariably the frontal potential preceded by several hundred milliseconds the conscious intention to move.

In conclusion, a slow surface-negative potential develops over the prefrontal cortical convexity of humans and monkeys before predictable behavioral acts. Operationally, the potential is most evident in the interval between a cue or warning signal and a second,

delayed stimulus that prompts the action. Consequently, it appears that the potential is a direct expression of the relationship of mutual contingency between temporally separate events. This cross-temporal contingency is a product of learning and at the same time a sign of prospective attention. In functional terms, the potential seems to be a manifestation of neural activity anticipating and mediating the behavioral action. When that action is motor, the prefrontal potential is probably a component of a larger gradient of potential negativity, which sweeps the frontal cortex from the prefrontal areas to the precentral strip and constitutes the neuroelectrical expression of the organization and execution of movement down the executive hierarchy of the frontal lobe. Thus, the preparation for movement, along with its electrical manifestations, proceeds down that hierarchy (see Chapter 8) from prefrontal to motor cortex. The prefrontal component of the slow negative wave would reflect the broader aspects of the neural organization of motor action, whereas the premotor and motor components would reflect more concrete aspects of that organization.

The source of the CNV, as well as of other related frontal potentials, is still in some respects unclear. As suggested ([Sasaki and Gemba, 1982](#)), these potentials may represent the cumulation of innumerable potential dipoles generated by neurons (pyramids) that are orthogonally oriented with respect to the cortical surface. How these dipoles may be generated is still a matter of speculation. Are they the result of excitatory postsynaptic potentials, neuronal spikes, or dendritic potentials? Any of these cellular phenomena may be the ultimate source of the frontal field potentials that precede behavioral action, including the CNV; all of them have been considered ([Caspers, 1959, 1961](#); [Creutzfeldt and Kuhnt, 1967](#); [Speckmann et al., 1972](#); [Somjen, 1973](#)), but the question remains unresolved. Nonetheless, we may assume that the surface negativity of the CNV

and related potentials is a first- or second-order phenomenon of neuronal firing and, thus, an expression of the involvement of prefrontal units in the cross-temporal sensory-motor integration that typically characterizes the performance of delay tasks. It is now known that some of the persistent activity of prefrontal neurons in temporal integration is attributable to their role in working memory. Thus, ultimately, the CNV may be, to some extent, a reflection of not only expectancy but also attentional set.

In the performance of a learned (instructed) behavioral task, the setting for and execution of a motor act are contingent not only on preceding stimuli but also on the rules of the task which the individual has learned beforehand; in other words, they depend on the associated context of the stimuli and the long-term representation or memory of the task, including all its perceptual and executive aspects. Attention and set are thus to some degree determined by history, and therefore subject to what has been called “top-down” influences. As argued in Chapter 8, the central representations of goal-directed actions are inseparable from their execution. They share the same neural substrate. For complex sequences of actions with uncertain or ambiguous properties and cross-temporal contingencies, that representational and operational substrate is the lateral prefrontal cortex. Prefrontal networks not only represent the rules but also are responsible for their implementation. Thus, those networks – in cooperation with others in posterior cortex and subcortical structures – are in charge of the preparation for the preparation (set) of the motor acts that constitute the behavioral sequence.

In the human, as well as in the non-human primate, there is evidence of the participation of the prefrontal cortex in rule-guided set and in context-dependent shifts of that set. High-frequency TMS ([Pascual-Leone and Hallett, 1994](#)) of medial or lateral prefrontal regions has been shown to facilitate or impede set shifting;

that is, the change from one task-rule to another ([Rushworth et al., 2002a, 2002b, 2005; Vanderhasselt et al., 2006a, 2006b](#)). Whether the effect is excitatory or inhibitory seems to depend on the parameters and location of the area stimulated and the measure of shift performance (e.g., reaction time). TMS of the dorsolateral prefrontal cortex has been shown to disrupt attention shifts between the visual and auditory modalities ([Johnson et al., 2007](#)). In the aggregate, the TMS data indicate the participation of prefrontal regions in attentional set shifting.

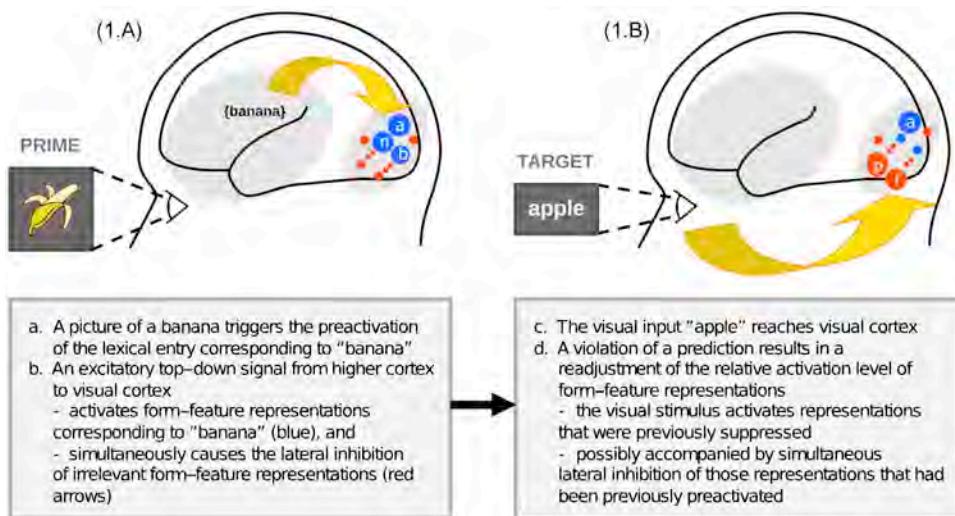
The role of prefrontal regions in attention is also supported by electrocortical studies on humans performing set-shifting tasks. In one study ([Nagahama et al., 2001](#)), the task required either high-level attentional set shifting with significant switch cost or low-level shifting between stimulus-response associations without shift cost. Neural activity in anterodorsal prefrontal cortex was high only in attentional set shifting, whereas in posteroventral prefrontal cortex activity was high not only in attentional shifts but also in lower level sensory-motor shifts. The authors of the study conclude that the anterodorsal region controls higher order attention, whereas the posteroventral area may be related to lower level shifting with minimal attentional demand. The two levels of attentional control conform to the executive hierarchical order in the frontal lobe: anterior prefrontal for representation and execution of abstract and complex rules, and posterior prefrontal for those of simple stimulus-response associations.

Another paradigm for the test of set shifting is the Wisconsin Card Sorting Test (WCST) (see Chapter 5), which demands from the subject the change of categorizing principle (color or shape) of visual images; the task thus demands choices in accord with the categorizing rule, which shifts from time to time. Recording evoked activity by means of magnetoencephalography (MEG) during

WCST performance, the authors of another study (Perianez et al., 2004) identify three frontal regions successively attuned to set shift: inferior frontal gyrus, anterior cingulated cortex, and supramarginal gyrus, in this temporal order. That order would again reflect the order, roughly hierarchical from the bottom-up, of areas involved in the attentional control of set shifting. Microelectrode recording also reveals the neuronal correlates of set shifting. The most telling evidence of cellular involvement in this attentional function comes from monkeys performing rule-changing tasks.

Whereas the expectancy wave and the readiness potential appear to be manifestations of attentive set on the frontal substrates in intentional movement, recent electrophysiological studies emphasize the perceptual aspects of attentional set. Indeed, all perception is the classification of objects in the environment in accord with prior experience (Hayek, 1952).

Therefore, all perception carries the expectancy that objects in the experienced environment will meet the criteria of classification. In a structured behavioral task, attentional set (or cognitive control) will descend top-down from the prefrontal cortex to prepare sensory cortex for the expected sensory percepts in the context of that task. The two mechanisms of perceptual attentional set – inclusionary and exclusionary – are seen to interact in a lexical prediction task (Dikker and Pylkkänen, 2013). In that task, a trial consisted of the presentation of a (priming) visual object before a target lexical matching (predicted) or non-matching (non-predicted) stimulus. MEG signals recorded from prefrontal (inferolateral), mid-temporal, and visual cortex showed amplitude differences in a particular wave appearing 100 ms after each stimulus, depending on the congruence or non-congruence of the visual and lexical stimuli (Figure 6.5).



**FIGURE 6.5** Effects of lexical prediction and violation on the amplitude of a magnetoencephalography (MEG) response to visual stimuli. During presentation of the prime picture (1.A), the word “banana” is pactivated, which elicits top-down modulation to visual cortex from the prefrontal cortex. This excites relevant form-feature representations (a, b, n) and the suppression of competitors (e.g., p, l). Later, with presentation of the unexpected word “apple” (1.B), previously suppressed p and l are activated, possibly with reciprocal exclusionary inhibition of a, b, n. (From Dikker and Pylkkänen, 2013, with permission.)

None of the top-down, executive phenomena described thus far in this section can be easily separated on physiological grounds from the other executive functions of the prefrontal cortex described below. Especially narrow is their relation to the next function we deal with, working memory, which was considered, even by Baddeley, the first to describe it in detail, as a kind of attention focused on an internal representation (Baddeley, 1983, 1993). Thus, working memory could be rightfully considered part of the attentive set: the attentive set elicited by a sensory cue or memorandum presaging a motor response related in some manner to that sensory stimulus.

## B. Working Memory

The adaptation of microelectrode recording techniques to the behaving animal allowed the exploration of cellular discharge in the prefrontal cortex of animals performing tasks for which this cortex is deemed essential, notably delay tasks. The main objective of this kind of research has been the analysis of neuronal firing changes related to the various sensory and motor events that take place during those tasks. The timing and course of these changes provide insight into the specific aspects of performance in which prefrontal neurons are involved. The first target of chronic microelectrode studies was the cortex of the dorsolateral convexity of the frontal lobe, particularly the area of the sulcus principalis, in monkeys performing delayed-response tasks (Fuster and Alexander, 1971; Fuster, 1973; Goldberg and Fuster, 1974; Kubota et al., 1974; Niki, 1974c) or delayed-alternation tasks (Kubota and Niki, 1971; Niki, 1974a, 1974b).

Later, the activity of prefrontal units was also examined in other species, prefrontal areas, and forms of behavior. Single-unit studies contribute to our understanding of the role of the prefrontal cortex in sensory-motor integration, especially cross-temporal integration. For that, the evidence

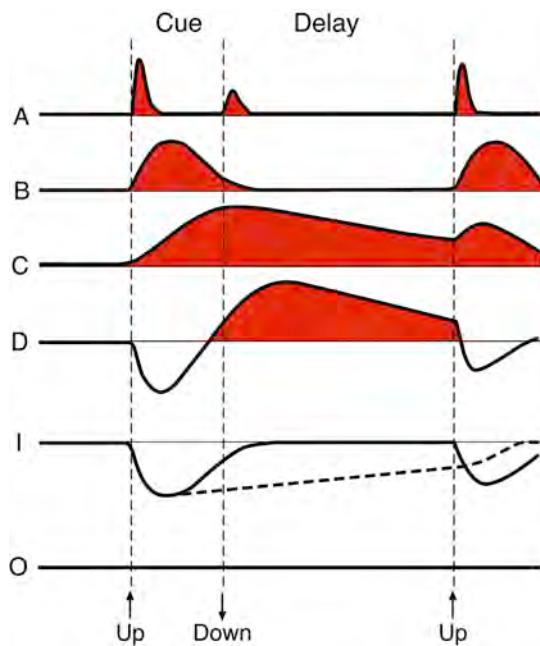
from single-unit analysis in delay tasks has been crucial, because these tasks are uniquely suited to testing cross-temporal integration.

Essentially, it will be recalled (see Chapter 4), delay-task trials consist of the presentation of a usually visual cue, the memorandum for the trial, followed by an enforced delay, and a motor response dependent on the cue. The cue and the appropriate response vary randomly from trial to trial. In principle, then, changes of unit activity during cue presentation are related to the acquisition of relevant sensory information, whereas changes occurring during the delay may be related to the retention of that information or to the preparation for response, and changes concomitant with that response may have to do with the motor process. Also, *a priori*, the magnitude of those changes may depend on selective attention of one form or another (sensory, motor, or internalized, i.e., working memory).

Temporal correlations have been observed between the frequency of prefrontal cell discharge and the main events in delay-task performance trials. In several studies, observations of this kind have led to the classification of single cells into various types. In an early study (Fuster, 1973), one such classification was made on the basis of unit records obtained during the performance of the classical, direct-method, delayed-response task (Figure 6.6). It should be borne in mind, however, that all such classifications are only descriptive and, by themselves, provide little more than broad indications concerning the functions of the cells they classify. As we have learned in recent years, there is substantial variability in the patterns of discharge of prefrontal cells during working-memory tasks (Shafi et al., 2007).

### **The Memorandum**

The memorandum (literally, the item *to be remembered*) is the sensory cue that initiates a trial in a delay task and that the subject must remember for a later choice-response that in



**FIGURE 6.6** Types of single-unit activity in the prefrontal cortex of the monkey during delayed-response performance. Heavy line marks deviations from spontaneous intertrial activity. Arrows mark displacements of the opaque screen between the animal and the test objects. (From Fuster, 1973, with permission.)

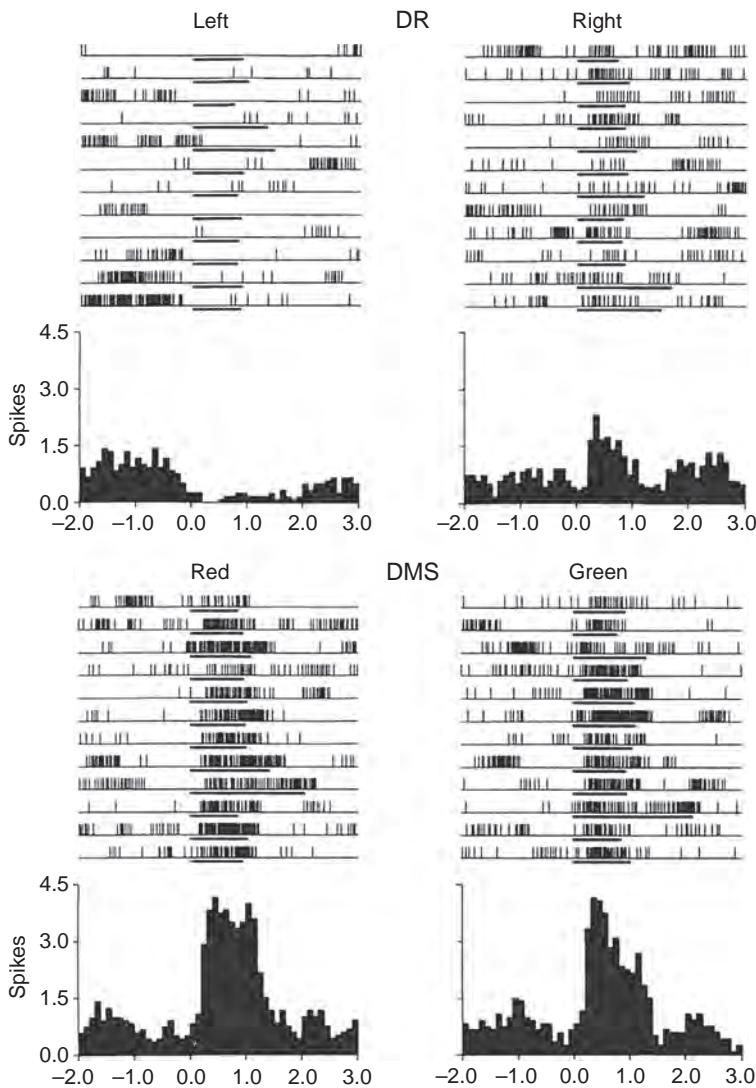
some manner is contingent on that cue. A large proportion of units in the lateral prefrontal cortex exhibit a transient increase in spike discharge at the start of every trial, when the sensory stimulus or memorandum is presented that the animal must retain through the delay. That cellular reaction is non-specific, unrelated to any particular memorandum and apparently related to the directing of attention to it. Ordinarily, it has a relatively short latency (less than 150 ms) and, in the direct-method delayed-response task, may be elicited simply by the alerting auditory or visual stimuli that precede or accompany the cue (Fuster, 1973; Goldberg et al., 1980).

In some units, however, the reaction differs in firing frequency depending on the particular

feature of the cue, which varies from one trial to another and which the animal must perceive and remember for correct response. In these units, the response to the cue differs from the start depending on the sensory features of that cue, and may be inhibitory for some cues and excitatory for others (Figures 6.1 and 6.7). Thus, the cues ordinarily used in delayed response (e.g., right and left) or in delayed matching (e.g., red and green) may elicit different reactions in a given unit (Fuster, 1973, 1975; Niki, 1974c, 1975; Kubota et al., 1980; Fuster et al., 1982; Watanabe, 1986, 1992; Quintana et al., 1988). Such units appear to distinguish visual, auditory, proprioceptive, or kinesthetic features. Yet, overall, the reactivity of prefrontal neurons to sensory stimuli is less specific than that of neurons in sensory association areas (Kojima, 1980; Kubota et al., 1980; Fuster and Jervey, 1982; Miller et al., 1996).

To sum up, during working-memory testing, prefrontal units react to two categories of input: first, task-related input, invariant across trials, that connotes the behavioral significance of sensory information and that the animal uses as an anchor of attention; and second, trial-specific input that distinguishes one cue from another and that varies from trial to trial. In some of the units the effect of the first input predominates, and in others that of the second, but a mixture of the two seems to influence almost all of them. The non-differential reactivity to the cue and its precursors is probably evidence of a role of prefrontal units in sensorial attention directed to the common attributes of all the cues and trials. That reactivity may be related to the attentional set that we have discussed in the previous section.

Memorandum-differential reactivity, on the other hand, probably reflects prefrontal unit involvement in the encoding or activation of the specific sensory information that the cue carries. Both components, attentional and sensory-specific, are most evident during visuomotor tasks, in units of the eye fields of



**FIGURE 6.7** Responses of a cell to the memorandum in two delay tasks: delayed response (DR) and delayed matching-to-sample (DMS). Records are aligned with the start of the memorandum (horizontal bar); on the abscissa, time in seconds. Note that the cell responds differently to the two DR cues and with a heavy non-differential activation to the two DMS cues. (From Fuster et al., 1982, with permission.)

the monkey's arcuate prefrontal region (area 8). There, the first component can be seen to be related to ocular movement or fixation, both of which are manifestations of visual attention, and the second component to particular

features of visual stimulation, including the location of a punctate stimulus in the visual field (Suzuki et al., 1979; Goldberg and Bushnell, 1981; Suzuki and Azuma, 1983; Bruce and Goldberg, 1984, 1985; Goldberg et al., 1986).

However, the oculomotor component of attention is not necessary for the cell reaction to occur, either in the arcuate region or elsewhere in the prefrontal cortex; attention to a visual event may activate the discharge of many units in the absence of eye movement. This relationship to sensorial rather than motor aspects of attention is especially evident in anterior prefrontal areas (principalis and inferior lateral convexity) also during visuomotor tasks (Sakai, 1974; Suzuki and Azuma, 1977; Suzuki et al., 1979; Mikami et al., 1982). Units in those anterior areas seem to be attuned more to the behavioral significance and other characteristics of sensory stimuli, including their location in space (Kojima, 1980; Mikami et al., 1982; Vaadia et al., 1986; Barone and Joseph, 1989b; Funahashi et al., 1989), than to the eye movements that those stimuli may elicit in the context of the behavior in which they take place.

To conclude, the behavioral significance of a memorandum, that is, its attention-attracting quality and its importance for behavior, is a critical factor in the reactivity of many prefrontal cells to it. This is not only a reasonable inference from earlier cited studies, but also a clear conclusion from many later ones (Pigarev et al., 1979; Suzuki et al., 1979; Kojima, 1980; Watanabe, 1981, 1986; Pirch et al., 1983; Thorpe et al., 1983; Ono et al., 1984; Inoue et al., 1985; Yajeya et al., 1988; Sawaguchi et al., 1989; Yamatani et al., 1990; Sakagami and Niki, 1994).

### The Delay: Persistent Neuronal Activity

One of the most remarkable findings of prefrontal single-cell research is that of units whose discharge undergoes sustained elevation during the delay period; that is, during the time interposed between the sensory cue and the animal's response to it. As Figure 6.8 illustrates, the sustained activation of these cells may cover delays of up to 1 min or longer between the two events (memory period). Firing usually reverts to the spontaneous rate as soon as the trial ends. Because the firing of many of these cells is obviously related, at least temporally, to the retention of the cue, our group has been calling them "memory cells" almost from the time when we found them. From the beginning (Fuster and Alexander, 1971), we attributed to them a short-term memory function, which eventually we identified as working memory.

Memory cells can be found practically anywhere in the prefrontal cortex, but are most common in its dorsolateral area, around the sulcus principalis. Numerous investigators (Niki, 1974c; Funahashi et al., 1989; Miller et al., 1996; Romo et al., 1999; Takeda and Funahashi, 2002) have identified them in that region of the cortex of monkeys performing delay tasks (e.g., delayed response, delayed matching-to-sample). By our definition, the discharge of memory cells is higher during the delay, in the mnemonic retention of the memorandum, than in inter-trial periods, when the animal does not need to



**FIGURE 6.8** Activity of a prefrontal unit during five delayed-response trials. In each trial, a horizontal bar marks the cue period and an arrow the end of the delay (i.e., the presentation of the choice stimuli). Note the activation of the cell during the delay: over 30 s in the upper three trials, 60 s in the lower two trials. (From Fuster and Alexander, 1971, with permission.)

retain any particular stimulus. The duration and time-course of prefrontal neuron discharge during the delay vary considerably between units. Furthermore, because of differences between studies with regard to the temporal parameters utilized (e.g., the length of the delay), it is difficult to make generalizations in that regard. Yet, from the results of investigations in which delays of a certain minimum duration (about 5 s) have been used, it is possible to identify common patterns conforming to those (C and D) of Figure 6.6 (Fuster, 1973; Batuev et al., 1979; Fuster et al., 1982; Kojima and Goldman-Rakic, 1982; Funahashi et al., 1989).

Having found the first memory cells in the prefrontal cortex, we later found them in other cortical regions (Fuster and Jervey, 1981; Koch and Fuster, 1989; Zhou and Fuster, 1996), as well as in the mediodorsal nucleus of the thalamus (Fuster and Alexander, 1973). As we shall see, these other structures probably cooperate very closely with the prefrontal cortex in working memory, and their memory cells reflect that cooperation. Nevertheless, nowhere do such cells seem so numerous as in the prefrontal cortex. In our experience, however, the prefrontal memory cells are not so closely tuned to the physical properties of the memorandum as some cells in sensory association areas of the inferotemporal cortex (Fuster and Jervey, 1982; Fuster, 1990) or the parietal cortex (Zhou et al., 2007).

Before discussing further the memory function of the delay-activated cells of the prefrontal cortex, which we call memory cells, let us briefly consider the evidence of their involvement in the broader function of the temporal integration of behavior, which working memory serves. Indeed, the working memory of cells in the prefrontal cortex, or any other cortex, is only understandable in the context of the behavior of the animal. Both the mediation of cross-temporal contingencies with working memory and its prospective purpose are the results of prior learning.

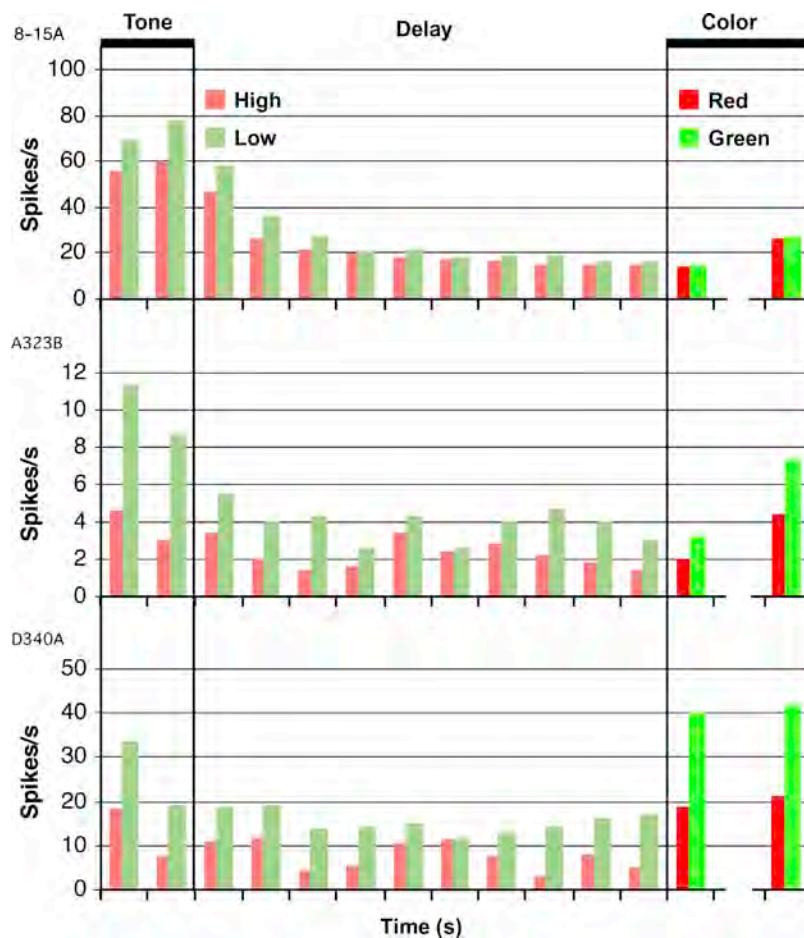
Like the CNV, the activation of prefrontal cells that outlasts the cue and persists during the delay is a product of learning. Support for this assertion lies in the evidence that, in the untrained animal, unconditioned stimuli of the same duration and characteristics as the memorandum elicit prefrontal cell reactions of considerably less magnitude and duration than the cue or memorandum itself in the trained animal (Fuster, 1973). In other words, delay activation cannot be attributed exclusively to the physical properties of the cue or interpreted as a form of sensory after-discharge. A relationship between learning and prefrontal unit reactions is also revealed during the learning of a go/no-go task (Kubota and Komatsu, 1985). During that learning, the following changes are observed: (1) an increase in task-related cells in all cortical layers; (2) an increase in the magnitude of unit reactions to the (visual) stimuli; (3) an increase in the number of cells responding in more than one event period of the task; and (4) a shift toward more tonic and less phasic cell reactions to the stimuli. The development of unit activity as a function of learning has also been reported in the medial prefrontal cortex of the delay-task performing rat (Batuev et al., 1990).

Another property of delay activation is its relationship to behavioral performance; in other words, to how well the animal performs the task in which memory cells are detected. A direct relation has been observed in many experiments (e.g., Batuev et al., 1979; Watanabe, 1986) between the level of delay activation and the level of performance; that is, the number of correct responses that the animal makes. Furthermore, the introduction of distracting stimuli (e.g., auditory) during the delay period has been seen to result in decreases in both delay activity and correct performance (Fuster, 1973). These observations suggest that delay-activated prefrontal cells participate in a neural process ensuring correct performance of the task. Their elevated activity between the cue and the response appears to reflect

the successful bridging of the temporal gap between the two. A clear example of prefrontal-cell mediation of cross-temporal contingencies ([Fuster et al., 2000](#)) is provided by memory cells that retain an auditory tone during a memory period to associate it later with the appropriate

color, in accord with the rule of a “learned-synesthesia” task ([Figure 6.9](#)).

Indeed, the presence of a cross-temporal contingency is the most critical factor for delay discharge, whether the contingency is mediated by working memory or by some other temporal



**FIGURE 6.9** Cross-modal and cross-temporal association. Task as in [Figure 6.1A](#), with tone–color association across a delay. Event sequence in a trial: (1) 2 s tone; (2) 10 s delay; (3) two colors simultaneously presented; (4) animal rewarded for choosing the color that matches the tone by the task rule – green if low-pitch tone, red if high-pitch tone. (Tone and color position change at random from trial to trial.) Average firing frequency histograms from three prefrontal units that prefer the low-tone/green-color combination according to the task rule. During the low-pitch tone memorandum, the cells fire more than during the high-pitch tone memorandum. That preferential firing for low-tone persists throughout the delay. At the time of presentation of the two colors, the preference of the cells is for the color, green, that is associated with the low tone. (From [Fuster et al., 2000](#), with permission.)

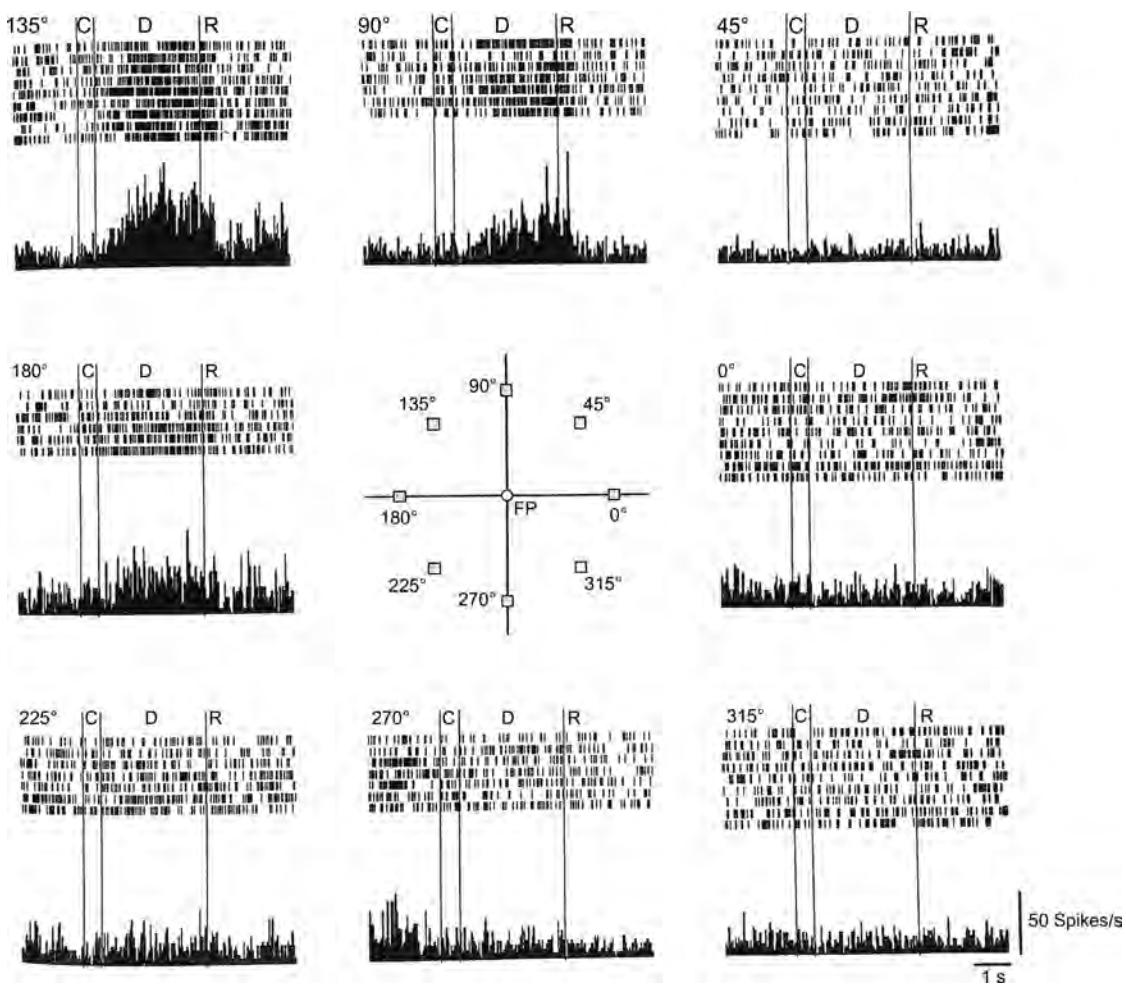
integrative function. That discharge can be directly attributed to the behavioral relationship of mutual dependency between the two essential events that temporally flank the delay: the cue or memorandum on one side and the choice-response on the other. The importance of the cross-temporal contingency for delay firing can be made evident also by excluding the contingency from the behavior of the animal. This can be accomplished, in the delayed-response task, by depriving the cue of its significance as the indicator of a particular choice and motor response, while preserving the same basic paradigm; that is, the cue, a delay, and the stimuli that prompt the animal to make a choice (albeit without reward). Under these conditions, the activation or inhibition of cellular delay firing disappears (Fuster, 1973). A possible reason for this disappearance of delay activity is the abolition of the reward incentive, which may normally play a role in the discharge of the cells during the delay. The fact remains, however, that by eliminating the prospective significance of the cue we also eliminate the need to mediate a cross-temporal contingency, whether that contingency is between the cue and the response or between the cue and the reward. It is the necessity to mediate contingencies between temporally separate events that drives prefrontal memory neurons during the delay. But that mediation, as discussed below, results from the confluence of two factors bearing on prefrontal cells: (1) the necessity to retain the cue or memorandum, in other words, working memory proper; and (2) the preparation for the forthcoming motor choice, in other words, attentional motor set. Let us evaluate the roles of both, memory and motor set, on delay activity.

The delay discharge of many prefrontal units closely depends on the particular attribute of the cue or memorandum that is to determine the animal's choice of response when the delay is over (Niki, 1974a; Fuster, 1975; Niki and Watanabe, 1976a, 1976b; Fuster et al., 1982; Kojima and Goldman-Rakic, 1982, 1984;

Quintana et al., 1988; Funahashi et al., 1989; Bodner et al., 1996; Romo et al., 1999). These units are obviously influenced by the memorandum proper and engaged in its retention (Figures 6.9 and 6.10). Because their differential cue-specific firing occurs when the cue is no longer present, we can assume that those units take part in the retention of that cue. It is important to note, however, that other cells, such as those that show non-differential elevations of delay discharge (e.g., the cell in Figure 6.8), may also participate in that memory function, as they may encode the features of the cue that are common to all memoranda in the particular delay task the animal is performing (e.g., size, form, contrast, luminance). These features, as a result of the associative learning of the task, are very much a part of working memory (active *cognits*; see Chapter 8).

Cue-differential memory cells are also evident in spatial delay tasks in which cues and responses are spatially dissociated (e.g., a left cue means response to the right and *vice versa*, or a red cue means response to the left and a green cue means response to the right). These cells unquestionably reveal their memory role (Niki and Watanabe, 1976b; Funahashi et al., 1990; Quintana and Fuster, 1992). In general, cue-coupled memory cells show a peak of activity at cue presentation or at the beginning of the delay, and then a gradual descent of that activity toward baseline in the course of the delay (types C and D in Figure 6.6).

Does memory-cell recording reveal any form of memory topography in the prefrontal cortex of the monkey? To date, no one has been able to provide an unambiguous answer to this question. Some general principles, however, seem to emerge. Memory cells are more abundant in the lateral prefrontal cortex, particularly the banks and depth of the sulcus principalis, than in other prefrontal areas. Memory cells for eye saccades toward specific cued locations are especially common in area 8 (the frontal eye field) and area 9. In the



**FIGURE 6.10** Discharge of a prefrontal cell in an oculomotor delayed-response task. Except for the response, the monkey keeps the eyes fixated on a central point in the visual field (FP). A trial begins with the appearance of a point of light in one of the eight locations shown in the central diagram. A delay of 3 s follows (D), during which the animal must retain the position of the cue (C). At the end of the delay, the animal, to be rewarded, must respond (R) by briefly directing the eyes to the cue location. The unit is activated during the delay of trials in which the cue is in the left upper quadrant. (From Funahashi *et al.*, 1989, with permission.)

latter area, Goldman-Rakic and her colleagues (Funahashi *et al.*, 1989, 1990, 1991) identified conglomerates of cells apparently encoding working memory for distinct locations in visual space (Figure 6.10). By discrete cortical lesions they were able to selectively produce defects in working memory for saccades in specific

directions ("mnemonic scotomas"). From those results, in addition to the location of direction-specific memory cells, they inferred the presence of "memory fields" in that part of the dorsolateral prefrontal cortex.

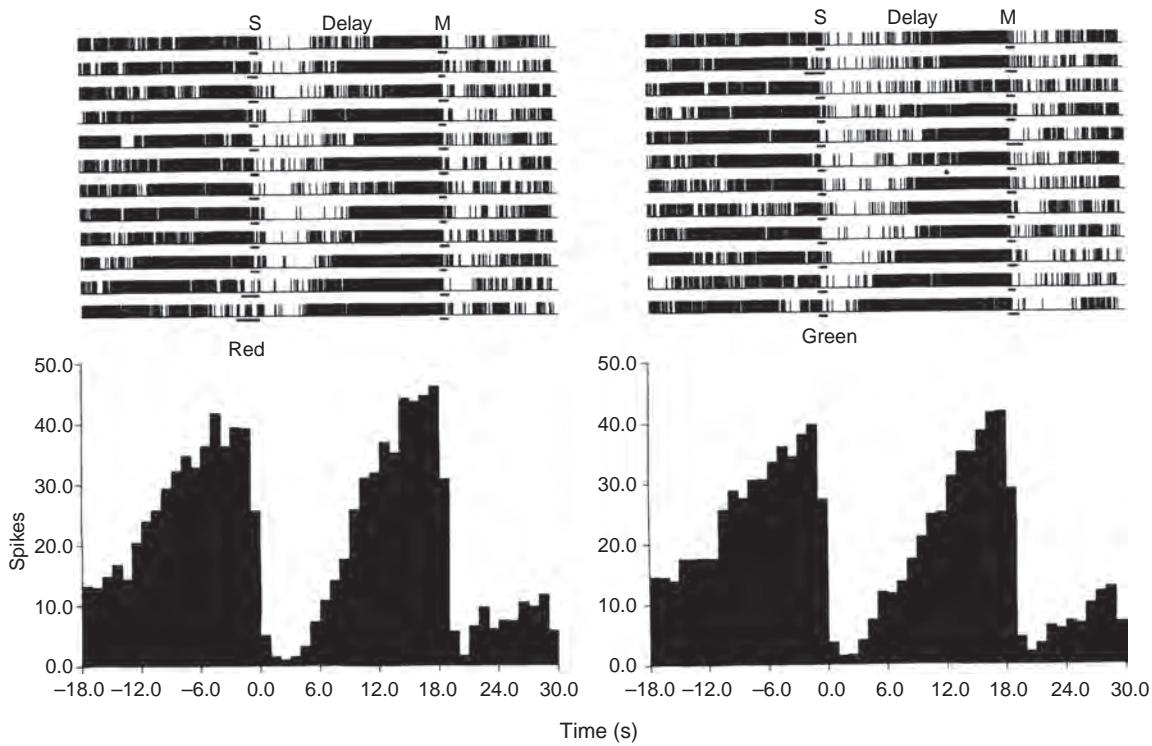
By recording units from monkeys performing alternatively a spatial and a non-spatial

visual task (delayed response and delayed matching), we observed in the upper dorsolateral convexity (above sulcus principalis) a predominance of cells that were preferentially delay-activated in the spatial task, not in the non-spatial one (Fuster et al., 1982); the converse was true in the inferior convexity (below the sulcus principalis), where non-spatial (color) memory cells seemed to predominate. Others (Wilson et al., 1993) report a similar pattern of distribution. Based on this apparent dichotomy, Goldman-Rakic (1995) argued for prefrontal mnemonic modularity. Her views are in accord with the terminal distribution in the prefrontal cortex of the two cortical pathways, one for “where” and the other for “what” information, coming from parietal and temporal cortices, respectively (see Chapter 2). Thus, the cortex dorsal to the sulcus principalis would constitute a special domain for spatial working memory, whereas the ventral cortex would be a special domain for non-spatial working memory, in particular visual working memory.

Because in most spatial delay tasks, such as spatial delayed response and delayed alternation, the location of the animal’s response is determined by the cue from the moment it appears as the memorandum at the start of the trial, the differential cue specificity that some cells exhibit during the delay period of those tasks may actually be spatial-response specific; in other words, the differential delay discharge may reflect not different cues but different response locations. In delayed alternation, where the response in one trial, right or left, is the “cue” for the next, the influence of that cue on delay discharge is indistinguishable from that of factors related to the impending response. In fact, we now have abundant evidence that, during the delay, many prefrontal “memory cells” are engaged not so much in working memory of the cue or memorandum as in the preparation of the motor response that it calls for. The first evidence came with the discovery of memory cells that did not show

the descending patterns of delay discharge of types C and D (Figure 6.6), but instead accelerated their discharge as the motor response approached.

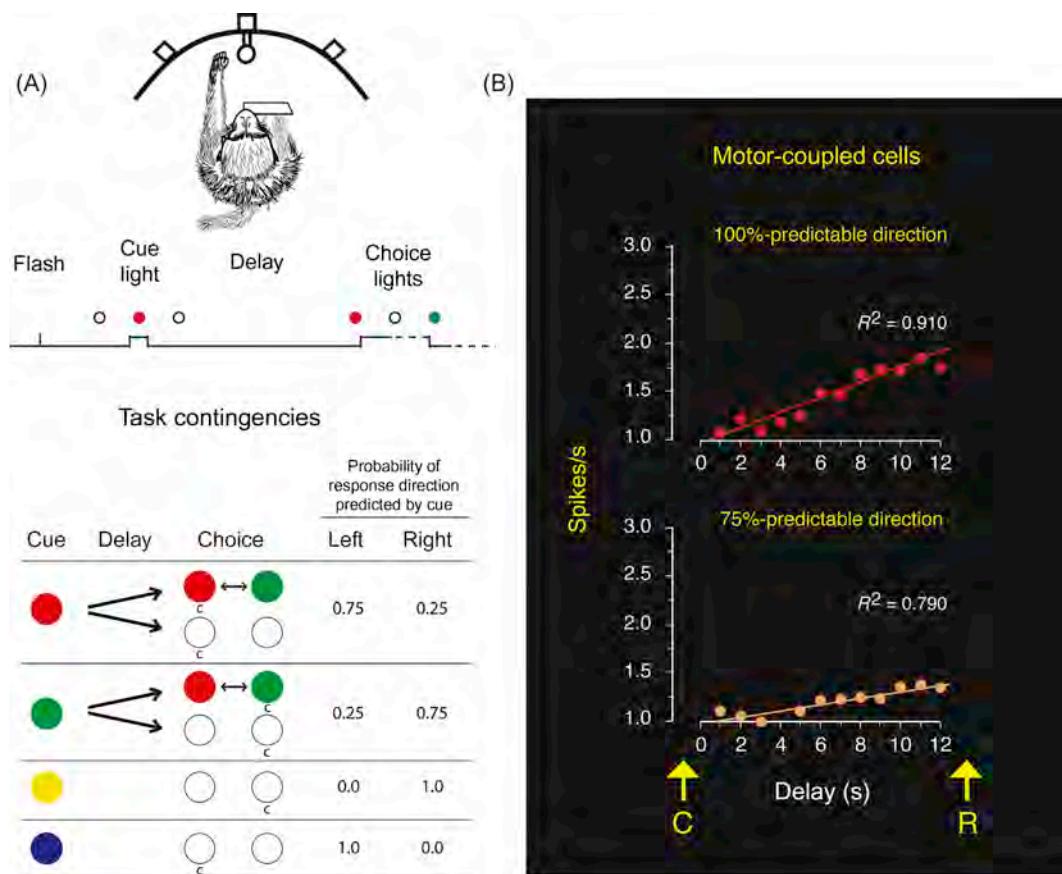
It is now clear that a substantial proportion of prefrontal units undergo firing changes closely related to motor action, whether the action is a delayed response or some other kind of preinstructed movement. The relationship is most apparent in so-called motor-coupled delay-activated cells, which respond differently to different movements – such as more during a manual response to the left than one to the right, or *vice versa* – depending on the side of the manual choice at the end of a trial in a delay task. In such tasks, while memory cells attuned to retention of the memorandum tend to undergo a decrease in firing as the delay progresses (types C and D), motor-coupled cells tend to do the reverse: their firing accelerates as the motor response approaches. Probably because of insufficient cell sampling, in our early studies we did not notice these accelerating motor-coupled cells. In later studies with delayed matching-to-sample (Fuster et al., 1982) we encountered striking examples of anticipatory motor-coupled discharge, such as that of Figure 6.11. The phenomenon can be well observed especially in tasks where the animal can anticipate the timing of a motor act (Niki, 1974a, 1974b; Sakai, 1974; Niki and Watanabe, 1979; Kojima et al., 1981; Komatsu, 1982) and the reward for it. Its functional significance – anticipatory motor set – becomes apparent in a delay task with separation between cue and response in both space and time (Quintana and Fuster, 1992, 1999). Figure 6.12A describes the task. In essence, it is a combination of delayed matching and position discrimination with delay. The color of each cue, at the beginning of a trial, indicates with a given degree of probability the direction of the manual response at the end of the trial. Two colors connote direction with absolute certainty, whereas two others do so with less than 100% probability.



**FIGURE 6.11** Rasters and frequency histograms from a prefrontal cell during delayed matching-to-sample with two sample colors, red and green: at the sample (S), the monkey is presented with a color in a stimulus-response button, which the animal must press and extinguish (thus acknowledging having seen it). Through the delay that follows the animal must retain the color of the sample. At the time of match (M), the two colors are presented simultaneously side by side and the animal must choose the one matching the sample. Note the marked acceleration of firing before the sample and during the 18s delay before the match. Because the trials occur more or less at regular intervals, the cell seems to anticipate the motor response to the sample as well as the choice. There is no significant difference in the discharge of the cell between red-sample (left side of the figure) and green-sample (right side of the figure) trials. (*From Fuster et al., 1982, with permission.*)

As expected in that task, some cells were found to be related to color: their activity at the cue and during the delay was significantly higher with one color than with the others (cue-coupled memory cells). These were cells of the kind described earlier in this section, and their firing during the delay usually exhibited a descending trend. Other cells – motor-coupled cells – showed the opposite: their firing was coupled to response in one direction and, during the delay, had a tendency to accelerate. Then there were some cells of mixed type, attuned to both cue and response.

The most remarkable feature of the motor-coupled cells was that the slope of acceleration of their firing during the delay was proportional to the degree of probability with which the monkey could predict the direction of the forthcoming manual response (Figure 6.12B). That relationship strongly indicates that motor-coupled cells are actually involved in the neural mechanisms that lead to a motor response. In the first place, the phenomenon can be conceived to reflect the activation of prospective motor memory, the scheme of the action; in this sense, it is a phenomenon of motor working



**FIGURE 6.12** (A) Task with temporal and spatial separations between cues and responses (below, contingencies between them). The monkey sits in front of a panel with three small stimulus-response buttons in a row above a pedal, where the animal's hand rests at all times except to respond to stimuli. After a warning signal (dim diffuse flash), one of four colors appears in the central button. A period of delay ensues, at the end of which, the two lateral buttons turn red and green or both white. If those two buttons are colored, the animal must choose the one matching the cue; if they are white, the animal must choose left for red cue, right for green cue, right for yellow cue, and left for blue cue. Thus, during the delay, if the cue has been yellow or blue, the animal can predict the rewarded response direction (right or left, respectively) with 100% probability, whereas if the cue has been red or green, it can do it with only 75% probability (left if red, right if green). Colors and direction of correct choice change at random from one trial to the next. Abbreviation: c, correct choice. (B) Average discharge of motor-coupled cells during the delay of trials with 100% predictable response direction (top graph) and 75% predictable response direction (lower graph). Note that the acceleration of discharge during the delay is related to predictability. Abbreviations: C, cue; R, response. (From Quintana and Fuster, 1999, with permission.)

memory. Further, however, since during the delay the response has not yet occurred but is about to occur, it is reasonable to suppose that, during that time, the cells are engaged in priming the efferent apparatus for the predicted

movement. If predictability is high, preparation is more feasible and effective, and the cells are more closely engaged in it; that is, for movement upward from the pedal and to the right, or left. If predictability is low, preparation is

less feasible and less effective; the cells can only prepare a hand movement in a roughly upward direction toward the response buttons, without definite laterality until the choice lights appear.

To summarize, in the delay that precedes the choice, different kinds of prefrontal neurons seem to take part in two complementary functions serving temporal integration, in this manner mediating the temporal contingency across the delay. One type of cell would serve a memory function by preserving sensory information for the short term, while another would serve a preparatory function, setting the motor apparatus for the consequent response.

It may be, however, that the aggregate of those cue- and response-related units is engaged in both sensory and motor function by virtue of the mutual association between cue and manual response that has been established in the trained animal. This implies that those cells participate in the representation of the cue-response association itself; in other words, that they are part of the neural network that represents both the cue and the response (see Chapter 8). An associative role of this kind is most apparent in units whose reactions to stimuli are contingent on the behavioral significance of those stimuli. They respond to a stimulus if the latter has become a signal for an instrumental motor response (Kubota et al., 1974, 1980; Sakai, 1974; Suzuki and Azuma, 1977; Ito, 1982; Joseph and Barone, 1987).

### Mechanisms of Working Memory

The persistent activity of prefrontal cells during the delay of a working-memory task (e.g., delayed matching) contains information about the memorandum. This can be easily inferred from the cells that show memorandum-differential delay activity, especially if that activity is related to behavioral performance. The clear implication from those data is that during that period some activated networks are attuned to the specific memorandum of the trial and that activation is essential for

good working-memory performance. But those networks are inextricable from other, more widely distributed networks that represent other aspects of the task, among them its rules, the approaching behavioral response and the expected reward; their activation undoubtedly contributes also to the accuracy of performance. We must therefore view the memorandum-encoding networks as being nested or embedded within networks that encode those more general aspects of the task. In the previous section, reference was made to cells presumably in those networks that are attuned to and prepare the motor response (motor-coupled cells). The following discussion deals with the generic, task-related mechanisms of working memory, with emphasis on the role of the prefrontal cortex in these mechanisms.

#### A. RE-ENTRY

Single-unit studies do not support the concept of a special working-memory center or system localized in the prefrontal cortex. For one thing, memory cells have been found also in the thalamus, in the basal ganglia, and in other cortices of association, notably the inferotemporal cortex (Fuster and Jervey, 1982; Miyashita and Chang, 1988; Miller et al., 1993), the posterior parietal cortex (Gnadt and Andersen, 1988; Mazzoni et al., 1996), and the anterior parietal cortex (Koch and Fuster, 1989; Zhou and Fuster, 1996; Romo and Salinas, 1999). There are some general differences; whereas memory cells can be found in the prefrontal cortex for practically any sensory modality, those in inferotemporal, posterior parietal, and anterior parietal cortex appear to engage mainly, if not exclusively, in the retention of visual, spatial, and tactile information, respectively.

Single-unit studies, however, support the concept of a prefrontal substrate of executive memory cooperating with other brain structures, cortical and subcortical, for the maintenance of working memory and its behavioral utilization. That function would be widely

distributed, much like its neural substrate, albeit under a degree of prefrontal executive “top-down” control. The mechanisms of that control are complex, because they involve operations at many levels, from the local prefrontal circuitry to the extensive corticocortical circuitry in which the prefrontal cortex is enmeshed.

One basic mechanism, however, seems to operate in working memory at all levels: reverberating re-entry. Yet, given that the prefrontal activation in working memory results from re-entry in multiple networks (task, memorandum, motor set, reward expectation), it can be reasonably hypothesized that some of the re-entry may be local, within the prefrontal cortex itself, whereas some may be based on the activity in wide-ranging circuits involving the prefrontal cortex together with other cortices. Let us begin with the more general, task-related characteristics of re-entry in working memory.

With Zipser et al. (1993), we constructed a spiking computer model of a neural network to account for the behavior of cortical cells in working memory. Although our model was inspired by the behavior of inferotemporal cells (Fuster and Jervey, 1982; Fuster, 1990), it turned out to predict rather well the behavior of neurons in other cortical regions, notably the prefrontal cortex. Its architecture was essentially recurrent, with every unit connected by re-entry to all others. In our model, input and output values corresponded to spiking probabilities (Amit, 1990). The model was trained by use of the *back-propagation* algorithm (Rumelhart et al., 1986). This is a method for optimization and error reduction, forcing the network to self-adjust its synaptic weights to yield specified input–output relationships while inputs change over time. A periodic load signal acts as a gate; when it is open, the network accepts an input value and holds it in memory. Thus, the net is trained to sample and hold input values and to adjust its weights to reproduce as best it can the input–output relation. After training, the synaptic weights stay fixed.

In the fully trained network, a memory task (e.g., delayed matching) can be simulated by loading an input value (the memorandum) and holding the gate open throughout the delay or memory period. At the end of the delay, without a new input value, the gate is closed by a new load signal. The output units reproduce then the input value. This last operation is unremarkable, because the network has been trained to do precisely that. What is remarkable is that during the delay the intermediate units of the network – the *hidden units* – adopt patterns of discharge that considerably resemble the patterns of real cells in a delay task. In sum, the model tells us that the patterns of firing of cortical cells during working memory can be explained as manifestations of the re-entrant activation of cells that are associated with one another in recurrent networks with fixed synaptic weights.

A number of other local or intrinsic computational models, based on unit data and empirically guided theory, postulate that at the foundation of working memory lie long-lasting, quasi-stable changes of synaptic dynamics and membrane conductance. The functional architecture of these models almost invariably includes re-entry, but in addition some of them include the stabilizing role of certain neurotransmitters, notably dopamine and  $\gamma$ -aminobutyric acid (GABA) (Wang, 1999; Compte et al., 2000; Brunel and Wang, 2001; Durstewitz et al., 2000a, 2000b; Tegnér et al., 2002). Rao et al. (2000) postulate that pyramidal cells engage in the persistent activity that maintains working memory, while GABA interneurons are responsible for the inhibition of distracting or irrelevant information. Wang (2006) describes a prefrontal microcircuit model of attractor dynamics (attractors are quasi-stable states) that incorporates two fundamental features: (1) re-entrant circuitry with slow-acting *N*-methyl-D-aspartate (NMDA) receptors for persistent working-memory activity; and (2) GABAergic interneurons for balance

between excitation and inhibition, and for inhibition of interference. The model reproduces single-unit behavior in working memory with remarkable fidelity (Figure 6.13). Furthermore, by adding a second-layer network to the one producing persistent working-memory activity, and by inducing the second layer to integrate that activity in time, the model simulates the ramping discharge of motor-coupled cells such as those described in the previous section. Upon reaching a given threshold, that integrated discharge would lead to the all-or-none output on which the decision is predicated. Multiple feedback re-entry may enable the storage of multiple items in working memory (Carter and Wang, 2007; Warden and Miller, 2007).

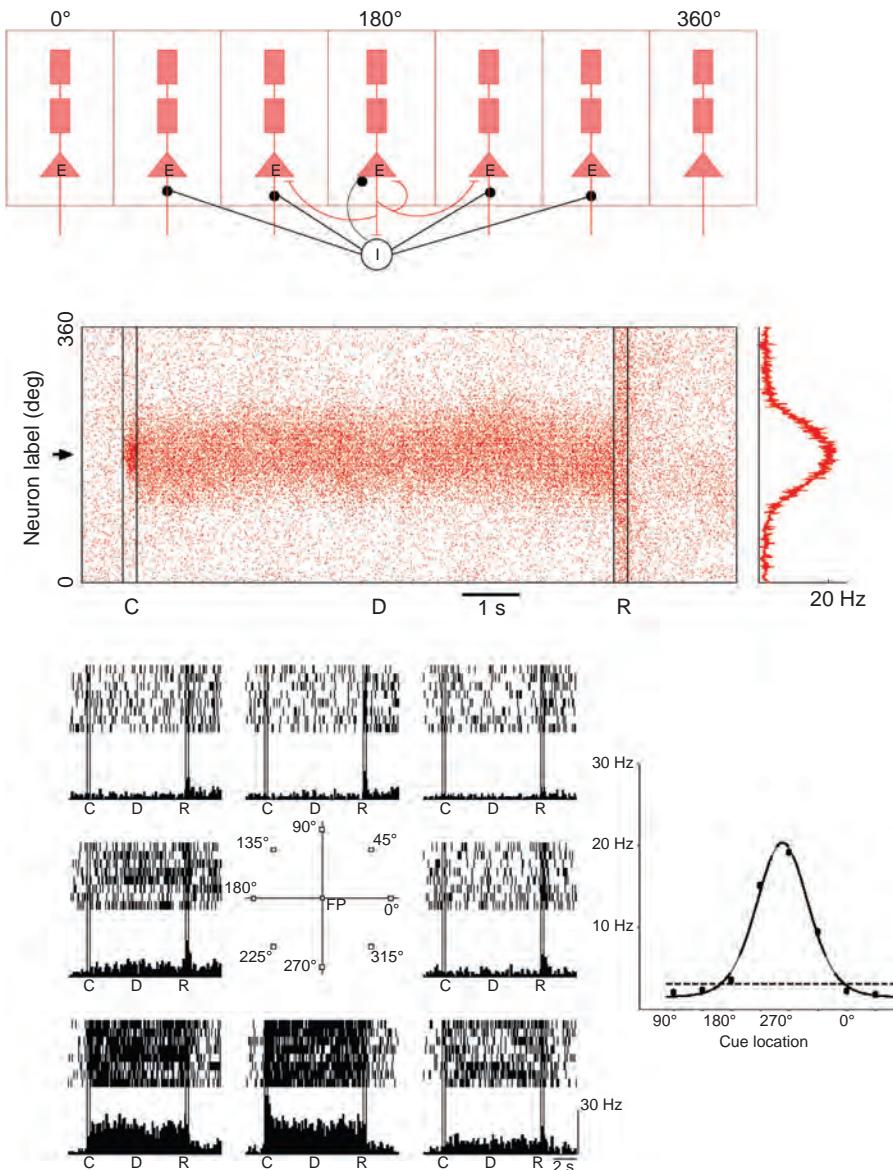
At a more global level, the re-entry dynamics of working memory underlies the functional interactions of the prefrontal cortex with other structures. Evidence for this can be found in the results of experiments combining reversible lesions with microelectrode recording in the behavioral setting. In one of our studies (Alexander and Fuster, 1973; Fuster and Alexander, 1973), we focused on the role of the reciprocal connections between the prefrontal cortex and the mediodorsal nucleus of the thalamus. We reasoned that these connections, which are reciprocal, could constitute a reverberating circuitry for working memory. Consequently, the inactivation of one of the two components of that circuitry would disrupt the neuronal activity in the other and as a result impair working memory. Indeed, the cooling of a large portion of the lateral prefrontal cortex during a delayed-response task resulted in a diminution of the firing frequency of neurons in the parvocellular portion of the nucleus; their spike activity was reduced both between and within trials. Most characteristic and significant were the diminution and abbreviation of activity during the delay. These cellular phenomena accompanied the deficit in performance that predictably results from prefrontal depression. The output of prefrontal cortex to

the caudate nucleus was investigated by similar means in a visual discrimination task (Nishino et al., 1984). Here, prefrontal cooling abolished reactions of caudate cells to visual stimuli, reactions presumably related to the execution of the motor response.

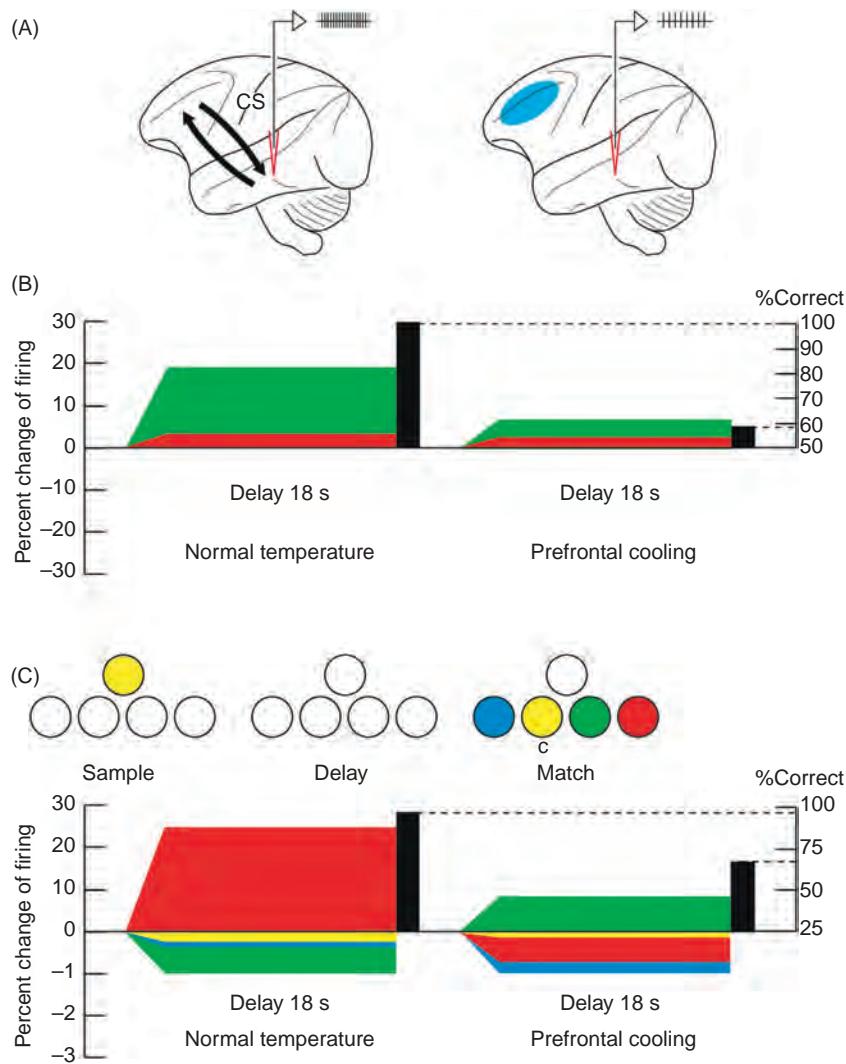
Other studies have explored by similar means – cooling one cortex, recording with microelectrodes from another – the role of corticocortical re-entry loops in working memory. One such study (Fuster et al., 1985) examined the functional relationships between prefrontal and inferotemporal cortex in a visual working-memory task (delayed matching-to-sample) with colors. The cooling of either cortex, prefrontal or inferotemporal, induced marked excitatory and inhibitory changes in the neuronal activity of the other. These changes were observed in the spontaneous discharge of cells as well as in their reactivity to the cue or memorandum. Three significant findings emerged:

- The cooling of lateral prefrontal cortex depressed the elevated delay-activity of some cells in the inferotemporal cortex.
- In either inferotemporal or prefrontal cortex, the units whose reactions to the colored memoranda were most affected by the cooling of the other cortex were found to be more common in supragranular than in infragranular cell layers.
- Whereas the reactions of some units to those stimuli could be increased or decreased by remote cooling, the net effect of the cooling was a diminution of their color differentiation, either at the cue or during the delay (Figure 6.14), or both; in no case was a cell seen to discriminate the colors of the memoranda better under remote cooling than at normal cortical temperature.

Since most corticocortical fibers originate and terminate in upper cortical layers (see Chapter 2), the finding that cells in those layers are especially susceptible to some of the effects of remote cortical cooling supports the



**FIGURE 6.13** Working memory maintained by a spatially tuned network activity pattern (“bump attractor”) in an oculomotor delayed-response task (as in [Figure 6.10](#)). *Top*: Basic architecture of the model. Pyramidal cells (E) of similar preferred cue (spatial location, between 0° and 360°) are interconnected by local excitatory connections and send inhibitory feedback upon themselves through interneurons (I). *Middle*: Simulation. C, cue; D, delay; R, response. Pyramidal cell activity is labeled along the y-axis according to preferred cue location (0–360°). Time on x-axis. A dot in the raster indicates a spike of a neuron whose preferred location is at  $y$ , at time  $x$ . Note sustained firing at preferred location during the memory period (delay). At right, distribution of average population firing during that period. *Bottom left*: Firing activity of a cell at eight locations of the cue in the visual field. The cell prefers the 270° location. *Bottom right*: Delay-period tuning curve of the cell’s firing, with Gaussian fit. The horizontal dashed line indicates average intertrial discharge. (*From Wang, 2006, with permission.*)



**FIGURE 6.14** Cooling dorsolateral prefrontal cortex on inferotemporal neurons during performance of delayed matching-to-sample. (A) Schematic diagrams of inferotemporal–prefrontal connections (arrows), inferotemporal recording microelectrode (in red), and the prefrontal area (in blue) reversibly depressed by cooling prefrontal cortex – bilaterally – to 20°C (CS, central sulcus). (B) Average activity of an inferotemporal cell during the delay in delayed matching with two colors (graph colors match colors of the stimuli-memoranda). The cell is significantly ( $p < .05$ ) activated during retention of green. Prefrontal cooling diminishes the color-differentiation of the cell during the delay (memory periods) and causes the monkey's correct performance to drop from 100 to 59% (black bars). (C) Delayed matching with four colors (c, correct choice). Average activity of another inferotemporal cell in four-color task. This cell is significantly ( $p < .05$ ) and preferentially activated during retention of red. Prefrontal cooling eliminates this activation while task performance drops. (From Fuster et al., 1985, with permission.)

inference that those effects are the result of altering – most likely depressing – reverberating neuronal activity between the two cortices in working memory. This conclusion is reinforced by the evidence (see Chapter 4) that cooling either prefrontal or inferotemporal cortex, but not parietal cortex, impairs delayed matching-to-sample (Bauer and Fuster, 1976; Fuster et al., 1981). Two other studies (Quintana et al., 1989; Chafee and Goldman-Rakic, 2000), also by combining cooling and unit-recording methods in delay tasks, provide evidence of functional interactions between prefrontal and parietal cortex in working memory.

The just-mentioned evidence of functional interactions between prefrontal cortex and other cortices points to three related facts of great importance to our understanding of the mechanisms of working memory: (1) the widely distributed nature of the cortical substrate of working memory; (2) the importance of corticocortical re-entry loops (interrupted by cooling) in working memory; and (3) the controlling role of the prefrontal cortex over the selection and maintenance of its content.

At the theoretical level, the wide cortical distribution of working memory is a basic assumption of many large-scale network models of that cognitive function (Sporns et al., 1991; Tononi et al., 1992; Zipser et al., 1993; Amit, 1995; Dehaene and Changeux, 1995; Brunel, 2000; Koene and Hasselmo, 2005; Ashby et al., 2005; Chadderton and Sporns, 2006; Pulvermüller and Garagnani, 2014). Again, the functional architecture of these models, some of which extend to subcortical structures and neurotransmitter systems, includes re-entry and the potential for reverberation.

## B. OSCILLATIONS

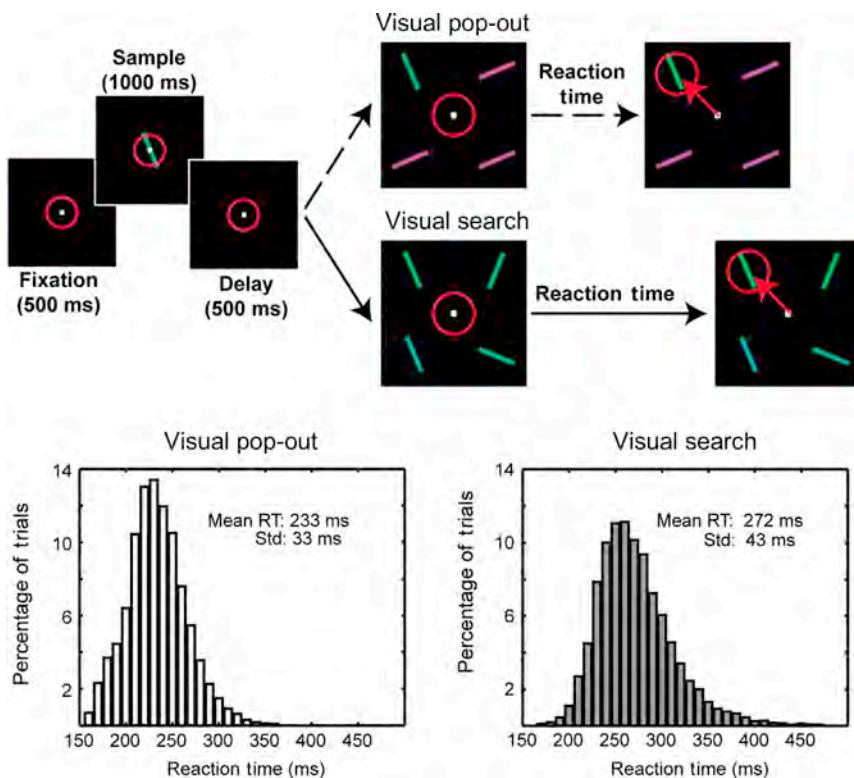
A natural phenomenon of reverberating re-entry in the brain is oscillation. This is one of the reasons why neuroelectrical oscillations in working memory have been the subject of intense scrutiny in electroencephalographic (EEG),

electromyographic (EMG), local field potential, and unit records (see review by Wang, 2010). The results are mixed and so far inconclusive, in several respects. A problem in some of these studies is the use of short delays or memory periods. Such delays preclude the assumption of a steady state in working memory. The problem is aggravated by the evidence that the maintenance of working memory is confounded by task-related temporally coincident factors such as reward expectation and attentional motor set.

Oscillations in the theta band (Raghavachari et al., 2001; Tsujimoto et al., 2006), the alpha band (Leiberg et al., 2006), and the gamma band (Lutzenberger et al., 2002; Kaiser and Lutzenberger, 2005; Wang, 2010; Roux et al., 2012) have been identified in the prefrontal cortex during cognitive performance involving one degree or another of working memory. Not uncommonly, prefrontal oscillations are coherent with oscillations of the same range in posterior cortical areas. In their review, Benchenane et al. (2011), highlight the presence of prefrontal oscillations in different frequency bands, which they postulate reflect dynamic relationships of prefrontal cortex with other brain formations: in working memory and attention, beta/gamma oscillations would reflect relations with visual cortices (bottom-up and top-down), whereas theta oscillations would reflect relations with the hippocampus.

A study by Buschman and Miller (2007) describes prefrontal–posterior coherence in the 22–45Hz range during a working-memory task that requires “top-down” search of visual features (Figure 6.15). At a general level of analysis, such coherence has been adduced as one indication of the cortical span of memory networks (Ruchkin et al., 2003). Oscillations in the high-gamma range (80–150Hz) during cognitive activity, including working memory, have been identified in humans (Canolty et al., 2006; Wang, 2010).

An empirical study of multiple representations in the prefrontal cortex during working



**FIGURE 6.15** Top: Visual pop-out (bottom up) and search (top-down) tasks. Bottom: Average reaction time of the animal in the two tasks. (From Buschman and Miller, 2007, with permission.)

memory (Siegel et al., 2009) reveals memorandum-specific phase relations between spikes and underlying oscillations in the 32 and 3 Hz ranges in local field potentials. This points to the importance of phase-locking, not only as an indicator of re-entry but also as an encoder of working-memory content in specific network synchronies.

Nevertheless, no particular form of oscillation has thus far been specifically related to working memory in the prefrontal cortex or elsewhere. Persistent unit activity in prefrontal or parietal cortex during working memory does not involve the appearance or enhancement of oscillations (Compte et al., 2000; Joelving et al., 2007). It seems that oscillations in practically all frequency ranges can occur in various

cognitive states in various cortical regions, prefrontal cortex being no exception, but working memory involves such a diversity of simultaneously activated re-entrant circuits that no single frequency stands out as being attributed in particular to working memory. In fact, given that working memory is a form of attention (to an internal representation), we would expect in that state of memory something like the EEG “desynchronization” that accompanies arousal, with the disappearance of slow frequencies and the advent of multiple higher frequencies.

Some of our unit data from the parietal cortex in working memory are in accord with that expectation and provide an explanation for the absence of oscillations that could be identified as typical of that memory state

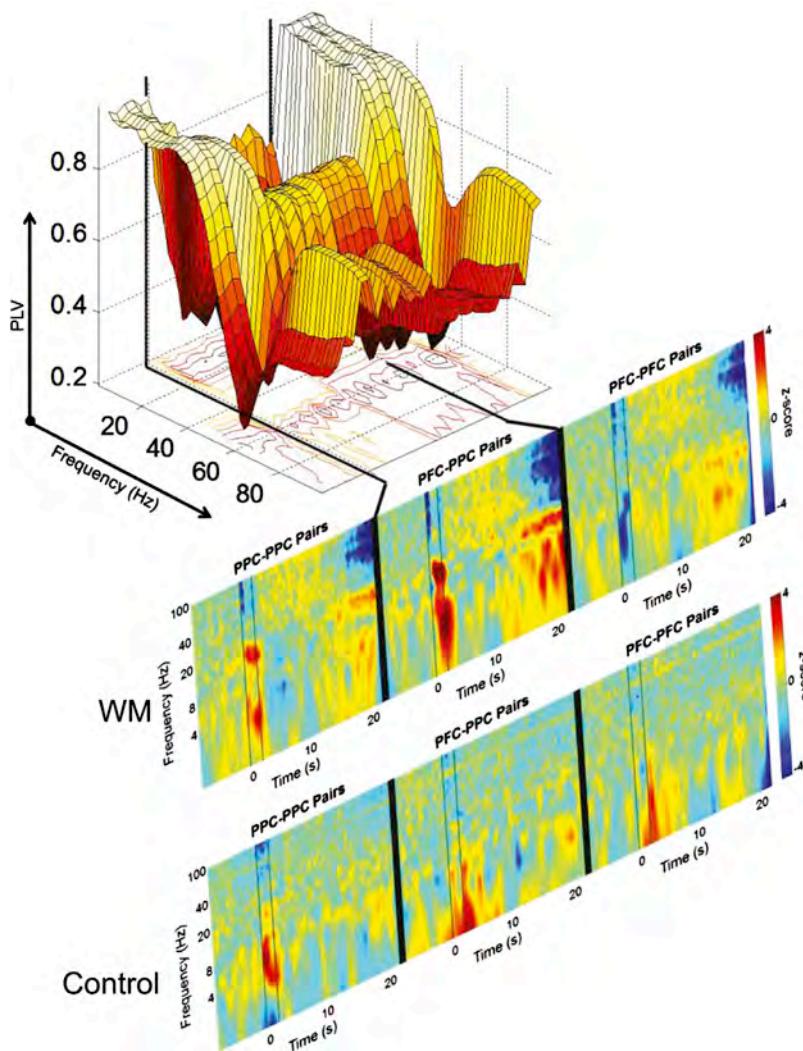
([Bodner et al., 2005](#)). The computational analysis of interspike intervals in the delay period of a haptic working-memory task revealed a characteristic fragmentation and proliferation of patterns of cell discharge when compared with intertrial baseline. It seemed that, as the cortex entered working memory, its cells fell into a variety of attractors, almost simultaneously or in rapid succession. In other words, if we define an attractor as a quasi-stable frequency, and if we consider such a frequency as the expression of activity in a given re-entry loop, the cells appeared to be recruited, almost at the same time, into a variety of re-entry loops, each with its own reverberating frequency. This suggests that the cells are part of the many associative networks that define the various attributes of the memorandum. In fact, an oscillation can be reasonably interpreted as the “signature” of a given network whose elements fire in synchrony and periodically as an expression of re-entry.

A logical consequence of these facts and suggestions is the wide variability of firing frequency patterns that can be discerned in cortical spike trains during working memory ([Shafi et al., 2007](#)). That variability of patterns, especially if they are oscillatory, portends the activation of a multiplicity of networks in that process. Some of these networks are presumably local, others far-flung ([Verduzco-Flores et al., 2009; Pulvermüller and Garagnani, 2014](#)).

Two electrophysiological studies conducted on the non-human primate confirm these views. In particular, they provide evidence of (1) the multiplicity of networks that are activated in prefrontal cortex during working memory; and (2) the probabilistic nature of their activation in consonance with the encoding of memoranda. The first study, conducted by [Wimmer et al. \(2014\)](#), examines the characteristics of prefrontal cell firing in a spatial working-memory task. In the resting state, they identify a variety of “bump” attractors in that firing: these are quasi-normal distributions of firing frequency that succeed one another in

the course of time. During the delay or memory period, some of those attractors drift around their mean in a manner that is consistent and predictable, in accord with the spatial location of the memorandum and the consequent behavioral response. The resting firing distributions, as well as their memorandum-specific shifts, can be predicted in accord with a spiking model based on bump attractor dynamics. If we assume that a bump attractor represents – in the time domain – a position in space, it seems reasonable to infer that the attractor reflects the probabilistic activation of the underlying network upon arrival of the input (memorandum) and its retention in working memory. Thus, a probabilistic change in the firing of many cells in the network would predict with precision the behavioral response. An important consideration is that the attractors are already present at rest and are “nudged” by the memorandum to a given mean frequency of oscillation in order to retain that memorandum in working memory. It is not hard to imagine that a bump attractor in the penumbra of the resting state is recruited and further activated for the working memory of the memorandum together with others representing other attributes of the task, including its rules (see below).

The other study ([Ardestani et al., 2015](#), in review; [Figure 6.16](#)) investigates prefrontal and parietal surface field potentials in spatial and non-spatial working-memory tasks, as well as a control task with no working-memory requirement but with the same delay interval between test stimuli (20 s). At rest, as well as during task performance, oscillatory phase locking (synchrony) was found to be higher within regions than between regions, especially in the low-frequency range (<40 Hz). In the course of task performance, two phenomena stand out: (1) a peak of low frequency during and immediately after the presentation of the sensory cue (the memorandum in working-memory tasks; a neutral, unambiguous, stimulus in the control task); and (2) in the delay or working-memory period,



**FIGURE 6.16** Phase-locking value (PLV) modulations during task performance. *Top:* In three-dimensional representation, cumulative PLV (for entire working-memory trials) between electrode pairs: PFC-PFC, within prefrontal; PFC-PPC, prefrontal-parietal; and PPC-PPC, within parietal. *Bottom:* Dynamic course of PLV in working-memory (WM) and control task-trials. Note larger cumulative magnitude and longer duration of time-frequency clusters in the delay of WM tasks than in control tasks (the latter without memorandum-retention requirement).

a proliferation of high-frequency (>20 Hz) oscillations, especially in the gamma range (>60 Hz).

To sum up, it is safe and reasonable to conclude that any given oscillation is the manifestation (the “signature”) of an active cognit.

The comodulation of several oscillating frequencies in working memory is likely to be the expression of several active cognits nested within one another. Therefore, the study of oscillations in working memory teaches us that

this function consists essentially of the temporary activation of a multitude of memory networks (cognits) reverberating at their particular frequencies. When activated in working memory, those networks integrate across time the perception–action cycle toward its goal (e.g., the reward in a delay task).

### C. STIMULATION

As we have seen in Chapter 4, the application of electric current by implanted electrodes to the prefrontal cortex of monkeys performing a delay task could produce either a disruption (Weiskrancz et al., 1962) or a facilitation (Stamm, 1964) of performance, depending on the timing and parameters of stimulation. In either case, the effects were most apparent when the stimuli were applied to the cortex of the sulcus principalis. The effects were interpreted as a disruption or an enhancement of working memory (with spatial memoranda).

More recent research on human subjects has used two forms of stimulation of the cortex through the scalp, under the heading of non-invasive brain stimulation. For reviews, the reader is referred to Jacobson et al. (2012), Manenti et al. (2012), and Dayan et al. (2013). One form of stimulation, pioneered by Pascual-Leone and his colleagues, consists of the application of pulses of induced magnetic current and is called transcranial magnetic stimulation. The other is transcranial direct current stimulation (tDCS). Both methods of stimulation are assumed to affect large segments of cortical tissue, and are thus considered appropriate for the “modulation” (enhancement or depression) of large-scale networks; that is, executive cognits in the case of the prefrontal cortex.

The application of TMS pulses to dorsolateral prefrontal regions induces a deficit in the performance of sequence learning (Robertson et al., 2001) and working-memory tasks (Mull and Seyal, 2001; Mottaghy et al., 2002). Working memory is also impaired by parietal TMS. When TMS pulses were applied to the two

cortical regions at different times in the course of a verbal working-memory task (Mottaghy et al., 2003), it was found that the interference effect occurred when the stimulus was applied earlier in parietal than in prefrontal cortex. This suggests a posterior to anterior progression of information processing, in accord with the perception–action cycle (see next section).

Whereas TMS to the prefrontal cortex induces deficits in working-memory performance, tDCS of that cortex with appropriate polarity and stimulation parameters induces the converse: the facilitation of working memory. This implies that the latter form of stimulation enhances physiological excitatory processes more than the former. The anodal (positive) stimulation of left dorsolateral prefrontal cortex induces increased accuracy in the performance of working memory (Fregni et al., 2005; Zaehle et al., 2011; Berryhill and Jones, 2012; Hoy et al., 2013; Meiron and Lavidor, 2013), whereas cathodal (negative) stimulation does not. Two experiments show a significant interaction between the beneficial effect and two factors. One is gender, with males benefiting from left frontal and females from right frontal stimulation (Meiron and Lavidor, 2013). The other is level of education: aging adults with a good education benefit more from the stimulation than adults of similar age but with a poor education (Berryhill and Jones, 2012).

The beneficial effect of direct-current stimulation of the prefrontal cortex appears to be optimal with anodic current between 1.0 and 2.0 mA and to linger for minutes or hours after the stimulus has ceased (Ohn et al., 2008; Coffman et al., 2012; Hoy et al., 2013). In view of the importance we have given to phase-locking, re-entry, and oscillation in working memory, it is of interest that there are temporal correlations between prefrontal stimulation, working memory, and oscillatory activity. Zaehle et al. (2011) find that the anodal stimulation of left dorsolateral prefrontal cortex improves working-memory performance while at the same time amplifying

oscillatory activity in the theta and alpha bands. Conversely, the cathodal stimulation of the same cortex results in impaired performance and a diminution of activity in those frequency bands. It will be recalled that, in the monkey ([Figure 6.16](#)), working memory was accompanied by increased phase-locking in those bands, especially between prefrontal and parietal areas. This suggests re-entry between those areas when, in the maintenance of working memory, they are engaged in the mediation of cross-temporal contingencies at the top of the perception-action cycle.

#### D. PERCEPTION-ACTION CYCLE

The networks active in working memory contain not only information about the memorandum but also, most critically, about the task, its rules, and anticipated motor responses. Here, it seems necessary to restate the general principle first enunciated by [Jackson \(1882\)](#) (see Introduction) with regard to motor cortex and also intuited by him with regard to hierarchically higher executive cortices (premotor and prefrontal): the neural substrate for all executive functions is inseparable from, and practically identical to, the neural substrate that represents executive actions, past, present, and future. The difference in those higher cortices – with respect to motor cortex – is that the representative and operational substrates of action are much more complex. Their enactment requires the temporal organization of much more complex material contained in cognits of short- and long-term memory. Hence the critical importance of working memory for that enactment. The main point here is that working memory integrates multiple updated memory networks to pursue a future outcome. To that end, *representational* networks that transcend the prefrontal cortex become, thanks to this cortex, *operational* for a given period (e.g., a delay).

In other words, working memory is a component of the joint and orderly activation of posterior and anterior cortical networks in the perception-action cycle. Working memory fills

the temporal gaps between perception and action by reverberating re-entry between frontal and posterior representational networks. In working memory, as in any other form of selective attention, re-entrant corticocortical loops through prefrontal cortex fulfill the role of a “central executive.” Indeed, there is no need for an executive prefrontal “homunculus,” or anything of the like, to take full control of working memory or any other executive function.

Nonetheless, the operation of the perception-action cycle is not continuously and evenly balanced between activation of perceptual and executive networks. At some times, such as at the initiation of a delayed-response trial, the cycle is set into motion by perceptual input, bottom-up, which activates a cortical network (“ignites” it, as [Braitenberg, 1978](#), would say). At other times, such as during working memory or selective attention, the executive, prefrontal sectors of the network dominate and exert “top-down control” over perceptual sectors of the network and the perception-action cycle. This is, in the author’s opinion, the most plausible view of the “central executive,” thoroughly integrated in the cortical network at large and in the dynamics of the perception-action cycle. Any other view almost inevitably leads to an infinite regression toward an elusive commander.

In working memory, when the executive network dominates, the prefrontal cortex temporarily may be viewed as exerting what has been termed top-down “cognitive control” over posterior cortex ([Desimone and Duncan, 1995; Miller and Cohen, 2001](#)). That control, however, may be nothing other than the establishment and maintenance of excitatory reverberating activity between prefrontal and posterior cortices, together with collateral inhibitory control over competing and interfering perceptual inputs from sensory organs or from the cortex itself.

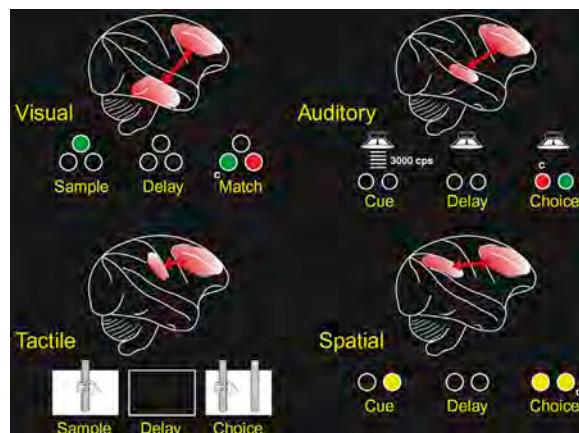
In addition to the experiments described above, by prefrontal cooling and recording posterior cortex units, there is a substantial literature supporting the top-down prefrontal control

of attention and working memory. Most of this literature pertains to the monkey, but some to the human as well. Some of it is experimental (Hasegawa et al., 1998; Miyashita and Hayashi, 2000; Fregni et al., 2005; Buschman and Miller, 2007), while some is based on computational modeling (Deco and Rolls, 2005; Gisiger et al., 2005; Gisiger and Kerzenberg, 2006). Buschman and Miller (2007) record cellular activity simultaneously from parietal and prefrontal cortex in monkeys performing two tasks (Figure 6.15): one requires the animal to direct its eyes to a stimulus among several others differing from it by color and orientation; the other task requires the eye-targeting of a stimulus defined by both orientation and color. The first is an easy pop-out task (bottom-up attention); the second is a more difficult search task (top-down attention). Prefrontal neurons detect the target first in top-down attention (search task); parietal neurons detect it first in bottom-up attention (pop-out task). A reasonable inference from these reaction-time and unit data is that bottom-up attention begins in the perceptual sector of the perception-action cycle, whereas top-down attention begins in the executive sector.

In working-memory tasks, the cue or memorandum presumably elicits first bottom-up attention and then, almost immediately, top-down attention as a result of the activation of perceptual and executive memory networks in posterior and prefrontal cortex associated with the cue. During the delay, both forms of attention, bottom-up and top-down, continue to operate between the two cortices as they engage by re-entrant reverberation in the *internal* perception-action cycle. Depending on the modality of the memorandum and the nature of the approaching action, different posterior and prefrontal areas are engaged in the cycle (Figure 6.17). That internal cycle persists until a second cue or prompting stimulus again externalizes the cycle through the environment and, again by activating perceptual and executive networks, leads to the choice or match, the decision, and the behavioral response.

#### E. RULES AND CONTEXT

The rules of behavior, the rules of a game, as the norms of etiquette, are hierarchically high cognits and habits distributed in premotor cortex, prefrontal cortex, and basal ganglia, from



**FIGURE 6.17** Schematic diagrams of the monkey's brain showing cortical areas of reciprocal interaction during working memory at the top of the perception-action cycle. The prefrontal cortex interacts (internal perception-action cycle) by reverberation with a different posterior cortical area depending on the modality of the memorandum (sample or cue) in the four working-memory tasks depicted under the brain diagrams.

where they modulate working memory, its content, and its context. They enter the perception-action cycle in the form of imagined schemas of action, or at the very least as a form of regulation of anticipated actions in the exercise of working memory toward goals.

Actions are prepared and executed in response to present or recent stimuli, with or without the assistance of working memory. The latter intervenes to mediate cross-temporal contingencies between the stimuli and the actions. In addition, however, an action is prepared and executed in accord with a set of rules that the individual has learned beforehand or has recently been instructed to follow. These rules specify what exactly the subject must do with the available stimuli or cues for optimal results; that is, for the attainment of maximum reward value. In the tests of rule effects on behavior or on frontal physiology, a rule is ordinarily symbolized by a stimulus or verbal command preceding a test trial or set of trials and instructing the subject on how to get set for and handle subsequent stimuli. Thus, rule shifts are behaviorally and cognitively equivalent to set shifts, although there can be attentional set shift without rule shift or working memory. The effects of rule shift in working memory, and its role in the preparation of probable motor action (attentional motor set), were epitomized by the motor-coupled cells of **Figure 6.12**.

Insofar as the rules have a temporal term, however – that is, insofar as the applicable rule at a given time depends on a certain pretrial cue and is only applicable at that time to that trial or group of trials – it can be considered part of working memory and subject to the same mechanisms that maintain or discard working memory. Thus, the rule can be viewed as an overlay of working memory, a layer of “conditional” working memory interacting with the particular sensory stimulus that serves as the memorandum or discriminandum for the trial.

Furthermore, insofar as the rules have been previously learned or are made of material

that the subject can associate with other material of previous experience, the rules are part of long-term memory. They belong to the category of high-level executive memories or networks that lie in the higher levels of the frontal executive hierarchy. As will be argued later in this volume (see Chapter 8), rules, like plans, programs, and schemas of sequential action, as well as the contents of executive working memory, are made of executive networks that differ structurally in synaptic makeup and hierarchical rank. Thus, the physiological evidence for the prospective coding of rules in frontal cortex can be reasonably interpreted as evidence for the representation of executive memory in that cortex. Naturally, it is also evidence for the role that that memory and its networks play an important role in working memory for the preparation or priming of action.

Essentially, all executive functions of the frontal lobe have a future perspective. Working memory has it by definition; indeed, working memory is active memory *for a future outcome*, whether this is the solution of a problem, the following of a rule, or the reaching of a biological goal. The anticipatory preparation for an action and its results is a hallmark of prefrontal physiology (“preadaptation”). Electrophysiology provides the most revealing access to the frontal substrate of executive imagination and anticipation.

The frontal regions that are involved in the coordination of motor actions are hierarchically organized, with the lateral prefrontal cortex on top, the premotor cortex under it, and the primary motor cortex at the bottom (see Chapter 2). This is the cortical extension of a hierarchy of pyramidal and extrapyramidal structures that in lower levels includes parts of the spinal cord, the cerebellum, the pons, the medulla, the tectum, and the basal ganglia. Since the writings of Hughlings Jackson in the late nineteenth century, it has been known that, in general, that hierarchical order reflects the order in which the representation and coordination of movements

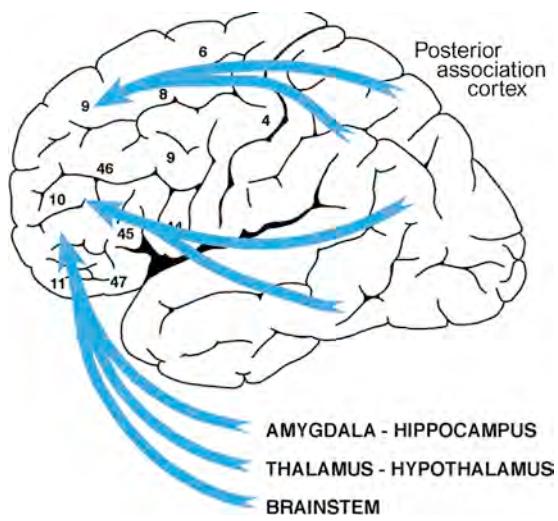
are organized. Thus, voluntary movements, defined by the muscle groups that produce them, are represented and organized in motor cortex, whereas movements defined by goal and trajectory are represented and organized in pre-motor and prefrontal cortex.

Much of the evidence gathered in this book strongly indicates that the prefrontal cortex, at the top of that hierarchy, represents and coordinates complex goal-directed sequences of behavior, especially if they contain cross-temporal contingencies – which working memory mediates. Those sequences are generally processed from the top-down through that executive hierarchy, although the process is far from unidirectional and strictly serial. Much of it takes place in parallel, with feedbacks every step of the way and long re-entrant loops through the lateral thalamus, the cerebellum, and the basal ganglia.

Cellular analysis reveals a temporal-spatial progression of recruitment of lateral frontal areas in the preparation and execution of action. The analysis of the reported findings from many studies (e.g., Alexander and Crutcher, 1990a; Requin et al., 1990; Di Pellegrino and Wise, 1991; Mushiake et al., 1991; Riehle and Requin, 1993), in addition to our own, leads to the following basic conclusions. The prefrontal cortex, at the summit of the hierarchy of frontal motor regions, is in charge of representing in its neuronal networks the most general and abstract aspects of a behavioral structure or “schema,” with its rules and habits. Its cells have the longest lead-times before actions, presumably intervening before cells in the other cortices in the preparation of those actions. From the prefrontal cortex downward, it appears that the organization and preparation of action progressively gains more concrete detail as it proceeds to premotor cortex and, ultimately, to the precentral motor strip, where the “microgenesis of the action” (Brown, 1987) ultimately takes place. As we will see, neuroimaging (see Chapter 7) corroborates this frontal “cascading” of motor processing.

### C. Decision-Making

From our discussion on animal and human neuropsychology (see Chapters 4 and 5), it has become evident that, in any setting, a decision is multifactorial. From the point of view of neurophysiology, that means that the decided output to executive action, in frontal cortex, must result from the processing of innumerable inputs from the environment, from the internal milieu and from other sectors of the cerebral cortex. Given that the prefrontal cortex operates at the highest level of the perception-action cycle, any decision made at that level must integrate a large variety of inputs vying for access to that cortical agency and through it to the cycle. Figure 6.18 depicts schematically

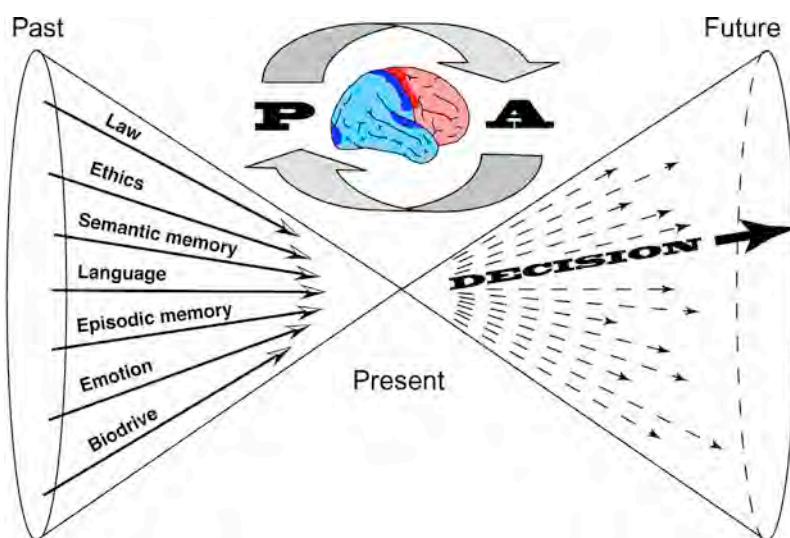


**FIGURE 6.18** Inputs to the perception-action cycle bearing on a decision. Afferents to the prefrontal cortex (areas numbered after Brodmann) modulate and steer the cycle toward the decision. The two sets of cortical arrows symbolize the inputs of information about external events as well as the cognitive history of experience with similar events. In addition, they carry abstract cognitive information on ethical principles and values. The subcortical inputs, coming from limbic structures, and entering the prefrontal cortex through its anterior cingulate and orbital regions, convey influences from the internal milieu regarding instinct, emotion, and biological drive.

the principal internal sources of those inputs. With regard to their role in the computation of action, some inputs are synergistic, some incompatible, and still others subject to compromise in probabilistic terms.

Whereas the decided action may be determined by an emergency, such as an immediate danger signaled by an external stimulus, often it results from the weighing of several competing probabilities, with each decision made in Bayesian terms and therefore based on prior experience. Much of the time, the decision results from expediency to obtain a discrete reward, as is the case in behavioral delay tasks at the time of the signal for choice. At other times, the decision flows from a combination of external and internal influences geared to reach a more or less distant goal. [Figure 6.19](#) depicts in schematic fashion the convergence of potential inputs to the present decision, and the divergence from the present of potential future decisions, from which that one is chosen.

In a novel, ambiguous, or uncertain situation, such as at the end of a delay in a working-memory task trial, the chosen decision is preceded by the activation of the lateral prefrontal cortex, in one or both hemispheres, under the influence of the sources of input schematically depicted in [Figure 6.18](#) ([Schultz, 2006; Glimcher, 2003; Rolls and Grabenhorst, 2008; Asaad and Eskandar, 2011; Kennerley et al., 2011](#)). In that situation, often the most immediate determinant of the decision is one sensory stimulus from the environment which, after processing through perceptual networks of posterior cortex, reaches the executive frontal cortex. Following processing in that cortex by way of high-level executive networks, the stimulus unleashes the decision through a cascade of processing down the frontal executive hierarchy. In a formal task, those high-level networks include the context and the rules of the task ([Bunge, 2004; Durstewitz et al., 2010; Buschman et al., 2012; Reverberi et al., 2012; Eiselt and Nieder, 2013](#)). In the end, the decision



**FIGURE 6.19** The two cones of decision meeting in the present and dynamically embedded in the perception–action (PA) cycle. One is formed by converging potential inputs from the past and the other by diverging potential decisions opening to the future. Each decision represents a vectorial result of the factors that weigh on it.

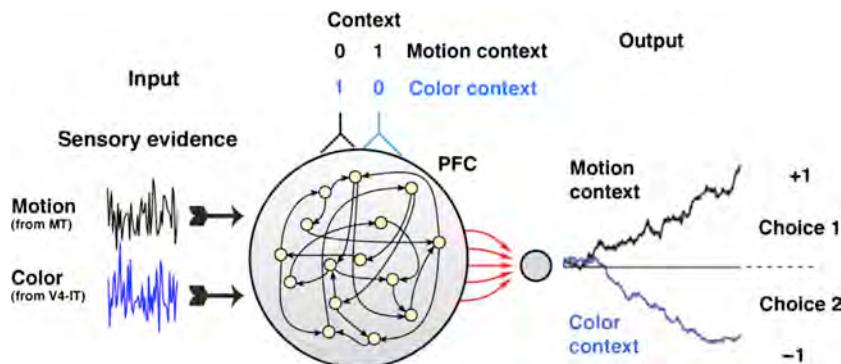
may be “vectorial,” the result of the computation of several synergistic factors of different weight in terms of saliency or motivation. Alternatively, or in addition, it may be Bayesian, based on the updating of probabilities of the role of one or many factors in prior experience or memory.

Because of the variety of circumstances under which decision-making takes place, its computational modeling is difficult. However, several attempts at such modeling have achieved success by limiting the hypothetical impact of a restricted number of factors and by simplifying the neural architecture of the model, in practically all cases including its re-entry (Wang, 2002; Rowe et al., 2005; Sigala et al., 2008; Stokes et al., 2013).

In one re-entrant network model, the relevant factors are reduced to two: an ambiguous visual stimulus and the “context” in which it appears (Mante et al., 2013). Monkeys were trained to select discrete visual stimuli, differing in motion or color, against a noisy background. Depending on a context-signaling stimulus preceding the noise-embedded stimulus, the choice had to

be made between the stimulus motion and the stimulus color. The animal, therefore, had to pay attention to the context signal to select the critical feature of the stimulus embedded in the noise. In records of prefrontal cell populations, as well as in the behavior of a simulating recurrent-network model performing the same task, context was seen to sway the entire population or network of cells to discriminate one parameter or the other (motion or color), and thus to make the fitting decision to it. The authors of the study conclude that one and the same network can perform both the sensory input selection and the integration of the appropriate behavioral response (Figure 6.20).

In any case, however, a decision and the prefrontal involvement in this decision are multifactorial, from the confluence of many kinds of signals upon the prefrontal cortex. Some of those signals are complex, such as the context in which that stimulus appears (see above, Mante et al., 2013). Such complex signals may be mixed and encode what Rigotti et al. (2013), based on primate cell data, call “mixed selectivity.”



**FIGURE 6.20** Empirical model of input selection and integration by a prefrontal cognitive network. The fully recurrent network was trained by back-propagation (Rumelhart et al., 1986), with synaptic strengths originally randomized, to make binary choices on ambiguous visual information in accord with an independent contextual input (two values, 0 or 1, for motion or color). Each unit in the network receives motion and color inputs (embedded in noise) as well as input on context. The contextual input instructs the network to discriminate motion or color. The network generates one output at the end of the stimulus presentation if the relevant evidence (context) point toward choice 1, or another if it points toward choice 2. The network is “read out” by a single linear readout of the weighted sum of the response of all units (red arrows). MT, V4, and IT: three areas of extrastriate visual cortex. (From Mante et al., 2013, with permission.)

To summarize, the neural signals of the involvement of the prefrontal cortex in decision-making may depend on the factors that determine the decision. That decision may be: (1) determined by only one factor, such as a critical external stimulus; (2) vectorial, the result of several synergistic factors with different weight; (3) "winner-takes-all," when one of the factors decisively outweighs the others; or (4) Bayesian, probabilistically based on the updating of prior memory.

## D. Monitoring and Prediction Error

One of the most important determinants of decision-making is the assessment of the consequences of previous actions. With regard to any particular action, that assessment is focused on three principal questions: (1) Was the action – on whatever criteria – correct or incorrect? (2) Was the action successful in yielding reward? and (3) Did the action come into conflict with other actions or with changing conditions in the internal or external milieu? (In other words, was the action in some respect maladaptive?) At the risk of anthropomorphizing the frontal lobe (which Pribram, 1973, called "the executive of the brain"), those are three critical questions for the frontal cortex, because the answers to them will guide future executive action. In the behaving organism, one executive function has been invoked to answer all three. That function is action monitoring. In recent years, a fourth question has entered the action monitoring methodology: (4) Did the action achieve its goal as predicted? Failure to do so is called *prediction error*.

All aspects of action monitoring can be construed as feedback within the dynamics of the perception-action cycle (see Chapter 8). That feedback may be internal or external. In the first instance, it may involve sensory inputs from proprioceptors, visceral receptors, and cognitive areas of the cerebral cortex; in other words, the internal cycle. In the

second, it may involve external receptors and sensory pathways, thus the external cycle. In either case, monitoring has been postulated to be a central executive function of the frontal cortex (Norman and Shallice, 1986; Logan and Gordon, 2001). Indeed, in Chapter 5 we saw how prefrontal syndromes can lead to faulty monitoring in memory retrieval (Shimamura et al., 1991; Stuss et al., 1994; Mangels et al., 1996; Siegert and Warrington, 1996), reality testing as in confabulation (Schnider, 2001, 2003; Gilboa et al., 2006), and error and reward contingencies (Swick and Turken, 2002). Again in the human, several studies point to the medial frontal cortex, especially the anterior cingulate, as an important neural node for the supervisory control of action, and thus for action monitoring (see Carter et al., 1999, for a review).

Electrophysiologically, the issue of frontal action monitoring has been approached in two ways: by recording event-related potentials and by single-unit recording. In the anterior cingulate cortex of the human, a negative potential has been detected in relation to the commission of errors in behavior tasks (Dehaene and Cohen, 1994; Gehring and Knight, 2002; Krigolson and Holroyd, 2007; Potts, 2011). That potential has been named the *error-related negativity* (ERN). Gehring and Knight (2002) find that, in healthy control subjects, the ERN is greater in error trials than in correct trials. In subjects with lateral prefrontal lesion, however, they find that ERNs for correct trials is equal to ERNs for incorrect trials. From this finding they infer a functional interaction between lateral and cingulate cortices that is essential for proper action monitoring and corrective behavior.

In the monkey, Schall and his colleagues (2002) investigated the monitoring of instructed eye saccades in a countermanding task. This is a task in which the animal is instructed to perform eye movements in the direction specified by a visual cue. Every now and then, while preparing an instructed saccade, the animal is given an imperative stop signal, upon which

it is supposed to take corrective action, such as delaying saccade initiation. The task tests the monitoring and supervisory control of eye movements. On the basis of research from the same laboratory and from others (e.g., Schlag-Rey et al., 1997), the investigators hypothesize the involvement of the SEF in those functions.

Microstimulation of the SEF strengthens their hypothesis (Stuphorn and Schall, 2006): weak stimulation facilitates performance of the task. The penetration of the SEF with micro-electrodes yields three types of cells (Stuphorn et al., 2000; Schall et al., 2002). The first is characterized by activity after errors, the second after successful withholding, and the third after reward. The presence of these cells, whose activity cannot be explained by sensory or motor inputs, confirms the inference that the SEF takes part in the monitoring of eye movements in accord with context and consequences. The extension of this research to the anterior cingulate cortex (Ito et al., 2003) shows in this cortex cells that, in addition to responding to errors, respond to the omission of earned reward. Others respond to unexpected reward. These findings, like those mentioned in the previous paragraph, add the anterior cingulate cortex to the control of actions and the monitoring of their consequences. Thus, as a result of their monitoring role, the anterior cingulate cortex and the SEF, presumably by way of excitatory and inhibitory outputs to the frontal eye field and lower structures, exert supervisory control of actions in accord with the context and the consequences of those actions.

Prediction error – called by some “surprise error” – links action monitoring to the predictive and preadaptive functions of the prefrontal cortex. In that sense, it is inseparable from the prospective functions of this cortex, with which we have dealt earlier: attentional set, working memory, and decision-making. In any of them, failure of expected outcome could be characterized as prediction error. In any case, prediction error, like other forms of action monitoring,

has been primarily attributed to the anterior cingulate prefrontal cortex (Braver et al., 2001; Modirrousta and Fellows, 2008; Potts et al., 2010; Shackman et al., 2011). Nonetheless, single-neuron studies indicate that the encoding of prediction error is distributed in anterior cingulate cortex, lateral prefrontal cortex, and caudate nucleus (Asaad and Escandar, 2011; Hayden et al., 2011).

## E. Inhibitory Control

Inhibitory control is another executive function of the prefrontal cortex that cannot be clearly separated from the others, in terms of either topography or physiology. Indeed, inhibition – whose prime neurotransmitter, GABA, is the most profuse of all neurotransmitters in the prefrontal cortex – is essential for all its cognitive functions. None of those functions is possible without effective inhibition. Attention, working memory, and decision-making, the major executive functions of the frontal cortex, essentially require not only the focus on what is relevant and necessary but also the inhibition of what is irrelevant and unnecessary. Inhibition is key to all three functions for efficiency in the pursuit of goals, for contrast in content and context, and for optimal use of the neural resources of the frontal cortex and related structures.

Inhibition is biologically a basic mechanism that serves all adaptive functions of the organism, sensory and motor. For example, the proper operation of the knee consists of not only the timely contraction of extensor muscles but also the timely inhibition of the flexor muscles. The focal excitation of the center of a retinal visual field is accompanied by the inhibition of its surround. So it is with practically every function throughout the nervous system, including cognitive functions, most particularly attention. While we focus attention on something important, we actively suppress, that is inhibit, what is extraneous or irrelevant. Thus,

prefrontal attentional set involves not only the priming of some parts of sensory and motor systems but also the inhibition of others. The same is true for working memory, decision-making, and probably also monitoring.

That places inhibition at the center of all prefrontal executive functions, but because of its wide distribution, it defies localization more than any other. For reasons of methodology, however, it is useful to divide the substrate of inhibitory control into two major domains. One is intracortical, which we can name intrinsic; it consists of inhibition at the highest cognitive levels, affecting mainly or exclusively selective cognition and cortical cognitive networks. The other domain of inhibitory control is extrinsic; it consists of inhibition by prefrontal (principally orbitofrontal) cortex of subcortical structures involved in the behavioral control of affect and impulsivity. In addition to GABA, both domains are endowed with profuse inhibitory neurotransmitters and receptors of the serotonergic 5-HT<sub>A1</sub> (Puig et al., 2004) and cholinergic muscarinic (Medalla and Barbas, 2012) categories, in addition to excitatory neurotransmitters and receptors (Dalley et al., 2008) to ensure a balanced excitatory–inhibitory interplay in cognitive control.

The study of oscillatory rhythms at rest and in cognitive functions has led to the widespread concept that oscillation in the alpha band (8–12 Hz) is a manifestation of a generalized cortical inhibition prevalent in the resting state. However, by undergoing certain local modulations, that oscillatory activity may support specific cognitive functions in specific cortical networks. It is extremely difficult experimentally to associate, on the basis of EEG and EMG records, any given cognitive function or content with a particular frequency of oscillation. Nonetheless, by frequency analysis and such related procedures as the analysis of phase-locking synchrony within and across cortical areas it has become possible to establish certain principles that apply to the excitation as well

as the inhibition of specific cognitive networks (Klimesch et al., 2007; Palva and Palva, 2007; Haegens et al., 2010; Sadaghiani et al., 2012; Crespo-García et al., 2013).

One such principle is that the transition from rest to cognitive activation, as in working memory, for example, is accompanied by an increase in the complexity of oscillatory patterns; that is, a fragmentation of the frequency spectrum prevalent at rest into multiple subcomponents at a variety of higher frequencies (Knight et al., 1999; Suffczynski et al., 2001; Klimesch et al., 2007; Palva and Palva, 2007; Haegens et al., 2010). This fragmentation (Figure 6.16), which is probably at the foundation of EEG desynchronization, points to the concomitant or serial activation of multiple cognitive networks and the lateral or recurrent inhibition of others; in other words, the activation of networks needed for present cognitive operations and the inhibition of others that represent irrelevant or interfering material.

These mechanisms of reciprocal network excitation and inhibition have been demonstrated within and across cortical areas in the studies cited in the previous paragraph. Their underlying inhibitory components can be reasonably considered the expression of the intrinsic inhibitory control essential for the successful performance of all the executive functions examined thus far in this section: attentive set, working memory, decision-making, and monitoring. Therefore, the involvement of the prefrontal cortex in intrinsic, intracortical, inhibitory control would derive from the participation of prefrontal executive networks in the ensemble of intertwined and hierarchically organized cognitive networks of the cerebral cortex, perceptual as well as executive.

The extrinsic inhibitory control by the prefrontal cortex is more easily substantiated anatomically and physiologically than the intrinsic one. The reason is because the former is firmly grounded in animal and human neuropsychology; as such, it has been discussed in previous chapters (see Bari and Robbins, 2013,

for a review). Neuroimaging will substantiate it further in Chapter 7. Essentially, it consists of the flow of inhibitory influences from the prefrontal cortex upon subcortical structures, especially the basal ganglia and limbic formations, involved in motility and its cognitive aspects. This component of inhibitory control has the effect of suppressing disorderly impulsivity and inappropriate behavior. As we have seen, its restraining actions are absent in animals with prefrontal lesions, in the immature human, and in certain forms of attention deficit/hyperactivity disorder syndrome and drug addiction. On psychological testing, the lack of inhibitory control results in untimely and erroneous behavioral responses in Stroop and reversal tasks.

Arguably a major source of extrinsic inhibitory control of behavioral responses is the right inferior frontal cortex (see Aron et al., 2004, for a review). However, it is reasonable to conclude from the bulk of the available data that the source of extrinsic inhibitory control is widely distributed throughout the prefrontal cortex, including its dorsolateral aspects, although it has major foci in its inferior and medial regions. Its main targets are the basal ganglia, the lateral thalamus, and the superior colliculus with regard to motility; and limbic formations, notably the amygdala, the hippocampus, and the hypothalamus, with regard to biological impulses and emotion. Of special interest in the latter respect is the inhibitory control of fear. The relevance of prefrontal influences on the amygdala for the inhibition of fear responses has been emphasized (Herry et al., 2010; Sotres-Bayon and Quirk, 2010).

The inhibitory inputs from prefrontal cortex to hippocampus may have a distinct cognitive relevance, for they may have a decisive impact on the encoding and retrieval of memory. Whereas forgetting is commonly considered a failure of memory, either in acquisition or recovery, there is considerable evidence that it may result from the active, voluntary inhibition of those memory processes (Levy and Anderson, 2002; Bjork, 2007). A combination of electrical

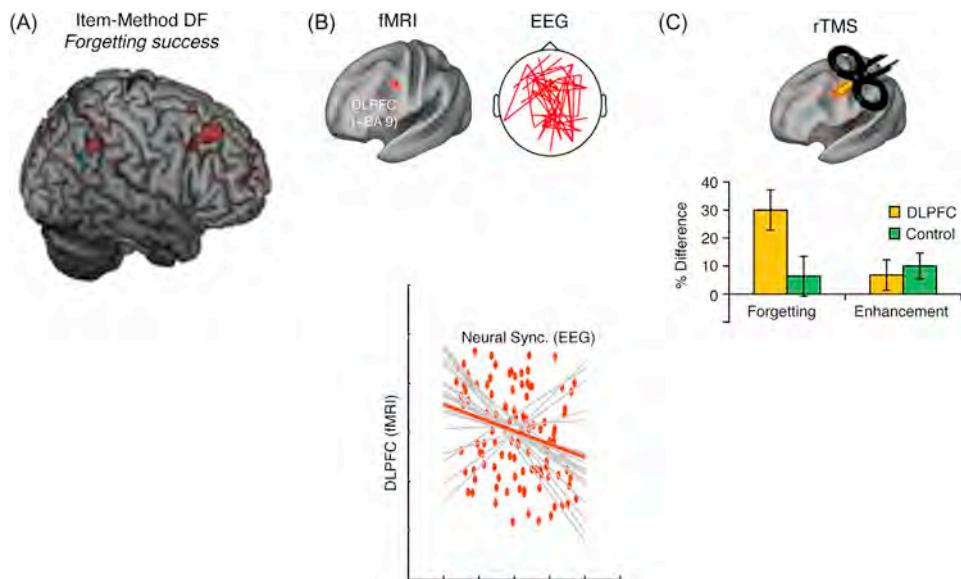
recording, imaging, and magnetic stimulation has revealed a role of prefrontal inhibition, presumably over the hippocampus, in deliberate forgetting. Using psychological tests suitable to expose what they call “motivated forgetting,” Hanslmayr and his colleagues (Hanslmayr et al., 2012; Anderson and Hanslmayr, 2014) have evinced three related phenomena (Figure 6.21): (1) the blood oxygenation level-dependent (BOLD) activation of dorsolateral prefrontal cortex in successful active forgetting; (2) the reduction of left prefrontal EEG synchrony during active forgetting; and (3) the facilitation of that kind of forgetting by repetitive TMS of left dorsolateral prefrontal cortex.

The last mentioned experiments on active forgetting suggest that the separation between intrinsic and extrinsic prefrontal inhibitory systems may be methodologically useful but is physiologically somewhat unjustified and misleading. Indeed, there is an undercurrent of present thinking that tends to view the prefrontal inhibitory control system as a central unitary entity exerting inhibition at various hierarchical levels (Munakata et al., 2011).

With this general, unifying conception in mind (Roberts and Wallis, 2000), the dorsolateral prefrontal cortex would represent in its networks the higher order schemas of behavior and their rules, whereas the orbitomedial prefrontal cortex would represent lower order schemas and rules. In the enactment of complex behavior and speech, both would act flexibly in tandem as a unit in the pursuit of goals and subgoals. In so doing, both cortices would exert their controlling inhibitory influences to suppress at all levels the irrelevant, the maladaptive, and the distractible with respect to those objectives.

## VIII. SUMMARY

Electrophysiological data corroborate the connective links of the prefrontal cortex. In accord with anatomical evidence, fiber



**FIGURE 6.21** Neural correlates of motivated forgetting. The subjects are instructed to actively forget certain items presented in a series for encoding in memory. (A) Areas in red show greater activation [functional magnetic resonance imaging (fMRI) oxygenation] during encoding items to be forgotten than items to be remembered. (B) Forget instructions activate left dorsolateral prefrontal cortex (DLPFC) and reduce alpha/beta (11–18 Hz) synchrony (in scalp diagram, electrode pairings show significant decreases in synchrony during forgetting compared to remembering); the two signals [fMRI and electroencephalography (EEG)] are negatively correlated on a trial-to-trial comparison (plot-graph below). (C) Stimulating DLPFC with repetitive transcranial magnetic stimulation (rTMS) increases forgetting without affecting enhancement. (*From Anderson and Hanslmayr, 2014*, with permission.)

connections of this cortex with other cortical regions, with the thalamus, and with the basal ganglia have been electrically traced. Significantly complementing and substantiating lesion studies, electrophysiological research has provided insight into the roles of the prefrontal cortex in sensory, motor, visceral/emotional, social, and executive functions.

Neuroelectrical impulses of sensory origin have access to several areas of the prefrontal cortex, whether by way of corticocortical connections or by way of non-specific nuclei of the thalamus. In the primate, some of these areas receive converging inputs of several modalities. On the basis of microelectrode studies, however, other areas seem to specialize in unimodal sensory processing: prearcuate and inferolateral areas in vision, orbital areas in taste and

olfaction. Microelectrode studies show a degree of bimodal and multimodal convergence at the single-cell level. Because of the abundant convergence of sensory inputs on the cortex of the prefrontal convexity of the primate, it is justified to consider most of this cortex as cortex of sensory association.

The prefrontal cortex also plays a role in sensorial attention, namely, in the selective control of the access of sensory inputs to higher cerebral structures, including the prefrontal cortex itself. Although the mechanisms of that top-down control are unclear, they can be assumed to involve the reciprocal connections of the prefrontal cortex with subcortical and limbic structures implicated in motivation, as well as with other neocortical regions implicated in cognition.

In addition to tracing prefrontal connections to motor structures, electrophysiology provides evidence of the prefrontal control of movement. Neuronal activity in the caudate nucleus, a major collector of output from the prefrontal cortex to motor systems, is modulated by abundant input from the prefrontal cortex. Eye movements are controlled and monitored with a high degree of precision by neuronal assemblies in two prefrontal eye fields: the arcuate cortex of area 8 and the SEF of the dorsomedial frontal convexity. Because of its involvement in eye and head motility, the first seems to be essential for motor aspects of attention, especially for governing the spatial orientation of telereceptors toward visual and auditory stimuli. The SEF seems to be essential for the execution of eye movement sequences and the coordination of the eyes and upper limbs. Microelectrode studies of the monkey's frontal eye fields highlight their sensory-motor character, a fundamental property of the prefrontal cortex as a whole. Microelectrode studies in the behaving monkey provide evidence that networks of the lateral prefrontal cortex represent movement sequences and categories of sequences; that is, abstract executive memory.

The bulk of the physiological evidence on the sensory and motor functions of the prefrontal cortex indicates that these functions cannot be understood in isolation, but must be viewed as part of integrative sensory-motor operations that transcend modalities of either sensation or movement. Those integrative operations are constituents of the representational and dynamic substrate for the perception-action cycle; that is, the circular flow of information between the organism and its environment that takes place in all forms of adaptive behavior. Prefrontal networks at the higher levels of the cycle are capable of integrating percepts and actions of high order of complexity and abstraction.

Orbital and medial areas of the prefrontal cortex control a variety of visceral and hormonal functions. The cardiovascular and respiratory

systems are particularly susceptible to prefrontal influences from those regions. These influences are mediated by the limbic and autonomic systems. The orbitofrontal inhibition of motor activity extends to instinctual and emotional behavior. Feeding and aggressive behaviors are normally kept in check by the orbital areas of the prefrontal cortex. Inhibitory output descends from those areas upon the hypothalamus and presumably controls both eating and aggression.

Those same prefrontal areas, orbital and medial, are implicated in the encoding of reward, the assignment of value, and the initiation and maintenance of reward-seeking behavior. In all three respects the orbitomedial cortex cooperates with the amygdala and other limbic structures. The orbital cortex, in particular, which is part of the dopaminergic circuitry at the base of the brain, is involved in the evaluation of reward value in terms of quality and quantity. Its neurons reveal a remarkable feature in the time domain that reflects a similar feature in dorsolateral prefrontal cortex: the anticipation of events. Orbitofrontal neurons are activated by expected reward as well as by its absence (prediction error). Also in parallel with the dorsolateral cortex, the orbitomedial cortex is part of the emotional perception-action cycle, which assists the organism in the pursuit of reward and emotional goals.

From the point of view of neuroeconomics, that is, the neural attribution of risks and benefits, the orbitofrontal cortex has the capacity to evaluate delay discount. Delay discount is the natural tendency to devalue rewards for which the organism has to wait. This tendency is at the root of the incapacity to postpone gratification, a characteristic of young children and of animals with lesions of the orbital prefrontal cortex. Accordingly, some cells in this cortex appear to value short-term over long-term benefit.

The electrophysiological correlates of five executive functions have been well substantiated: attentional set, working memory, decision-making, monitoring, and inhibitory control.

All five functions are intimately related; all have a prospective aspect and serve the temporal integration of goal-directed action. For the analysis of their electrical correlates, all five functions require testing in the awake and behaving organism, although neuroimaging (see Chapter 7) is increasingly contributing to that analysis.

Attentional set is the priming and preparation of sensory and motor systems for enactment of perceptual and behavioral actions with maximal efficiency and economy of resources toward the attainment of behavioral goals. It is the fastest and most flexible of all executive functions of the prefrontal cortex. It also has the widest cortical distribution. It has an inclusionary component for focus and an exclusionary component for the suppression of distraction and interference. The first is primarily based in dorsolateral cortex, the second in orbitomedial cortex. Both exert top-down control of attention. They have electrical manifestations in the form of slow surface potentials related to expectancy and preparation, as well as anticipatory neuronal discharge in the performance of goal-directed behavioral tasks.

Working memory is the temporary retention of information for prospective action. In complex goal-directed tasks, it bridges temporal gaps by mediating cross-temporal contingencies at the top of the perception-action cycle. Working memory can best be tested and its electrical correlates examined in delay tasks. The analysis of prefrontal cell discharge in these tasks reveals the presence of neurons that respond to various attributes of the sensory cue or memorandum that the animal must retain for correct response after the ensuing delay. During that delay or memory period, large numbers of prefrontal cells show elevated and persistent activity. Those are called *memory cells*, and can be found in all parts of the prefrontal cortex, but are especially common in lateral areas. Their principal function is to retain the memorandum across the delay. They serve

working memory in its strictest cognitive definition: the short-term memory of sensory information (the memorandum) for a prospective action toward a goal.

A working-memory network extends beyond the prefrontal cortex into posterior areas of the cortex of association, where memory cells can also be found. The posterior sectors of the network hold perceptual memory, the frontal sectors executive memory. The central mechanism of working memory is reverberation through re-entrant circuits within active networks. Reverberation by re-entry can take place at many levels, from the simplest, within small aggregates of prefrontal neurons, to the most complex, within large networks that encompass widely dispersed neurons of prefrontal and posterior association cortices. These are the widely distributed cortical networks that, in the resting state, harbor associative long-term memory and, in the dynamic state, serve working memory. In the latter state, they maintain memory active by re-entry through long corticocortical circuits at the top of the perception-action cycle, thus bridging temporal discontinuities in it. The re-entry in a working memory network usually takes the form of electrocortical oscillations.

In the human, stimulation of the left dorsolateral prefrontal cortex with anodal tDCS increases the accuracy of working-memory performance. Concomitantly, it increases oscillatory activity in theta and alpha bands.

At psychological and neurobiological levels, any decision taken by the organism is a multifactorial outcome. It is the result of the influences of inputs from many origins on to the frontal cortex. Some inputs come from the immediate environment, others from the internal biological milieu and its limbic substrate, and still others from cortical networks containing the memory and knowledge of the individual, from instinctual experience to rules and ethical principle. In the pursuit of a novel goal, in an uncertain or ambiguous situation,

the prefrontal cortex is called to choose among those many competing factors and influences in order to construct the proper goal and the schema of action leading to it. The analysis of risks and benefits from any prospective action will often be based on probabilities updated in Bayesian fashion by memory and current context.

The prefrontal cortex includes areas that are involved in the monitoring of actions and their consequences. The anterior cingulate cortex shows a distinct negative potential in response to errors of performance. In the same cortex, cells can be found that respond to prediction errors and unexpected reward. In a countermanding eye-saccade task, cells in the SEF respond to errors, error correction, and reward. From these medial cortices, excitatory and inhibitory outputs to lower structures mediate the supervisory control of actions in accord with their anticipated consequences.

Inhibitory control is the fifth executive function of the prefrontal cortex. It is the most widely distributed and assists all others, especially attention and working memory. It is indispensable for providing contrast to what is in focus in sensation, in movement or in active memory, as well as for control of distraction, impulsivity, and maladaptive social and emotional behavior.

Two major sectors of the prefrontal cortex take part in inhibitory control, both working top-down. One is dorsolateral (intrinsic inhibitory control). It exerts selective inhibitory control over the entire system of cognitive networks of frontal and posterior association cortex; it is essential for the effective operation of those networks in goal-directed behavior (cognitive control). That is the exclusionary aspect of attention as it applies to all executive functions of attentional set, working memory, decision-making, and monitoring. The other (extrinsic) sector of inhibitory control has its origin in orbitomedial prefrontal cortex. Its major targets are the basal ganglia and limbic formations. Through

these structures, it exerts inhibitory control over abnormal motility, impulsivity, and emotional and instinctive behavior.

However, the separation between intrinsic and extrinsic inhibitory control may be artificial. In its stead, it is more plausible to view the two as forming a unitary system contributing inhibitory control in a hierarchical manner: the orbitofrontal inhibitory control over the lowest, most elementary forms of motor and emotional behavior; and the dorsolateral inhibitory control over the higher, more elaborate, more complex patterns of rule-driven long-term behavior.

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# Neuroimaging

## OUTLINE

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## I. INTRODUCTION

More than a century ago, Roy and Sherrington (1890) postulated that the neural activity of brain structures, the energy they demand, and the blood flow to them are closely and directly related to one another. Although to this day the underlying physiological mechanisms remain obscure, those relationships have been in essence well substantiated. Plausible hypotheses can now be inferred concerning changes in one of those variables from measurable changes in another. This is true even for changes within small regions of the brain.

By the use of non-invasive methods, it is now possible to assess regional cerebral blood flow (rCBF) or metabolism, and in this manner, indirectly, the levels of neuronal activity in the depths of the brain.

Momentous progress resulted from the advent and development of radiographic scanning procedures (Ingvar and Lassen, 1975; Phelps et al., 1982). Following the systemic administration of compounds labeled with radioisotopes ( $^{133}\text{Xe}$ ,  $^{15}\text{O}$ ,  $^{11}\text{C}$ ,  $^{77}\text{Kr}$ ,  $^{18}\text{F}$ , etc.), these methods allow the visualization of blood flow and metabolism in many neural domains simultaneously. Using positron emission tomography

(PET), changes and differences in the concentration of radioactive tracers, and thus in neural activity, can be discerned in the millimeter range. Radioisotopes with a short half-life (e.g.,  $^{15}\text{O}$ , about 2 min) allow several repeated tests of an external variable (e.g., a stimulus) – and repeated measures of neural activation – with minimal radiation risk to the subject.

Continued progress has been achieved by developments in the use of magnetic resonance imaging (MRI), a non-invasive method introduced and used before PET for the study of brain structure. MRI scans the amounts of electromagnetic radiation emitted by brain structures as the nuclear particles of their chemical components are made to resonate in a strong magnetic field (Oldendorf, 1984). For structural imaging, the spatial resolution obtained by MRI is unsurpassed. In recent years, functional magnetic resonance imaging (fMRI) has been developed and applied to the analysis of temporal changes in oxygenation or blood flow (Ogawa et al., 1990; Cohen and Bookheimer, 1994; Kwong, 1995). fMRI, by the blood oxygen level-dependent (BOLD) method, has thus become the preferred method for imaging the course of oxygenation, and by inference neuronal activity, in nervous tissue. With the development of increasingly powerful magnets, the resolution and reliability of fMRI have greatly improved. At the same time, the models and analytical methods to assist it have also improved. For an overview of the basic principles and methods of neuroimaging, the reader is referred to the two volumes edited by Glabus (2005).

In the past few years, since the last edition of this volume, decisive progress has been made in the study of anatomical and functional connectivity in the prefrontal cortex. Diffusion tensor imaging (DTI; see below) is the method of choice for the anatomical study of brain connectivity in health and in neuropathology.

Resting state and functional connectivity have also advanced by the development of correlational methods that use discrete cortical

areas as the “seed” for correlating their oxygenation simultaneously with that of other areas. These methods are proving useful in the study of functional relations between the prefrontal cortex and posterior areas. Near-infrared spectroscopy (NIRS), a derivative of optical imaging, has also emerged as a valuable method, in the clinic and in neuroscience; although its spatial resolution is relatively poor, it has excellent temporal resolution. It is being used with success in neurobehavioral studies of the monkey’s prefrontal cortex.

## II. VALUE AND LIMITATIONS OF IMAGING

A decisive contribution of neuroimaging is the support it provides to the network models of cortical cognition. Its methods reveal active distributed networks in a way no other method has done before. The value of that contribution has increased with the utilization of DTI. DTI was introduced in neuroscience in the mid-1980s (Le Bihan and Breton, 1985; Taylor and Bushell, 1985). It consists essentially in the magnetic scanning of the orientation of water molecules in the structure of the tissue. By adjustment of imaging parameters, especially the latitude of the angle of detected orientation of water molecules, it becomes possible to map neural structures in remarkable detail. Because of their water content and mass, large myelinated pathways, such as corticocortical fascicles and commissures, are most readily portrayed by DTI. In that way, DTI serves as a tool to non-invasively reveal brain tractography. The method can also be used to map functionally active regions of the brain (Le Bihan et al., 2006).

Because connectivity is essential to cortical cognition, DTI is helpful to investigate cognitive networks (cognits) at rest and when they are functionally engaged in the perception–action cycle. Nonetheless, because the method reveals almost selectively myelinated fibers, it is limited

in its ability to reveal the finer, non-myelinated components of those networks. Therefore, it cannot image those presumably fine connections that develop with the acquisition of memory and knowledge.

In broad terms, most of the limitations of cognitive imaging derive from a mismatch between a complex technology that is still over-constrained (Logothetis, 2008) and a behavioral methodology that is underconstrained. The most basic problem of neuroimaging is the insufficient knowledge of the physiological relations between blood flow, neuron discharge, and energy metabolism. For almost two decades, a general model for the statistical analysis of multiple brain scans by linear regression has been widely utilized (Friston et al., 1995). The model and its variants have proven extremely useful, despite the fact that the variables in question, like most biological variables, can be assumed to vary physiologically in a non-linear fashion.

Another basic problem is that of neural inhibition. When active, inhibitory structures and neuron assemblies presumably exhibit increased blood flow and metabolism, like the excitatory ones. Then, the question is: What does a relative decrease in activity represent? A lesser activation? An inhibition from another structure? This is relevant here because prefrontal function has important inhibitory components. The issue will eventually be resolved by the concomitant recording of high temporal-resolution signals in addition to fMRI (e.g., NIRS) and electrical signals (e.g., single-unit recording, magnetoencephalography, electroencephalography, and local field-potential recording).

It has always been a major aim of neuroimaging to achieve the greatest possible resolution, the finest grain in the picture from the brain. With a structural resolution down to 0.5–1 mm in the human brain, MRI has achieved that goal to satisfy the needs of the clinician. That picture is not good enough for the neuroscientist, however, because it is still confounded by a low signal-to-noise ratio and high

variability within and between individuals. Both require special methods, such as statistical normalization and averaging.

The cognitive operations of interest to the neuroscientist in the prefrontal cortex (attention, decision-making, working memory, motor set, etc.) usually take a short time, from a few hundreds of milliseconds to a few seconds, a much shorter time than most imaging techniques take to render a set of successive computerized images. With  $^{15}\text{O}$  and BOLD fMRI we are moving closer to a temporal match, although the problems of low signal-to-noise ratio and high variability remain. Another limitation is the temporal lag and scatter of the activations that are measured as the response to discrete stimuli.

Yet another methodological obstacle encountered in the cortical imaging of cognitive functions stems from faulty assumptions concerning behavioral or cognitive variables and their neural representation. In some studies, a common line of reasoning runs like this: Region *A* is assumed to be critically involved in function *F*, which is assumed to be tested by behavioral paradigm *P*. By analyzing fMRI signals while the subject performs *P*, it is found that the region of interest *A* is the only one activated by *P*. Ergo, *A* is the neural seat, center, or module of *F*, which supposedly confirms the original hypothesis – tautology notwithstanding.

Surely, that is an oversimplification. Many studies run control tasks (where function *F* is presumably not involved), and then utilize the subtraction method on the signals from two tasks, one of them testing *F*, to assess the role of area *A* in *F*. Other studies include parametric manipulations of behavioral variables and relate them to activation levels in area *A* or elsewhere. Still others are conducted on the entire brain, without presuppositions or statistical weights for one hypothesis or another. Even with good design and rigorous analysis, however, the fact remains that a large proportion of imaging studies commit what Poldrack

(2006) calls the “reverse inference” error along the lines noted above. At worst, they come up with the spurious, discrete, and specific location of function *F*. At best, they come up with a “network” of cortical areas or clusters involved in function *F*. In either case, the location of that function, whether discrete or distributed, is often unjustifiably identified.

One trouble with that approach is that, as we have seen in previous chapters, any cortical area can participate in several cognitive functions. Take the “network” of spatial perception, working memory, or language. All three depend on several cooperating networks in posterior and frontal cortex (some of those networks serve all three functions). It is incorrect to infer, from imaging, *the network of spatial perception, of working memory, or of language*. It is correct, however, to infer a representational network *for* spatial perception, another *for* working memory, and yet another *for* language, the three of which may share some common nodes. Thus, what defines the network is not the function or the process, but the content of the representational substrate that is activated for the function or the process. The function and the process are as widely distributed as their representational substrate is. We cannot give much credence to spot-like images of isolated activation presumably identifying the neural substrate of a specific cognitive function or process. One such image may indeed simply mark a maximum of activation (“tip of the iceberg”) in a certain functioning network that is submerged under an arbitrarily high threshold chosen by the investigator as a criterion of reliability or to separate signal from noise.

Cognitive functions are interdependent. Memory depends on attention, perception on memory, working memory on long-term memory, and motor action on motor set and on all the others. What we observe while studying one of those functions may be the result of imponderable changes in another or in several others. This interdependence of functions makes it

often forbiddingly difficult to use the time-honored experimental procedure of holding one variable constant while studying the effects of another, whether that is to define the effect of a brain lesion or the activation of a neural structure. One reasonable approach to this problem, already mentioned above, was developed by Raichle and his colleagues in St. Louis and is now widely utilized; namely, paired image subtraction (Raichle, 1994). It consists of: (1) testing the individual subject on two tasks, the “target” and “reference” conditions, which differ only with regard to the variable or function under scrutiny (maximized in the “target task”); then (2) subtracting the image obtained during the “reference task” from that obtained during the “target task”; and finally (3) averaging the image differences from one or several subjects. The result is the *common relative* activation of brain regions by the relevant function. The measure, however, is still subject to some of the limitations noted above. To minimize them, the judicious choice of tasks (preferably more than two) is essential.

If the views of this book are correct, any task (e.g., a working-memory task) that requires temporally integrated actions (all memory tasks do) will bring into play at least three cognitive functions: memory, set, and inhibitory control. All may be taxed by the target task, and thus in the subtracted frontal image one function may parade for another. In any event, a greater activation in the target task than in any other task does not permit any categorical inference about the target function. To infer absolute functions from relative differences is an error that plagues all fields of cognitive neuroscience. It derives from the Aristotelian tendency to separate cognitive functions from one another and to give them independent homes in the brain. Besides, the error drives the data into the all-pervasive problem of induction: there is always an untested control task or function (the black swan).

This somewhat lengthy exposé of the limitations of neuroimaging should not dissuade

anyone from the use of a method that has already contributed immensely to cognitive neuroscience. The intention here is merely to promote the reliable application of that costly and powerful methodology to study a part of the brain, the prefrontal cortex, that impacts so many other brain structures and occupies such a central position in cognition. The updating of this chapter has been rather arduous because of the profusion of articles on prefrontal imaging in the past 7 years. Some of them are of questionable methodology or difficult to evaluate. For these reasons, the following review is selective and far from exhaustive.

### III. IMAGING PREFRONTAL FUNCTIONS IN COGNITION

Some of the first imaging studies focused on the prefrontal cortex and were conducted using radioisotope inhalation (Obrist et al., 1975; Risberg, 1980). With that method, Scandinavian investigators made the first important observations concerning prefrontal metabolism in cognitive processes. One of those observations was the relatively high rCBF in frontal gray matter when the subject was in wakeful rest, relaxed, and deprived of sensory stimulation. In that condition, activity in frontal, prerolandic, cortex was more than 20% higher than the average for the hemisphere, while in postcentral and temporal cortex it was lower than that average by comparable amounts (Risberg and Ingvar, 1973; Ingvar and Lassen, 1975; Roland and Larsen, 1976; Ingvar, 1978, 1979). The phenomenon was named "hyperfrontality." Ingvar (1979) interpreted it as evidence that, at rest, the posterior cortex was underactive for lack of sensory inputs, whereas the frontal "efferent" (motor) regions were overactive because they engaged in the idling inner synthesis or programming of behavior. An alternative explanation is simply that, in the absence of substantial sensory or motor processing, activity prevails in those

regions of the cortex, such as the frontal region, which are best innervated and therefore subject to the greatest internal input. The mere fact of being awake is bound to involve a plethora of inputs to that region, especially from brainstem and limbic sources, which other cortical regions do not receive. "Hyperfrontality," however, remains a somewhat inconsistent phenomenon, in terms of both incidence and degree, perhaps in part because of the difficulty in controlling the state of "rest."

fMRI studies have substantiated the activation of the frontal cortex at rest that Ingvar observed. Danker and Anderson (2007) show the concomitant activation of lateral prefrontal and posterior parietal cortex in both the retrieval and transformational demands of algebra problem solving. Raichle and others (Gusnard et al., 2001; Fox and Raichle, 2007; Mantini et al., 2007; Buckner et al., 2008) show the synchronous activation of several cortical areas, including medial and lateral prefrontal cortex, during conditions of rest or low cognitive demand. That synchronous activity is oscillatory in the low-frequency range (approximately 0.1Hz), and is negatively correlated (i.e., it has a tendency to diminish or disappear) with heightened attention and cognitive demand. It is assumed that the spontaneous activity reflects the neural activity of that so-called default network. Attention and cognitive operations would entail the departure of subcomponents of that network into higher frequencies not readily detectable by fMRI alone.

With the advent of DTI and advanced fMRI, the functional connectivity of the cortex at rest and in cognitive functions has been explored in depth (Sun et al., 2005; Cheng et al., 2012; Blumenfeld et al., 2014; Martino et al., 2013; Zald et al., 2014). Depending on the method of analysis and the width of the frequency band explored, several networks have been identified in addition to the original "default network." The issue has been thoroughly examined by Cole et al. (2010) in a comprehensive

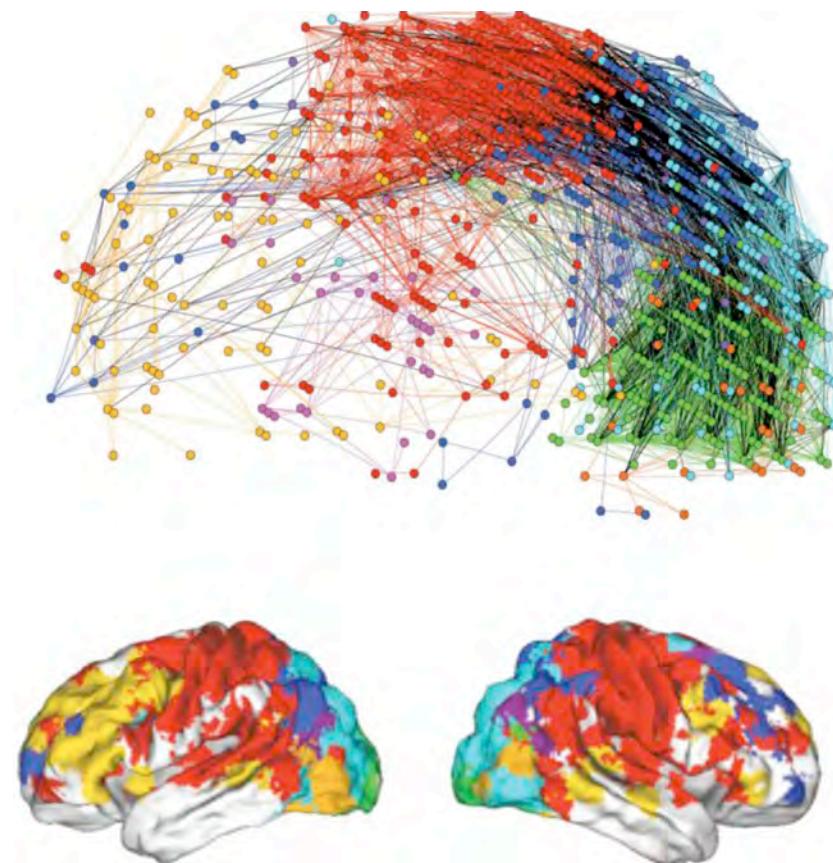
meta-analysis. The most widely used methods are seed-based correlation and independent component analysis, using fMRI alone or in combination with electrical recording. The joint recording and analysis of the two signals complements the study of synchronous electrical oscillations and phase locking discussed in Chapter 6, which was also intended to identify networks at rest through coherence analysis. In various studies, however, the distinction between a network at rest and in the active state is difficult for two reasons: (1) some studies identify “networks” without clearly separating the two conditions (rest and active state); and (2) the probability, defended in this book, is that a cognitive network activated by a given task is basically the same network that already exists in the resting state, albeit more active and finely modulated (see Chapter 8).

Imaging methods in the rest state substantiate certain key properties of the organization of cognitive networks, in obvious agreement with the construct of the functional architecture of those networks. This construct, including the central position of the prefrontal cortex, is presented in Chapter 8. Those key properties are essential to a theoretical system of cortical organization developed on the basis of imaging data by Bullmore and his colleagues ([Bassett et al., 2008; Bullmore and Sporns, 2009; Meunier et al., 2009](#)). The first property is the “small-world” principle, a mathematical derivative of graph theory stipulating that all the elements of a network, though physically distant from one another, are linked by a limited number of steps (nodes), that is, synapses in neural terms. Small-world architecture provides a system with high efficiency and robustness of information transfer and storage. The other property is the hierarchical organization of network architecture, with networks nested within networks, which as a whole constitute a hierarchy of networks of progressively higher abstraction or complexity.

In Bullmore’s hierarchical organization, as to some extent in this author’s ([Fuster, 2009](#)), there

are network “nodes” at the bottom, which form “clusters,” which in turn form “modules”; in sum, a large hierarchical lattice made of nested and renested networks to accommodate progressively more complex and at the same time more global items of information. My model, however, assumes a degree of flexibility and plasticity that Bullmore’s model does not have. Furthermore, as we will see in Chapter 8, my model is embedded in the perception-action cycle, which imparts to it a dynamics that other models lack. [Figure 7.1](#) results from the imaging of functional connectivity in subjects at rest ([Meunier et al., 2009](#)). The figure shows nodes, or small networks (circles) and connections (“edges” between nodes) within corresponding color-coded cortical modules. The relative sparseness of nodes and connections in frontal modules may reflect the fact that the subjects were at rest and more engaged in sensory – especially visual – imagery than motor imagery, apparently differing from [Ingvar’s \(1979\)](#) observation of “hyperfrontality” at rest with radio-isotope inhalation. The increasing dispersion of nodes and connectivity in progressively higher levels of the perceptual hierarchy of cortical areas, as the figure illustrates, is in accord with the hierarchical divergence of perceptual information.

It is on that background of widely distributed and hierarchically organized cognitive networks, minimally active at rest, that the cortex, under the initiative and direction of the prefrontal cortex (see next section), conjures up new plans with their goals and the means to attain them ([Schacter et al., 2012](#)). Insofar as the pursuit of those goals requires new temporal structures of behavior or speech, the temporally integrative functions of the prefrontal functions will be engaged. What follows in this chapter is a review of the contributions of neuroimaging to our understanding of those functions, which in the aggregate constitute what has been called cognitive control. All those cognitive functions operate, “top-down” and prospectively, on the



**FIGURE 7.1** Hierarchical modularity of human networks in the left hemisphere of subjects at rest. *Top:* Representation of connectivity between nodes in color-coded modules. *Bottom:* Surface view of the distribution of modules in both hemispheres. (From Meunier et al., 2009, with permission.)

system of cortical cognitive networks (cognits) that store long-term memory and knowledge.

### A. Planning

The imaging evidence that the prefrontal cortex is activated in the mental planning of motor action has a long history (Ingvar and Philipson, 1977; Roland et al., 1980a; Badre, 2008; Botvinick, 2008; Spreng et al., 2010; Harrison et al., 2011; Gerlach et al., 2011, 2014). In an early study, Morris et al. (1993) tested subjects in the performance of the Tower of London

(see Chapter 5), the puzzle-like test of planning ability designed by Shallice (1982). As the subjects perform the task, the investigators observe the activation of the left dorsolateral prefrontal cortex. That activation is greater in subjects who find the task especially demanding and take more time to perform it. Frontal areas are activated not only in the planning and execution of actions, but also in their semantic evocation. This is epitomized by a curious observation in an early study by Martin et al. (1996). Whereas the viewing of pictures representing animals elicited the activation of posterior cortical areas,

the viewing of tools (“action objects”) activated premotor cortex. In another study (Partiot et al., 1995), subjects were required to imagine and plan behavior in two sets of circumstances: one with strong emotional overtones and the other without them. The two mental operations activated different cortical domains. Whereas the emotional planning activated medial prefrontal and anterior temporal cortex, the non-emotional planning activated dorsolateral and polar prefrontal cortex in addition to posterior temporal cortex. The results seemed to support the involvement of dorsolateral areas in the cognitive and medial areas in the affective aspects of planning.

With the use of the BOLD fMRI method, the assessments of prefrontal activity in mental or task-related planning have become more precise. Almost uniformly, those assessments implicate the dorsolateral prefrontal areas in planning (Okuda et al., 2003; Addis et al., 2007; Badre, 2008; Botvinick, 2008; Harrison et al., 2011; Wunderlich et al., 2012). This is not surprising considering the deleterious effects of extensive frontal dorsolateral lesions on the capacity to form and carry out plans of action (see Chapter 6). Among the most remarkable in that respect are the studies from Schacter and his research colleagues at Harvard University. The bulk of this work was reviewed by Schacter et al. (2012).

One important finding of the Harvard group was that the same cortical area was activated by remembering a past memory as it was by imagining the same memory in the context of a future plan (Spreng et al., 2010). This finding is in good accord with the concept of cognit, a network of long-term memory activated and updated for short-term use in working memory or in future planning (see Chapter 8). Another finding of the same group, while scrutinizing the functional coupling between areas, was that the act of planning activates three major cortical “networks” of areas (Figure 7.2): a default network, a frontoparietal network, and a dorsal

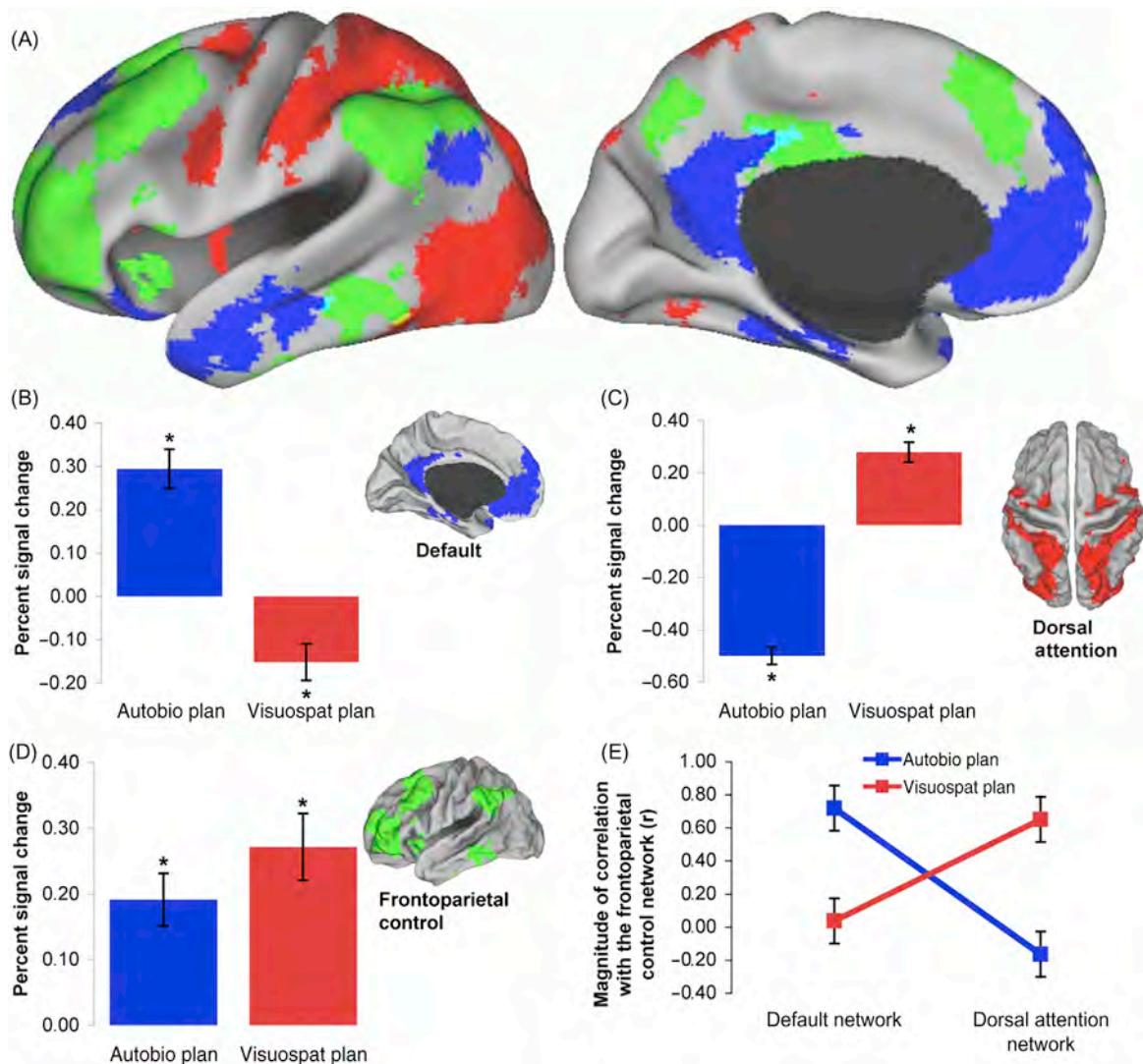
attention network, corresponding to those described by other authors in various behavioral settings and paradigms (Raichle et al., 2001; Hellyer et al., 2014; Sadaghiani and D’Esposito, 2014). Finally, the Harvard researchers (Gerlach et al., 2014) found that thinking about the pleasant outcome of a future plan activated limbic and ventromedial prefrontal areas closely related by neuropsychological studies to the experience of reward (see Chapters 4 and 5).

## B. Attentional Set

Attentional set is the preparedness of the organism for expected sensory information or action in the course of goal-directed behavior or speech. In either case, attentional set is exerted top-down by prefrontal cortex upon lower cortices, sensory or motor, as well as upon peripheral structures of sensory or motor systems. The anatomy of prefrontal fiber paths involved in the attentional prefrontal priming of sensory and motor systems was discussed in Chapter 2.

### Sensory-Perceptual Set

With the subject at rest and out of behavioral context, sensory stimulation induces complex patterns of activation over the surface of the neocortex. With unimodal stimulation (visual, auditory, or somatosensory) such a pattern usually shows focal activations in the primary sensory area for the modality of the stimulus and, additionally, in neighboring association areas. Another common finding already present in the early imaging literature is the concomitant activation of a frontal region that invariably includes or is restricted to a part of the prefrontal cortex (Roland and Larsen, 1976; Roland, 1981, 1984a; Roland and Skinhøj, 1981; Roland et al., 1981; Nishizawa et al., 1982; Risberg and Prohovnik, 1983). Listening to simple verbal stimuli (e.g., onomatopoeic words) may induce activation of prefrontal besides temporal auditory areas (Nishizawa et al., 1982); these activations are greater in the left than the right hemisphere,



**FIGURE 7.2** Functional connectivity in the course of autobiographical (Autobio) and visuospatial (Visuospat) planning. Default (blue), dorsal attention (red), and frontoparietal control (green) networks. (A–D) During either autobiographical or visuospatial planning, blood oxygen level-dependent (BOLD) signal changes in every connectivity “network” (\* shows significant difference from baseline). (E) During autobiographical planning, the frontoparietal control network is coupled with the default network and decoupled from the dorsal attention network. The reverse occurs during visuospatial planning. (From Schacter et al., 2012, with permission.)

whereas the opposite is true for non-verbal sounds (Roland et al., 1981). In general, the superior prefrontal area, roughly coinciding with the superior frontal gyrus and comprising major

portions of Brodmann’s areas 8 and 9 (Brodmann, 1909), is the prefrontal area most consistently activated by sensory stimuli of the three modalities: visual, auditory, and somatosensory.

In good agreement with neuroanatomical data (see Chapter 2), [Zatorre et al. \(1992\)](#) identified, by PET, the primary olfactory area in orbitofrontal cortex; the area on the right was more activated by olfactory stimulation than that on the left. Also, in anterior orbitofrontal cortex, the putative primary sensory area for taste was activated by gustatory stimuli ([Small et al., 1997](#); [De Araujo et al., 2003](#); [Kringelbach et al., 2003](#)).

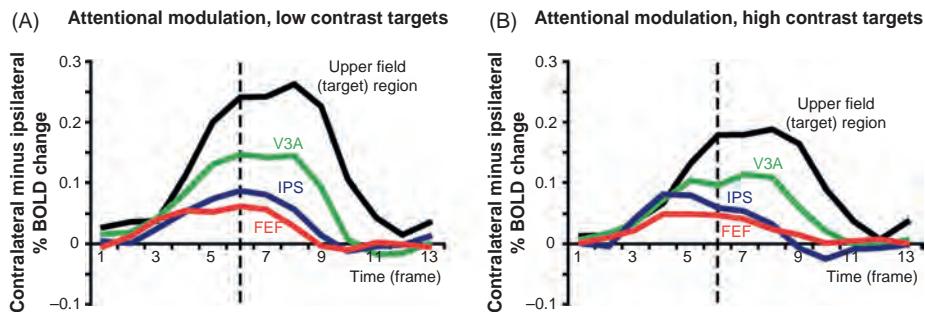
It will be remembered from Chapter 2 that, in the brain of the primate, each of three primary sensory cortices is the origin of a major pathway that courses through a series of cortical areas, projects to frontal cortex, and ends in prefrontal cortex. Those pathways probably terminate in the foci of sensory activation identified by imaging in the prefrontal cortex. The location and configuration of those prefrontal foci, which in some cases may be more extensive than the primary sensory areas of origin ([Ingvar, 1978](#); [Nishizawa et al., 1982](#)), depend on the modality of the stimulus and, more importantly, the formalities of its presentation. These formalities also appear to determine the degree of frontal activation induced by a sensory stimulus. Two aspects of the experimental situation are critical in this respect: the attention that the subject pays to the stimulus and the need to utilize the information it contains for behavioral action; in other words, the degree to which the stimulus elicits attentional motor set.

Already with the older rCBF detection and PET methods, and now with BOLD fMRI, it has become apparent that the greater the attention the subject pays to a sensory stimulus, the greater the activation of the prefrontal area activated by it. This can be observed by instructing the subject (1) to expect or merely imagine the stimulus in a certain sector of sensorium (e.g., a tactile stimulus on the tip of the index finger) ([Roland, 1981](#)); (2) to attend to or ignore the stimulus ([Risberg and Prohovnik, 1983](#)); (3) to discriminate the stimulus from another ([Roland and Larsen, 1976](#); [Roland, 1981](#); [Roland and Skinhøj, 1981](#); [Roland et al., 1981](#)); or (4) to

shift attention from one stimulus modality to another ([Roland, 1982](#)). The focusing of attention and the shifts of attention are generally accompanied by the activation of varying sectors of the polar, superior, and posterior aspects of the dorsolateral prefrontal convexity, including the frontal eye fields if the stimulation is visual. Right-left differences in activation are also observed; they appear to be mainly but not exclusively dependent on the verbal (left > right) versus non-verbal (right > left) nature of the stimulus attended to.

It is now clear that any task of stimulus discrimination, or of memory encoding or retrieval, that requires *focused attention* activates areas of lateral and medial prefrontal cortex besides posterior cortical areas of perceptual specialization ([Kosslyn, 1988](#); [Posner et al., 1988](#); [Pardo et al., 1991](#); [Dupont et al., 1993](#); [Grady et al., 1994](#); [Kapur et al., 1994](#); [Raichle, 1994](#); [Tulving et al., 1994a, 1994b](#); [Buckner et al., 1995](#); [Egner and Hirsch, 2005](#); [Weerda et al., 2006](#)). If the stimuli and/or the responses are verbal, left prefrontal cortex is prominently activated. The greater the attention demand in the task, the greater the activation. An excellent meta-analysis by [Wager et al. \(2004\)](#) substantiates the universality of these findings. Their article makes two important points: (1) prefrontal activations in attention are attributable to the executive functions of the prefrontal cortex, which include executive attention; and (2) the same cortical areas that in task execution are activated in perceptual attention are activated also in executive attention and, most notably, in working memory, which the author and others ([Curtis and D'Esposito, 2003](#)) treat as internalized executive attention.

In imaging studies subsequent to the previous edition of this book, neural manifestations of attentional sensory set have been recorded in the form of BOLD activation before an anticipated visual stimulus. Such activations ([Figure 7.3](#)) have been observed in a portion of the prefrontal cortex (frontal eye field), as well as in the visual cortex, when subjects anticipate



**FIGURE 7.3** Anticipatory activations of prefrontal and visual areas before the onset (dashed vertical line) of a visual target of low (A) and high (B) contrast. On the ordinate, percent blood oxygen level-dependent (BOLD) change difference between contralateral and ipsilateral field stimulation. Abbreviations: FEF, frontal eye field; IPS, intraparietal sulcus; V3A, visual area 3A. Upper visual field responses are shown for comparison. (From [Sylvester et al., 2009](#), with permission.)

a visual stimulus ([Sylvester et al., 2009](#)). The anticipation of musical sequences also activates a portion of the rostral prefrontal cortex ([Leaver et al., 2009](#)). The expectation of predicted sensory stimuli improves their working memory, as well as their retention in long-term memory ([Bollinger et al., 2010](#)).

### Executive Set and Motor Control

The counterpart to the sensory-perceptual set is the executive set, in other words, the preparedness for prospective action. Some of the earliest imaging studies of the involvement of prefrontal cortex in executive set were performed in the context of tasks that required anticipatory preparation for ocular or manual movement. Thus, prefrontal activations in attentional set for eye movements led to the concept of an “anterior attentional system” ([Posner and Petersen, 1990](#)). A part of that system, and one of the most consistently activated prefrontal regions in concentrated motor attention, is the anterior cingulate gyrus ([Posner et al., 1988; Raichle, 1994](#)).

The cingulate cortex, for example, is heavily activated in performance of the Stroop task ([Pardo et al., 1990](#)). In this task (see Chapter 5), the subject has to name – within time constraints – the color of a printed word for a

different color (e.g., the word “GREEN” printed in red). Activations of the anterior cingulate cortex and supplementary motor area (SMA) were also observed by [Taylor et al. \(1994\)](#) in another stimulus–response compatibility – or conflict – task. Furthermore, the anterior cingulate cortex, along with the left dorsolateral prefrontal cortex, is activated in a semantic retrieval task ([Petersen et al., 1989, 1990; Raichle et al., 1994](#)), where on every trial the subject is presented with a noun and must produce a related verb (e.g., “BIRD” – “FLY”). The areas of the presumed frontal executive-attention system are also activated by performance of the Wisconsin Card Sorting Test (WCST), the Tower of London, and Porteus mazes ([Rezai et al., 1993](#)). The ventrolateral prefrontal cortex and the SMA have also been seen selectively activated in preparation for rule-dependent action in a Stroop task ([Donohue et al., 2008](#)).

Because most of those tasks require effort to perform and the degree of activation appears to be correlated with that effort, [Posner et al. \(1988\)](#) and [Pardo et al. \(1990\)](#) concluded that the frontal attention system is made of cortical areas devoted to the “attention for action”; in other words, motor set. This concept is strengthened by the discovery that cingulate activation exhibits a different fine topography

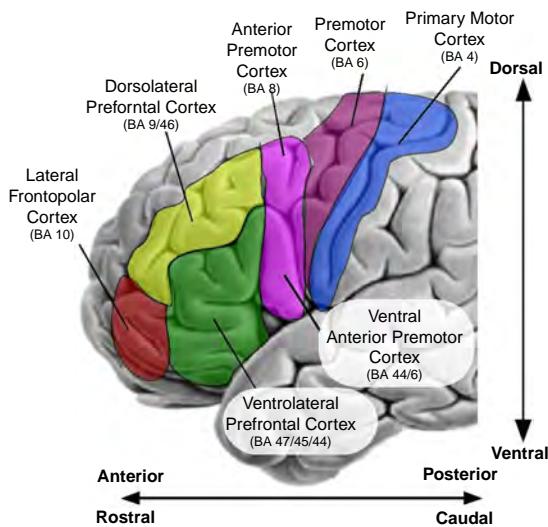
(somatotopy) depending on the nature of the required response in the task: oculomotor, manual, or vocal (Paus et al., 1993).

When the experimental subject performs repetitively a voluntary movement of a certain complexity (e.g., the alternating opposition of fingers), the primary motor cortex shows an activation and, concomitantly, the SMA, in the medial frontal lobe, usually does as well (Orgogozo and Larsen, 1979; Roland et al., 1980a, 1980b, 1980c; Roland, 1984b, 1985; Petit et al., 1996). If the movement is in or of an extremity, the cortical activation is only contralateral; otherwise (e.g., movements of tongue or lips), the activation is bilateral. The SMA activation is bilateral in all cases, except in the spoken language, where it is lateralized to the left. Other premotor areas may also show activation, especially if the movement is performed under sensory guidance (Roland and Larsen, 1976; Roland, 1981, 1982, 1984a). If the movement is repetitive but very simple, the activation may be circumscribed to primary motor cortex, accompanied by only minor increases in premotor cortex (Roland, 1985). However, if the movement is complex and requires the serial organization of skilled motor acts, then, besides the primary motor and premotor areas, prefrontal areas are activated, especially the superior prefrontal area (Roland et al., 1980a, 1980b, 1980c; Roland, 1984b, 1985; Iacoboni et al., 1996). The left dorsolateral prefrontal cortex is activated in right-hand writing (Horovitz et al., 2013). Only one prefrontal area, the frontal eye field of area 8, is activated in motility of conjugate eye movements (Melamed and Larsen, 1979; Müri et al., 1996). Other frontal areas, however, are also activated in the execution of sequential eye movements (Petit et al., 1996).

From the fine analysis of the imaging results thus far described in this section, there appears to be a frontal caudorostral pyramiding of activation with increasing complexity of serial movement, starting with primary motor cortex at the base and progressively involving

premotor and prefrontal areas. Automatic and simple movement (eye movement excepted) lights up only motor cortex. When the movement becomes complex and, above all, when it requires programming and temporal integration by rules, premotor and prefrontal areas are brought into play. At least one thorough imaging study (Cieslik et al., 2015), however, indicates a differential involvement within the dorsolateral prefrontal cortex. Whereas the anterior portion of that cortex is mainly involved in the preparation for movement (set), the posterior portion is mainly involved in its execution.

In any case, the pyramiding of activation, which reflects the progressive involvement of higher stages of the motor hierarchy, also reflects, in reverse, the down-flow (cascading) of neural processing toward action that we discussed in Chapter 6 and will further discuss later in this section (Figure 7.4). In other words, the hierarchical caudorostral representation of



**FIGURE 7.4** Rostrocaudal hierarchy of cortical areas harboring progressively more concrete action representations (cognits), from plans and rules in rostropolar prefrontal cortex to discrete muscular movements in motor cortex. Abbreviation: BA, Brodmann's area. (From Badre, 2008, with permission.)

actions reflects inversely the descending rostrocaudal involvement of frontal cortices in the processing of global actions toward their component movements. Accordingly, prefrontal activation is particularly strong, in fact greater than premotor activation, during mental exercises that require the tracking and integration of what, in the subject's mind, are temporally separate items of information. This is the case, for example, when the subject is asked to perform arithmetic operations internally, or to mentally skip every second word of a jingle, or to imagine successive ambulation through different places (Roland, 1985; Roland and Friberg, 1985; Kondo et al., 2004; De Pisapia et al., 2007; Danker and Anderson, 2007). When willed sequential acts are not only imagined but also carried out, then the prefrontal cortex, most prominently its lateral aspects, becomes activated, and thus is functionally involved in the execution of the acts as well as in their preparation (Seitz et al., 1990; Frith et al., 1991a).

Some studies have implicated the frontal cortex in the learning of complex sequences; in other words, in the acquisition of executive memory (Grafton et al., 1991, 1992; Jenkins et al., 1994). Jenkins et al. (1994) tested human subjects in the performance of motor sequences (key presses with auditory feedback). The subjects were scanned in three conditions: sequence learning, sequence overlearned, and rest. The prefrontal cortex was activated only during the learning of *new* sequences. Premotor cortex, including SMA, was also activated in the performance of overlearned sequences. The cerebellum and putamen were activated in the execution of all sequences. Raichle et al. (1994) observe left dorsolateral prefrontal activation in the learning of a verbal skill (verb generation; see below). All frontal motor action areas – motor, premotor, and prefrontal – have been found to be progressively activated as a function of practice, at least in the early stages of motor learning (Iacoboni et al., 1996). Dorsolateral and anterior cingulate activations

have been observed in the performance of tasks requiring the assessment of temporal order in series of events (Partiot et al., 1996). However, no appreciable prefrontal activation may be observed in the performance of mental operations that are routine or do not require substantial temporal integration (De Jong et al., 1996). Other imaging studies confirm that the prefrontal cortex is activated only in the learning and performance of complex behaviors, especially if they are new and require the mediation of cross-temporal contingencies (Koch et al., 2006; Fuhrmann et al., 2007; Sun et al., 2007); those contingencies may apply to behavior as well as reasoning (Kroger et al., 2002; Christoff et al., 2003). Once a complex task has become automatic, prefrontal activation during its performance diminishes (Poldrack et al., 2005).

When subjects are asked repeatedly to generate verbs associated with given nouns, substantial left prefrontal activations appear (Petersen et al., 1989, 1990; Frith et al., 1991b; Raichle et al., 1994; Fiez et al., 1996a). Just as importantly, as noted earlier, strong activations appear in the anterior cingulate region. As has also been mentioned, this activation probably has to do with executive attentional set. It is therefore possible that priming influences emerge from that anterior cingulate region that flow, perhaps somatotopically (Paus et al., 1993), upon the sectors of the motor apparatus to be mobilized in the short term.

An alternative or complementary possibility is that the influences from the anterior cingulate cortex are inhibitory, because certain parts of this cortex, especially area 24, have been identified as a source of motor inhibition. If this interpretation is correct, we can ascribe the anterior cingulate region to the sector of orbitomedial prefrontal cortex that has been postulated to be involved in the inhibitory control, or suppression, of distraction and interference. Poldrack and his colleagues (Aron et al., 2004; Aron and Poldrack, 2005) provide more direct evidence of that exclusionary component of

executive attention. Using a “stop-signal” task, they demonstrate descending inhibitory influences originating in the right inferior prefrontal cortex (IPC) and terminating in the subthalamus. Presumably, these influences exert the function of interference control, the complementary function of focused attention. It is also possible that frontal inhibitory influences of the same origin – inferior prefrontal – suppress interfering emotional memories by acting upon limbic structures (amygdala and hippocampus). This is the conclusion from another imaging study that includes the examination of those structures (Depue et al., 2007). A more recent study (Rodrigo et al., 2014) indicates that the inhibitory function attributed to the right IPC is shared by other prefrontal regions as well, including the homologous cortex of the left hemisphere.

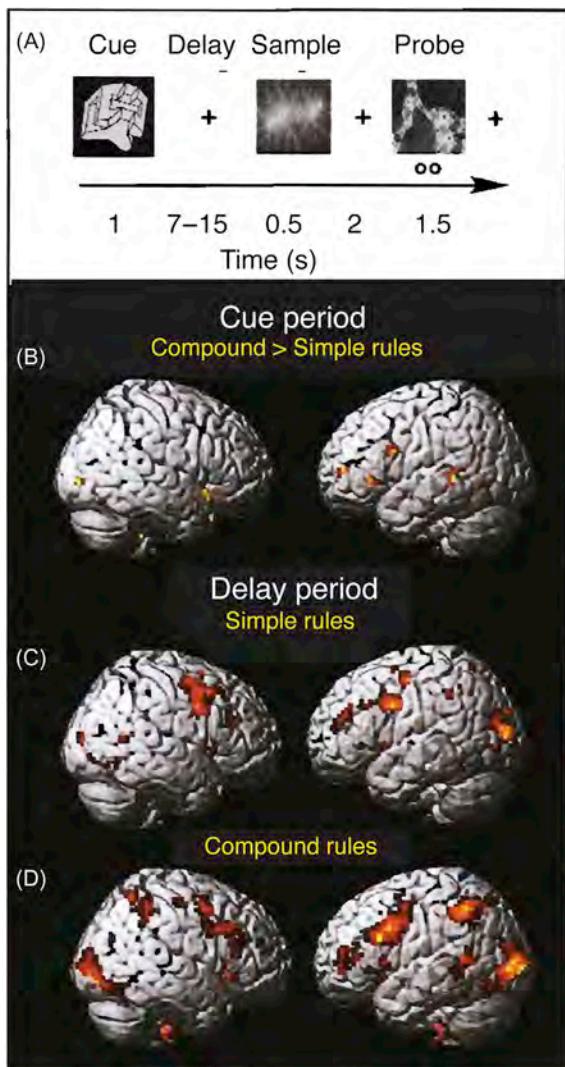
Rules are prescribed – or learned – strategies to carry out certain actions to their goal. A rule is represented in the nervous system, probably in the frontal lobe, in the form of a more or less abstract executive network, like a plan or a schema of action. Like these, the rule contains a conglomerate of associations and contingencies that dictate how the organism is to interact adaptively with its environment. Experimentally, in animals as in humans, rules may be encoded by sensory cues that symbolically instruct the individual on which rule to follow and, thus, how to respond to subsequent stimuli to reach the goal. Different rules are symbolized by different cues. In Chapter 6, we have seen the effects of rules on monkeys’ behavior and their single-cell correlates in the prefrontal cortex. Here, we deal with rules in the human and with their manifestations in functional imaging.

In anticipation of their implementation, different or competitive rules have been seen to activate different areas of lateral prefrontal cortex, as well as pre-SMA in the medial prefrontal cortex, especially on the left (Bunge et al., 2003; Bunge, 2004; Sakai and Passingham, 2006;

Haynes et al., 2007). It has been hypothesized (Crone et al., 2006) that rule switching is under the control of the medial cortex, whereas the actual implementation of a rule engages lateral prefrontal cortex with modality-specific posterior cortical areas, as in working memory (see below). In general, simple rules engage a few discrete cortical areas, whereas complex rules engage more, larger, and widely dispersed areas (Figure 7.5).

Now let us deal more specifically with the implementation and control of the action with two fundamental Jacksonian principles in mind that have been mentioned repeatedly in this book: (1) motor action is hierarchically organized in frontal cortex; and (2) the same neural substrate serves the coordination and its representation. A large body of evidence from neuroanatomy (see Chapter 2), neuropsychology (see Chapters 4 and 5), and neurophysiology (see Chapter 6), now corroborated by imaging and summarized in Chapter 8, indicates that the cognitive representations of actions are hierarchically organized by level of complexity and abstraction in the cortex of the lateral convexity of the frontal lobe. Networks representing the most concrete aspects of movement are situated in primary motor cortex. Above them, in premotor cortex, are the networks representing more complex actions, in the form of simple motor programs and trajectories (skeletal and ocular, even linguistic). Above, in prefrontal cortex, are the presumably wider networks representing conceptual or abstract and integrative forms of action, including schemas, plans, and rules. Probably, these higher forms of planned action are themselves hierarchically organized in the rostral prefrontal cortex.

In the execution of new and complex actions, it may be postulated (Fuster, 2003; and Chapter 8) that the highest hierarchical levels are ordinarily mobilized first in the prefrontal cortex; they consist of the schema, plan, or gestalt of the action and its goal at an abstract level. Then, still in prefrontal cortex or below,

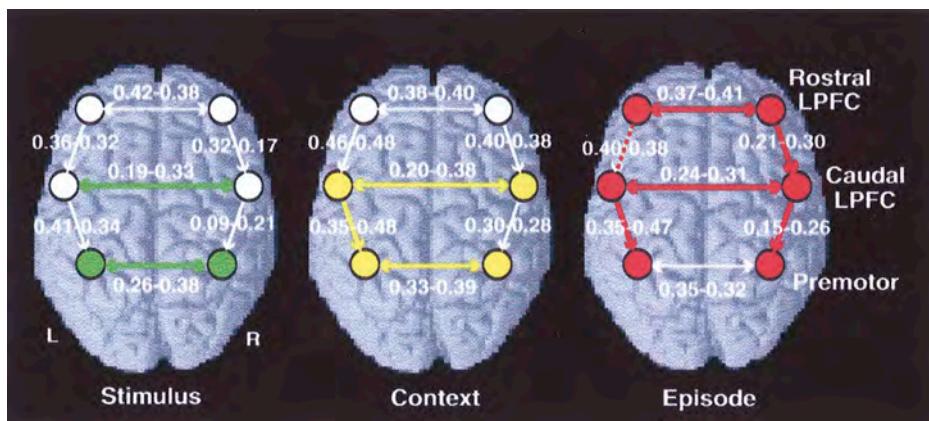


**FIGURE 7.5** (A) Trial structure in the implementation of an abstract rule. The subject sees a cue – a nonsense shape or word – associated with a specific rule to follow. The cue is followed by a long period of delay, during which the subject is supposed to keep the rule in mind. Then a sample stimulus is presented, followed by the probe, which may or may not match the sample. Depending of the rule (match or non-match), the subject presses one button or another. (B) Left hemisphere areas modulated by complex rule at the cue presentation period. (C) Activation by simple rule during the delay period. (D) Activation by complex rule during the delay period. (From Bunge, 2004, with permission.)

in premotor cortex, the intermediate levels are mobilized which represent subschemas of more concrete action. Finally, in motor cortex, the more concrete representations of action are mobilized to execute, through the pyramidal system, specific actions in a particular sequence.

Modern neuroimaging supports this postulated cascade of executive processing down the anterior-posterior frontal executive hierarchy (O'Reilly et al., 2002; Koechlin et al., 2003; Badre and D'Esposito, 2007; Koechlin and Summerfield, 2007). Especially revealing are studies (e.g., Koechlin et al., 2003; Badre and D'Esposito, 2007) with behavioral paradigms that make the motor response to a sensory stimulus contingent on progressively more distant associations of the stimulus or of the response; that is, distant spatially or temporally, or both.

The fMRI study by Koechlin and co-workers (2003) elegantly corroborates the hierarchical organization of frontal executive cortices proposed long ago by Hughlings Jackson (see Chapters 6 and 8 for further discussion). In their study, to follow the rules of the task, the subject must respond differently to three series of visual stimuli. In one series, the responses to the stimulus depend on a simple feature (color); in the second series, they depend, additionally, on the presence of an accompanying feature (pattern) that provides the “context” to the color; and in the third series, they depend on a recent instructional visual cue – a prior contingency, which the authors label an “episode.” Therefore, from the first to the third tasks, the motor response to a given stimulus is determined by information of increasing complexity and associative load. In the third task, the subject must also integrate information across time, including the prior “episode.” It is reasonable to infer that the executive representation or network is relatively simple in the first task, more complex in the second, and even more so in the third. The first task activates premotor cortex, the second activates, in addition, posterior prefrontal cortex, and the third, in addition, anterior prefrontal



**FIGURE 7.6** Diagram of effective connectivity deduced from the activation of frontal areas during the performance of the three tasks described in the text. Circles mark the approximate locations of activation in the regions indicated at the right of the figure. Frontal activations and path coefficients that significantly increase with the first task (stimulus alone), the second task (stimulus and context), and the third task (which includes prior contingency) are shown in green, yellow, and red, respectively. Abbreviations: L, left; R, right; LPFC, lateral prefrontal cortex. (Adapted from Koechlin et al., 2003, with permission.)

cortex (Figure 7.6). Moreover, in the third task, the *path coefficients* of activation reveal a processing cascade that originates in prefrontal cortex and courses through premotor to motor cortex. That processing cascade takes place not only serially but also in parallel (Charron and Koechlin, 2010). Note that the third task activates first the anterior prefrontal cortex, which not only harbors the most complex executive cognits but also plays a crucial role, presumably acting upon lower executive levels, in the temporal integration of behavior (see Chapter 8), a function that the third task requires the most.

The hierarchical cascading view of motor activation, it should be re-emphasized, implies not only serial processing in hierarchically organized structures, but also parallel processing. Indeed, it is a common misconception that hierarchical processing anywhere in the nervous system, or a model thereof, can be only serial. There is ample evidence, even from the imaging field (e.g., Bookheimer et al., 1995; Charron and Koechlin, 2010), indicating profuse parallel processing in the execution of action, whether or

not that processing takes place within a hierarchical organization of cortical structures.

Finally, we should not lose sight of the fact that the execution of any series of goal-directed actions, in the realms of behavior, speech, or reasoning, takes place in the dynamic framework of the perception-action cycle. Complex and novel actions within a complex and novel plan engage the highest levels of the cycle that run through anterior prefrontal cortex, which represents abstract and complex action. Automatic or overlearned sequences of action, however complex, engage shunts of the cycle through posterior prefrontal, premotor, and motor cortices. Feedback from action to perception, and through it to further action, is an essential feature of that framework at all levels. Feedback from lower stages must inform the higher stages of the executive hierarchy about the success or failure of an ongoing sequence.

Action monitoring, specifically the monitoring of the success or failure of action, is indispensable for proper processing at all stages of the perception-action cycle. Imaging has

proven valuable here, for it provides evidence of the activation of certain prefrontal structures, notably the anterior cingulate and orbitofrontal cortices, in that kind of monitoring (Walton et al., 2004; Schnider et al., 2005). This is important because these structures are part of the emotional perception-action cycle, which runs parallel to and interacts with the cognitive cycle that runs mainly through areas of the cortical convexity (see Chapter 8).

### C. Working Memory

Arguably, working memory is the most intensely explored cognitive function by imaging methods. The rationale for this research was undoubtedly spearheaded by the single-unit data from primates in delay tasks. The neuroimaging of working memory has been decisive in affirming the network concept of cortical cognition first advanced with microelectrodes.

Risberg and Ingvar (1973) were the first to make working memory – by another name – the direct subject of rCBF study. In their task, the subject was required to remember and recite – backward – lists of spoken digits. During performance, they observed increased rCBF in temporal auditory areas and, in addition, in a vast frontal region that included most of the dorsolateral prefrontal cortex, where the increase was the greatest. It is important to note, however, that the tests of sensory stimulation and discrimination used in many of the early studies on related subjects required active short-term memory, now commonly called working memory. Although working memory may not have been the primary subject of study, the tasks used in those studies often imposed a delay between sensory stimulation and verbal or manual response. That delay made them tests of working memory. The delay may have consisted of the time elapsed from the instructions of the experimenter to the subject's response, or may have been simply determined by the physical impossibility to compare two

stimuli simultaneously. Anyway, the tasks contained a temporal discontinuity that required the mediation of cross-temporal contingencies. Therefore, unintentionally, many investigators may have been challenging working memory, and their findings bear on working attention as much as they bear on working memory. Accordingly, some of the sensory activations observed in early studies were to some extent due to the working-memory aspects of the test situation. This may explain, at least in part, the simultaneous activation of sensory and lateral prefrontal areas in somesthetic (Roland and Larsen, 1976; Roland, 1982), visual (Roland and Skinhoj, 1981; Roland, 1982), and auditory (Mazziotta et al., 1982; Roland et al., 1981; Roland, 1982) stimulation tests.

In more recent years, many imaging studies have specifically targeted working memory. The majority have been conducted with the cognitive-subtraction framework, using control tasks almost identical to the target (memory) tasks but without the memory requirement. Because of the evidence obtained by lesions in the monkey, intense efforts have been directed toward imaging prefrontal activation in subjects engaged in performance of memory tasks with spatial cues. PET studies (Jonides et al., 1993; Petrides et al., 1993a, 1993b; Goldberg et al., 1996; Sweeney et al., 1996) evince the activation of dorsolateral prefrontal cortex, mainly on the right, during spatial working memory with visuospatial cues. All the studies show, in addition, a degree of concomitant activation of premotor and parietal areas. A number of fMRI studies also show the activation of the dorsolateral prefrontal cortex region by spatial working memory (McCarthy et al., 1994; Cabeza and Nyberg, 2000; Wager and Smith, 2003; Walter et al., 2003; Ranganath et al., 2004; Manoach et al., 2004; Curtis et al., 2005; Suchan et al., 2005; Curtis, 2006; Ricciardi et al., 2006).

Berman et al. (1995), using PET, show dorsolateral prefrontal activation during the performance of the WCST, which they attribute

to activation of visual working memory. More formal tests (i.e., delay tasks) of visual working memory have ensued. The present author and his colleagues (Swartz et al., 1995) investigated, with PET and a 2-fluorodeoxyglucose (FDG) radioisotope, the glucose utilization in cortical regions during performance of a visual non-spatial working-memory task: delayed matching-to-sample with visual cues (abstract pictures). The objective was to substantiate, in the human, single-unit evidence that dorsolateral prefrontal cortex is critical for working memory of not only spatial but also *non-spatial* information (see Chapter 6). Subjects performed two tasks: the memory task (delayed matching-to-sample) and a no-memory task (immediate matching-to-sample). On each trial of the memory task, the subject had to memorize for 8 s an abstract display for subsequent match. In the control task, memorization was not necessary, for the match was immediate. The results show that the memory task activated bilaterally parts of prefrontal areas 9, 10, and 46. It also activated premotor and motor areas, as well as visual areas of the temporal and occipital lobes.

Cohen et al. (1994), using fMRI, had previously shown the activation of prefrontal areas (middle and inferior frontal gyri, especially on the left) in subjects performing a non-spatial visual working-memory task (recognition of a pattern in letter sequences). A special case of visual working memory is that of working memory for faces, where dorsolateral prefrontal areas have been seen in some studies to be activated together with the cortex of the fusiform gyrus, an area involved in face recognition (Mecklinger et al., 2000; Postle et al., 2003; Gazzaley et al., 2004, 2007; Ranganath et al., 2004; Rama and Courtney, 2005).

The lateral prefrontal cortex, especially on the left, is activated also in verbal working memory (Paulesu et al., 1993; Petrides et al., 1993b; Andreasen et al., 1995; Fiez et al., 1996b; Smith et al., 1996; Cabeza and Nyberg, 2000; Wager and Smith, 2003; Crottaz-Herbette et al., 2004;

Bedwell et al., 2005; Buchsbaum et al., 2005; Goldstein et al., 2005; Narayanan et al., 2005). Upon observing the simultaneous activation of the supramarginal gyrus (Brodmann's area 40) and Broca's area, Paulesu and collaborators (1993) claimed to have identified the neural basis of the phonological loop, an essential component of working memory, according to Baddeley (1992). Bilingual subjects have been noted to show the same prefrontal area activated during working memory of two languages, Chinese and English (Xue et al., 2004). In addition, the left lateral prefrontal cortex is activated in the working memory involved in mental arithmetic (Kondo et al., 2004; De Pisapia et al., 2007).

One seemingly universal finding of those who have explored the matter is that, regardless of the nature of the material in working memory, the degree of prefrontal activation is directly related to the memory load (Postle et al., 2001; Druzgal and D'Esposito, 2003; Jaeggi et al., 2003; Linden et al., 2003; Cairo et al., 2004; D'Arcy et al., 2004; Leung et al., 2004; Habeck et al., 2005; Kirschen et al., 2005; Narayanan et al., 2005; Zarahn et al., 2005). In other words, prefrontal activation increases as a function of the number or complexity of the items that the subject must retain in working memory. That relationship may or may not be linear, but in any case it reaches a maximum or asymptote, beyond which memory load makes no difference. Load-related activation, however, may be affected by practice.

There are few solid facts from neuroimaging concerning the localization of specific working-memory content in lateral prefrontal cortex. The only seemingly solid evidence is that the left lateral prefrontal cortex is *more* involved in verbal working memory than the right; conversely, the right lateral prefrontal cortex is *more* involved in spatial working memory than the left. Imaging attempts to dissociate different kinds of working memory within lateral prefrontal cortex have had only limited success and their results are certainly not uniform across studies (Smith

et al., 1995; Owen et al., 1996; Courtney et al., 1996). The spatial versus non-spatial dissociation that unit studies suggest in the monkey (Fuster et al., 1982; Wilson et al., 1993) has not been unambiguously demonstrated by imaging in the human. In one attempt to do this, Courtney et al. (1996) used two target tasks, one with working memory for faces and the other for spatial location, against a sensorimotor control task. Whereas they observed clear dissociation between face and location in posterior cortex, they were only able to detect a tenuous frontal dissociation – statistically, but not evident in the printed images.

Several reasons may lie behind the difficulty in finding clear-cut specialization of prefrontal areas in different types of working memory. Two stand out in accord with our thinking: (1) working-memory content is widely distributed in prefrontal networks, not discrete “modules”; this is consistent with the network view of cortical cognition to be expanded in Chapter 8; and (2) the individual variability of executive-network distribution is so great as to confound any attempt to localize any memory content within any discrete portion of lateral frontal cortex; again this is not only consistent with, but also a direct consequence of, the associative idiosyncrasy of executive networks, as these networks may encode problem-solving strategies that vary from one individual to another.

One earlier study, by D'Esposito et al. (1995), supports both reasons and interpretations. They conducted fMRI on subjects performing two working-memory tasks, one with semantic and the other with visual material. The results showed that: (1) both tasks activated roughly the same region of dorsolateral prefrontal cortex; and (2) there was considerable individual variability of the prefrontal region activated. The same investigator, D'Esposito, has contributed decisively to the discovery that areal differences in the activation of frontal cortex reside in the *dynamics* of working memory, more specifically, in the temporal

transition – and integration – from perception to action, at the top of the perception–action cycle. This is discussed below.

Repeatedly, this book has emphasized the role of the prefrontal cortex in attention, perceptual as well as executive attention. In the previous section we mentioned some imaging signals related to perceptual attention. In the coming section we will deal with signals related to executive attention or set. Now, with working memory, we are dealing with attention directed to internal representations. There are two ways in which that form of attention impacts on the process of working memory and its manifestations in cortical imaging: (1) the selective access to, or encoding into, prefrontal working memory; and (2) the attentive or “cognitive” control of prefrontal cortex over areas of posterior cortex involved in working memory. The latest methods of BOLD fMRI, event-related fMRI among them, allow us to approach both issues.

What does neuroimaging have to say about which prefrontal areas act as the attentive gate to working memory? Here, in the first place, to judge from a series of functional imaging studies, it appears that the lateral prefrontal cortex, with its innumerable cortical (from posterior cortex) and subcortical inputs, plays a crucial role (Li et al., 2004; Kondo et al., 2004; Sakai and Passingham, 2004; Buchsbaum et al., 2005; Curtis et al., 2005; Postle, 2005; Roth et al., 2006; Yoon et al., 2006). Also playing a crucial role in attentive gating is undoubtedly the medial prefrontal and the anterior cingulate cortex, the latter a pivotal component of the “anterior attention system,” either by itself or with lateral cortex (Posner et al., 1988; Posner and Petersen, 1990; Petit et al., 1998; Raichle, 1994; Osaka et al., 2003; Kondo et al., 2004; Lenartowicz and McIntosh, 2005).

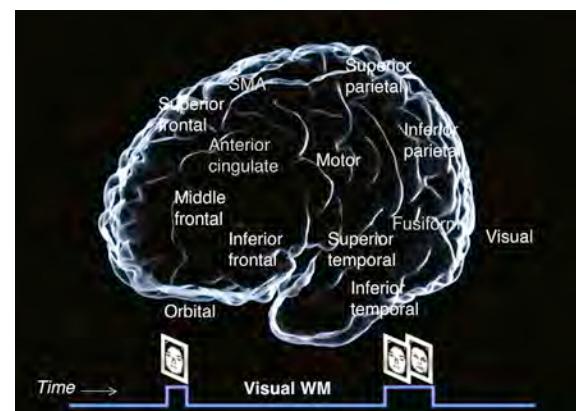
The other question is: Which cortical areas, in addition to prefrontal cortex, participate in the maintenance of working memory? The question is important because it bears directly on the structural substrate and mechanisms of

that maintenance. We have already noted, in passing, that relationships have been observed between working-memory content and the particular area of posterior cortex that is activated in addition to prefrontal cortex. Some interpret those relationships as evidence that the attentive control of working memory, that is, the selection of material within it, may indeed be exerted top-down by prefrontal cortex, but the actual maintenance of working memory takes place in areas of posterior cortex specialized in the sensory characteristics of that material in temporary storage (see reviews by [Curtis and D'Esposito, 2003](#); [Wager and Smith, 2003](#)).

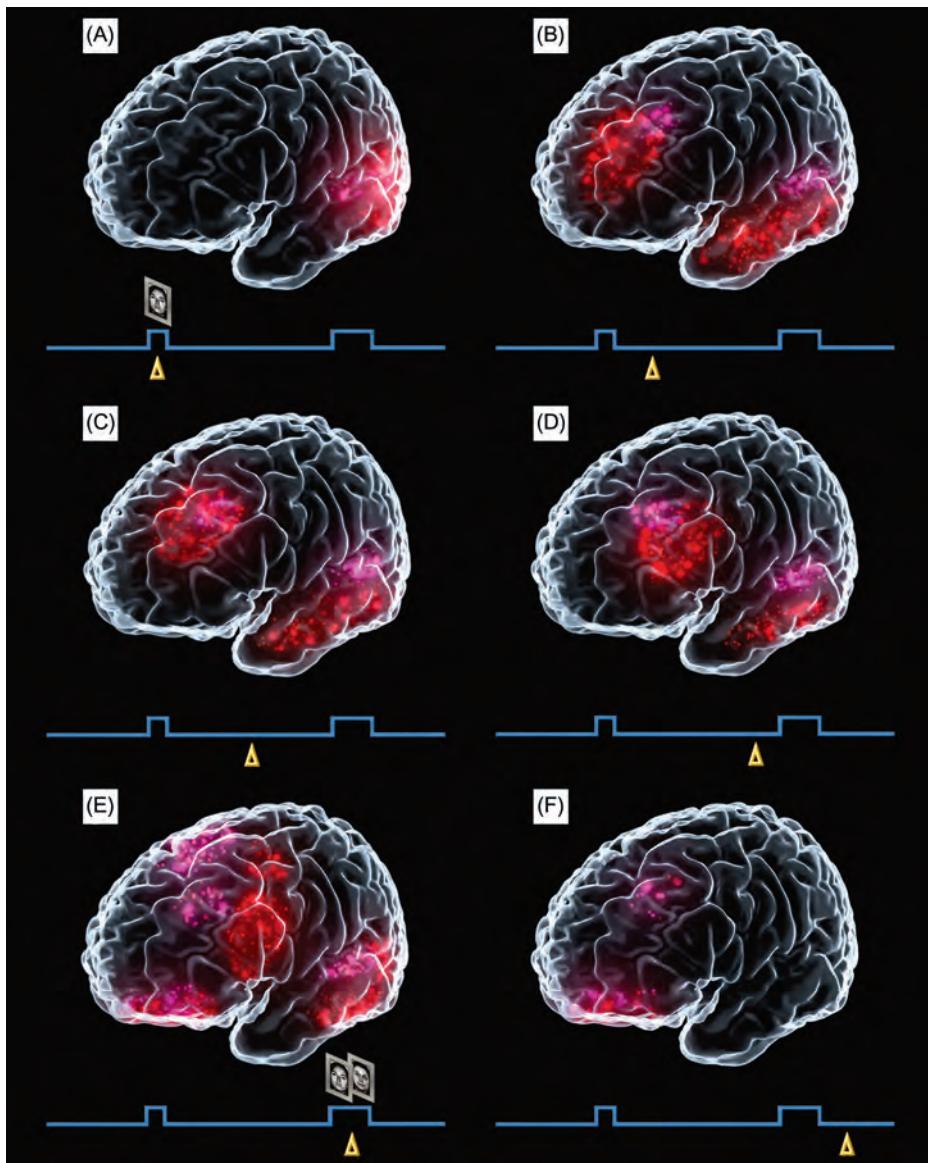
In the light of the theoretical approach to be further elaborated in Chapter 8, these relationships may be interpreted somewhat differently. This argument departs from the tenet that both anterior and posterior areas harbor extensive interconnected networks that represent perceptual and executive long-term memories, including all the associated sensory and motor elements of a working-memory task. In the performance of the task, all the subnetworks representing those elements are activated in an orderly manner – the executive ones first in prefrontal cortex – by perceptual attention to cues, rules, or instructions. During the delay, the memory period of the task, the relevant task components in *long-term memory* stay activated in frontal and posterior areas, respectively, to maintain working memory (that is one reason why working memory has also been called “active memory”). Memory maintenance is then assured by reverberating re-entry between frontal executive and perceptual networks. In that way, temporal integration takes place in working memory at the top of the perception-action cycle. Now, because the executive formalities of working-memory tasks differ little from each other in tests of different sensory modalities, we should expect more constancy of activation in prefrontal (executive) cortex across sensory memoranda, and conversely, less constancy in posterior areas, which should more

faithfully reflect the modality of the memorandum. This is what the bulk of imaging studies of working memory show. Some of those studies even suggest the dynamic kinship, if not the structural identity proposed here, between working memory and long-term memory ([Lee et al., 2000](#); [Rypma and D'Esposito, 2003](#); [Mitchell et al., 2004](#); [Ranganath et al., 2004](#)).

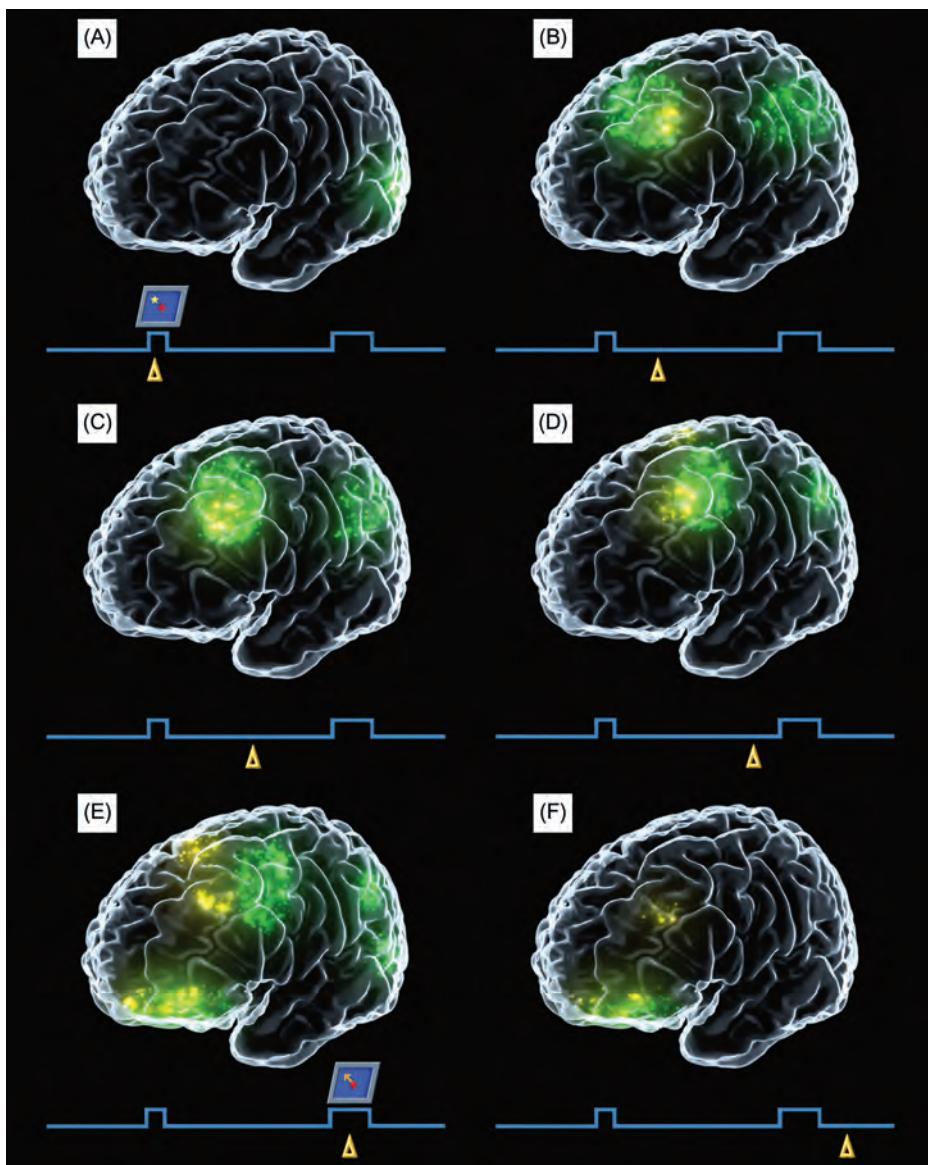
[Figures 7.7–7.10](#) illustrate the dynamics of working memory and, in the light of lesion and microelectrode data (see Chapters 4–6), suggest the structural identity of working and long-term memory. The figures are stills from motion pictures made with the assistance of Allen Ardestani and personnel of the University of California, Los Angeles, Laboratory of Neuro Imaging: Arthur Toga (director), Amanda Hammond, and Kim Haber. [Figure 7.7](#) displays the location of various cortical areas on the three-dimensional imaging maps of subsequent



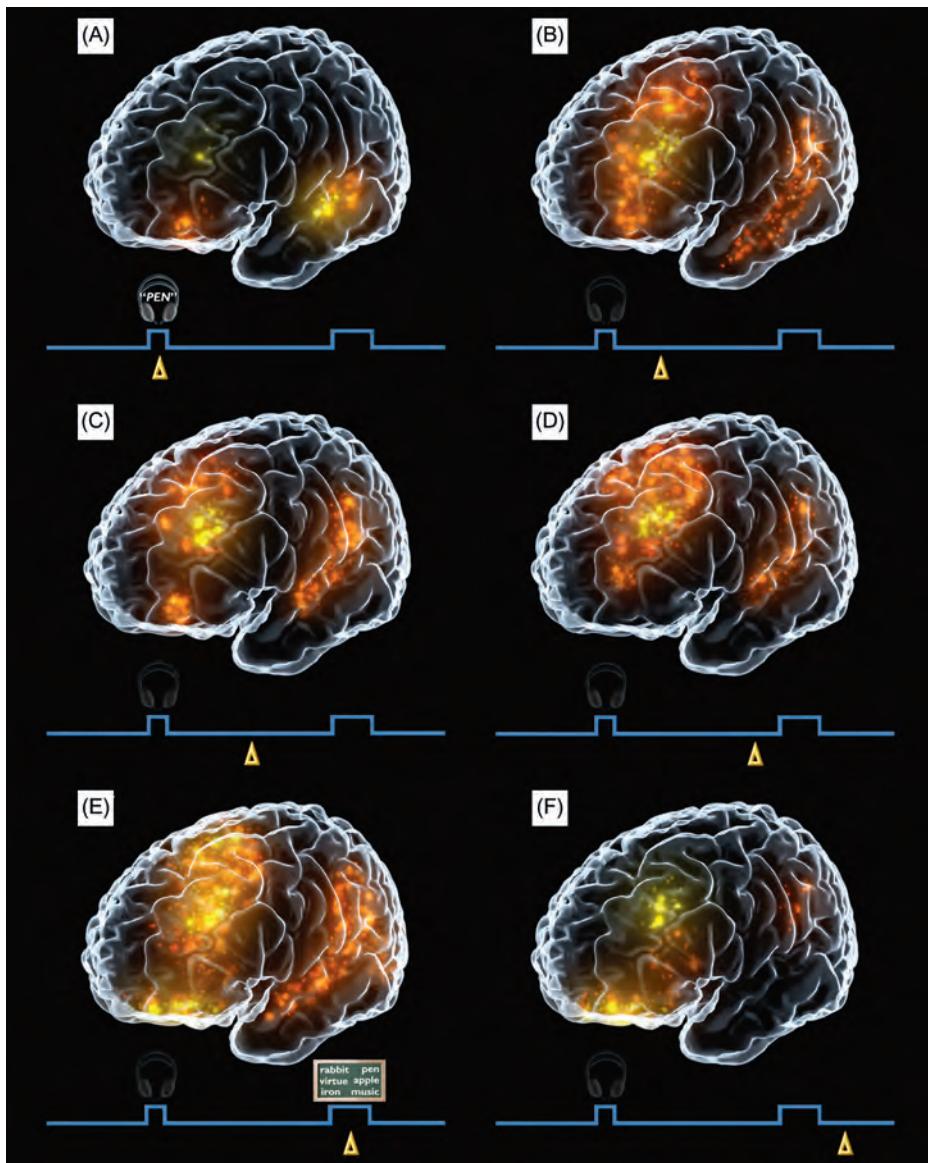
**FIGURE 7.7** Outline of left cortex used in subsequent figures ([Figures 7.8–7.10](#)) to mark areas activated in working memory. Areas in convexity cortex are designated with white labels; those in mesial cortex with gray labels. Abbreviation: SMA, supplementary motor area. *Below:* Temporal display of a trial in a typical visual working-memory (WM) task, delayed matching-to-sample, with faces. The first upward inflection of the timeline marks the time of presentation of the sample face; the second inflection that of the choice faces. The delay (memory) period, between sample and choice, lasts 20s.



**FIGURE 7.8** Relative (above-baseline) cortical activation at six moments in time (marked by yellow triangle) in the course of the visual memory task in Figure 7.7. Activations of convexity cortex in red, of medial cortex in pink. (A) At the sample, the activation is restricted to visual and posterior inferotemporal cortex; (B) in early delay, it extends to lateral prefrontal cortex, anterior cingulate, anterior inferotemporal cortex, and fusiform cortex; (C) in mid-delay, it persists in prefrontal, inferotemporal, and fusiform cortex; (D) in late delay, it migrates to premotor areas, persisting in inferotemporal and fusiform cortex; (E) at the response (choice of sample-matching face), it covers visual, inferotemporal, and fusiform cortex in the back, and extends to motor areas (including frontal eye fields), supplementary motor area, and orbitofrontal cortex in the front; (F) after the trial, activation lingers in anterior cingulate and orbitofrontal cortices.



**FIGURE 7.9** Cortical activation at six moments in time (yellow triangle) in the course of a spatial memory task: the memorandum, in (A) is a star at a certain position on the screen – eye fixation on center, red cross. Activations of convexity cortex in green, of medial cortex in yellow. (A) At the cue-memorandum, the activation is restricted to visual cortex; (B) in early delay, it extends to lateral prefrontal, anterior cingulate, and posterior parietal cortex; (C) in mid-delay, it persists in prefrontal and posterior parietal cortex; (D) in late delay, it migrates to premotor areas (including supplementary motor area) and frontal eye fields, persisting in posterior parietal cortex; (E) at the response (eye saccade to position of the cue), it covers visual and inferior parietal cortex in the back, and extends to frontal eye fields, supplementary motor area, and orbitofrontal cortex in the front; (F) after the trial, activation lingers in anterior cingulate and orbitofrontal cortices.



**FIGURE 7.10** Cortical activation at six moments in time (yellow triangle) in the course of a verbal memory task: the memorandum, in (A) is a word through earphones. Activations of convexity cortex in orange, of medial or sulcal cortex in yellow. (A) At the cue-memorandum, the activation is restricted to auditory cortex, superior temporal gyrus, and inferior frontal cortex; (B) in early delay, it extends to lateral prefrontal, anterior cingulate, and superior-temporal and parietal association cortex; (C) in mid-delay, it persists in prefrontal and temporoparietal cortex; (D) in late delay, it persists in prefrontal and migrates to premotor areas, while persisting in temporoparietal cortex; (E) at the response (signaling whether the cue word is on the screen), it covers visual and temporoparietal cortex in the back, and extends to frontal eye fields, supplementary motor area, inferior frontal, and orbitofrontal cortex in the front; (F) after the trial, activation lingers in anterior cingulate and orbitofrontal cortices, and language areas.

figures. Figures 7.8–7.10, of visual (faces), spatial, and auditory (verbal) working memory, respectively, result from graphically pooling the imaging data from the following publications (those preceded by an asterisk are based on meta-analysis of other studies): Courtney et al. (1997), Petit et al. (1998), D'Esposito et al. (2000), Pollmann and Von Cramon (2000), \*Duncan and Owen (2000), \*Cabeza and Nyberg (2000), Mecklinger et al. (2000), \*Wager and Smith (2003), Crottaz-Herbette et al. (2004), Buchsbaum et al. (2005), Goldstein et al. (2005), and \*Rajah and D'Esposito (2005).

Essentially, the figures depict in color the areas that are commonly activated, or the groupings of adjacent clusters of activation, in the above publications. Where the imaging data from those publications are insufficient to infer the cortical dynamics of working memory, we have availed ourselves of single-unit data from the non-human primate performing analogous working-memory tasks, albeit with differing timescales. Also helpful to infer the frontal dynamics of working memory have been the human data from Koechlin et al. (2003) and Badre and D'Esposito (2007) discussed in the previous section (Executive Set and Motor Control); these data support the dynamics of the frontal executive hierarchy while, in the course of working memory, perception leads to executive set and subsequent action (Chapter 8).

The figures homogenize the sizeable variance of a great many studies; furthermore, many of those studies do not provide any assessments of the time-course of activations in working memory. Similar such assessments, obtained from single-unit data in monkeys performing similar but not identical tasks, may fall considerably short of approximating the dynamics of working memory in the human cortex. In other words, extrapolation, interpolation, and inter-species differences may deprive us of a precise spatial and temporal picture of the cortical dynamics of working memory in the human brain. Nonetheless, because of the remarkable

uniformities across studies, which is particularly evident on meta-analysis, the author believes that the picture obtained is good enough to provide at least three conservative conclusions of normative character:

1. Working memory activates simultaneously a region of prefrontal cortex and a region of posterior association cortex. The evidence that this is the case is consistent with the notion that the reverberating re-entry between the two regions lies at the foundation of the maintenance of working memory. That may, indeed, be the key mechanism of working memory (see Chapters 6 and 8).
2. The region of posterior cortex activated in working memory depends on the sensory character of the memorandum in working memory. That region coincides with the region that neuropsychological evidence implicates in the learning, discrimination, and long-term memory of material of that particular modality. This evidence, together with the imaging data, supports the notion that working memory consists in the *ad hoc* sustained activation by prefrontal cortex of a posterior associative network of long-term memory that represents the memorandum (Chapter 8).
3. During working memory, as a cross-temporal contingency is mediated and its members (sensory and motor) are integrated, frontal activation has a tendency to migrate from prefrontal cortex to motor cortices. This migration of activation may reflect not only the continued maintenance of working memory but also the preparatory set for the consequent action. Indeed, it may reflect the preprocessing of action down the frontal executive hierarchy, within the perception-action cycle: from the anterior frontal, more abstract, representations of the action to the posterior frontal, more concrete, representations of that action (see next section and Chapter 8).

Since the previous edition of this book, several authoritative reviews have appeared that confirm and expand the empirical evidence presented in this chapter concerning the neuroimaging of working memory (Soto et al., 2008; Rawley and Constantinidis 2009; Ikai and Curtis, 2011; Courtney, 2012; Gazzaley and Nobre, 2012). Despite some evidence of *content* heterogeneity (Cieslik et al., 2015) (e.g., between right and left hemispheres, between areas), there is universal agreement that the dorsolateral prefrontal cortex is substantially activated in the working-memory maintenance of information of any modality. That activation is invariably accompanied by the concomitant activation of one or several areas in parietal or temporo-occipital cortex, depending on the nature of the material in working memory. Furthermore, recent reviews mention the commonality of the same anatomical substrate of networks (cognits) for several cognitive functions, notably attention and working memory. Both would modulate top-down activity in subcortical and posterior cortical regions.

In a review, Sreenivasan et al. (2014) come to conclusions very similar to ours. As I proposed long ago (e.g., Fuster, 1995), and those authors essentially corroborate, working memory is a widely distributed activation of cognitive networks (cognits), in posterior cortex as well as frontal cortex. As stated in Chapter 6 and further developed in Chapter 8, a memorandum in working memory is essentially maintained by re-entrant coupling between both cortical regions. Posterior networks (cognits) are precisely tuned to the sensory qualities of memoranda, while prefrontal networks are tuned to their executive qualities. Together, those qualities are encoded in the dynamics of large-scale neuronal populations cooperating in the perception-action cycle.

## D. Decision-Making

Whether in the context of a behavioral task or in daily life, the decision to act one way or another is always a multifactorial phenomenon,

the result of the interplay of assorted neural and humoral influences upon the prefrontal cortex, especially if those influences are unexpected or complex and call for unprecedented action. Note that under no circumstances, however, will the prefrontal cortex or any of its parts make the decision by itself. Rather, that cortex will enable the decision in cooperation with the rest of the brain within the framework of the perception-action cycle. Note also that none of the decision-determining influences or their consequences need be conscious.

Two major categories of inputs converge on the prefrontal cortex to bias or determine the action to be decided by the brain in the perception-action cycle. One is the composite of influences from the cortex itself, posterior and frontal, which contain the perceptual and executive cognitive networks named cognits. These cortical influences presumably include ethical imperatives. The role of cortical influences on decision-making has been exposed, at least in part (see above), by imaging the cortical activation that precedes and accompanies decided choices in working-memory tasks.

The other composite of brain influences comes from the biological drives and motivation, often conflicting with one another, which have their origin in the limbic brain and can be lumped together under the rubric of emotional input, as they are commonly driven by emotion and accompanied by emotional expression. The orbitomedial cortex has been identified as the prime source or transmitter of biological influences to the lateral prefrontal cortex. Some of these influences come from the lower centers in the diencephalon. They carry information from the sphere of biological states and drives. Various tasks have been used to identify and measure these influences on decision-making and behavior, such as the Iowa Gambling Task (see Chapter 5) and other tasks that measure the weight that the individual places on the benefits and risks of his or her prospective actions. Other tasks measure the emotional

weight of context ("frame") or the role of uncertainty; still others the so-called valence (value) of external stimuli.

Earlier neuroimaging during performance of some of these tasks revealed, in some cases only sketchily, that the orbitomedial prefrontal cortex is subject to internal or environmental influences related to: (1) risk or reward (Rogers et al., 1999; Elliott et al., 2000; O'Doherty et al., 2001; Montague and Berns, 2002; Clark et al., 2003; Gottfried et al., 2003; Fukui et al., 2005; Blair et al., 2006; Daw et al., 2006); (2) context (De Martino et al., 2006; Windmann et al., 2006); (3) uncertainty (Critchley et al., 2002; Hsu et al., 2005; Schnider et al., 2005); and (4) pleasure or pain (Blood et al., 1999; Anderson et al., 2003; De Araujo et al., 2003; Kringelbach et al., 2003; Rolls et al., 2003). Through orbitomedial cortex, influences related to these factors appear to reach the lateral prefrontal cortex and thus lead to, or bias, decisions. Conversely, inhibitory influences from lateral cortex flow down upon orbitomedial cortex and exert control over emotional behavior, even countermanding some of the decisions originating there (Bari and Robbins, 2013). Some of these influences, in the human, may come from the ethical sectors of cognition, as mentioned above.

More recent functional neuroimaging shows that the gratification after a successful decision feeds into ventromedial prefrontal cortex and probably, in addition, posterior cingulate cortex, ventral striatum, nucleus accumbens, and insula (Hardin et al., 2009; Eryilmaz et al., 2014). Similar findings have been obtained using the Iowa Gambling Task. Appetitive choices on a food menu lead to activation of ventrolateral cortex and the anterior cingulate region, in addition to the taste area (Piech et al., 2010). Risk, anxiety, disappointment, and regret activate the anterior insula (Mohr et al., 2010). The anterior cingulate is activated when a fear prime is interposed in a cross-temporal contingency between behavioral events (Luo et al., 2014). Medial prefrontal cortex is activated by personal dislike

of another human being (Izuma and Adolphs, 2013). The fusiform gyrus, the amygdala, and the ventrolateral prefrontal cortex are activated by the detection of aversive features in the perception of emotional facial expressions (Bajaj et al., 2013).

Generally related to those studies, and specifically to so-called *neuroeconomics*, an important field of neuroimaging has developed greatly since the last edition of this book. Neuroeconomics is the study of the neural mechanisms of evaluation of risks and benefits (rewards). Imaging research in this field substantiates the manner in which different biological values and secondary values, such as money, influence the activity of prefrontal areas, thereby influencing decisional choices. Seminal in this respect is the work of Koechlin and his colleagues (Koechlin et al., 2003). Their studies, and those of other investigators on the subject of neuroeconomics, led to the following two categories of inferences:

1. There is a hierarchy of basal and medial structures of the brain, including the insula, the ventral striatum, the amygdala, the cingulate cortex, and the orbitomedial cortex, that are activated by pleasant or aversive events and stimuli. This conglomerate of structures encodes these events and stimuli for their reward value (valence), positive or negative, thereby influencing decisions integrated by the cortex at large, especially the dorsolateral prefrontal cortex (Summerfield et al., 2006; Hardin et al., 2009; Kouneiher et al., 2009; Charron and Koechlin, 2010; McGuire and Botvinick, 2010; Mohr et al., 2010; Prévost et al., 2010; Smith et al., 2010; Fitzgerald et al., 2012; Eryilmaz et al., 2014). Even within a broad category of rewards, there seems to be a hierarchical organization in basal prefrontal cortex. For instance, one study (Sescousse et al., 2010) shows that the viewing of erotic pictures activates specifically a more posterior – phylogenetically older – paralimbic prefrontal

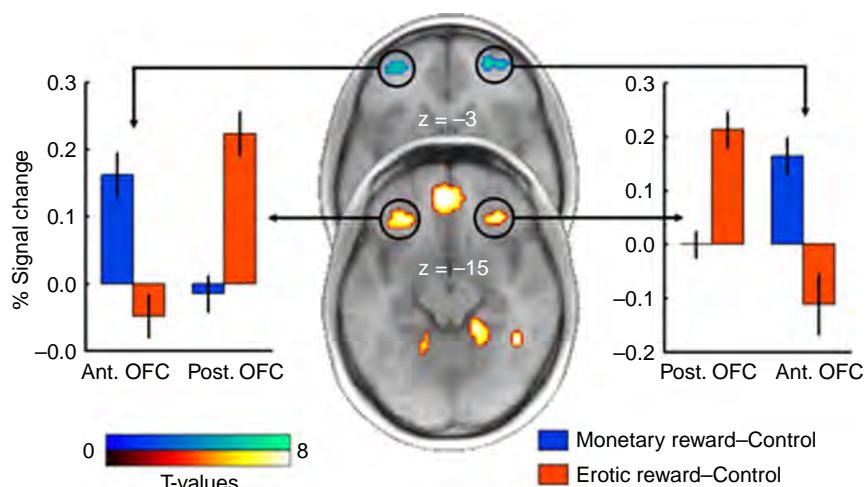
area than monetary gain, a derivative/cultural reward, which activates specifically a more anterolateral – phylogenetically newer – orbitofrontal area (Figure 7.11).

2. That conglomerate of ventromedial reward-related structures, as we will see in Chapter 8, constitutes a large part of the infrastructure for the emotional perception-action cycle, which runs parallel to, and interacts with, the cognitive perception-action cycle of the neocortex. The two cycles interact in the anterior cingulate cortex, which feeds collateral connections into the frontal cortex of the convexity. As Morecraft et al. (2012) state, based on modern neuroanatomy, “the cingulate areas form a pivotal limbic–motor interface that could provide critical sources of cognitive, emotional and motivational influence on complex motor function.” A decided course of complex, goal-directed motor action would commence in the rostromotor prefrontal cortex, at the top of the executive

hierarchy, and cascade down toward motor cortex, as Koechlin and others (Koechlin and Hyafil, 2007; Badre et al., 2009; Azuar et al., 2014) have postulated from functional imaging data. Using ultra-high-field fMRI at 7T, Bode et al. (2011) demonstrated the initiation of a decided action sequence in rostromotor prefrontal cortex at a preconscious level, that is, *before* conscious awareness of it. Surely not coincidental is the evidence presented in a previous section that the rostromotor prefrontal cortex is important for the imagination and formation of future plans. The organization of a sequence of goal-directed actions will then proceed through posterior prefrontal cortex, premotor cortex, motor cortex, and the pyramidal system.

### E. Monitoring and Preventing Error

Functional neuroimaging is making substantial contributions to our understanding of the



**FIGURE 7.11** Posteroanterior dissociation in the orbitofrontal cortex depending on reward type. Areas responding to monetary reward are displayed in blue–green and those responding to erotic reward in red–yellow. Plots of mean percent signal change, not independent from whole-brain signal, are shown only to illustrate the double dissociation between monetary/erotic rewards and anterior (Ant.)/posterior (Post.) orbitofrontal cortex (OFC). Activations are overlaid on an average anatomical scan of all subjects. Error bars indicate SEM. (From Sescousse et al., 2010, with permission.)

role of the prefrontal cortex in the detection and avoidance of errors. It has also spearheaded vigorous debate about the involvement of certain prefrontal areas closely related to the limbic system in the predictive attribution of value to the expected outcome of one's own actions. Especially vigorous has been the theoretical and empirical discussion of the neurobiological aspects of failed expected outcome; in other words, of what has been called *prediction error*.

Successful choices in any kind of behavioral task elicit the activation of medial and basal (orbital) areas of the prefrontal cortex. This is epitomized by the post-trial activation of those areas in practically all tests of working memory, as reviewed earlier in this chapter (see Figures 7.8–7.10). The phenomenon simply confirms the involvement of those areas in rewarding experience, as discussed in previous chapters. The temporal correlation between reward and neural activation, however, does not establish a causal relationship between the two, nor does it clarify the physiological or behavioral consequences of reward gratification.

More in tune with any attempt to clarify those consequences are the results of imaging experiments using behavioral paradigms that allow the parametric treatment of value and the analysis of neural signals related to *predicted* success or failure. By such experiments, predicted risk, displeasure, and decreased value have been related to activation of the anterior insula (Magno et al., 2006; Hardin et al., 2009; Mohr et al., 2010; Prévost et al., 2010), a transitional area between orbital prefrontal cortex and limbic cortex assumed to process aversive emotions such as anxiety, disappointment, and regret.

The ventrolateral prefrontal cortex is activated in the *avoidance* of conflict or uncertainty (Piech et al., 2010; Badre et al., 2012), whereas the orbitomedial prefrontal cortex is activated by expected or unexpected reward or pleasure (Ramnani et al., 2004; Hardin et al., 2009; Mitchell et al., 2011; Smith et al., 2010; Hampshire et al., 2012; Sescousse et al., 2013).

Most consistently, the activation of the medial – anterior cingulate – prefrontal cortex appears to be an outcome predictor, whether that outcome is good or bad, and also a detector of probable conflict (Knutson and Cooper, 2005; Brown and Braver, 2007; Brown, 2009; Magno et al., 2009; Potts et al., 2011; Alexander and Brown, 2011; Bode et al., 2011; Forster and Brown, 2011; Nee et al., 2011; Kim et al., 2012). By inference, several authors attribute to the anterior cingulate cortex a role in the cognitive control of prospective action; in other words, the transition from uncertainty, fear, or failure to effective preventive action.

That transition from prediction to action, however, can only be understood as the result of integration of affective information with motor behavior, and of emotion with cognition. This is the conclusion that Shackman et al. (2011) reach in their landmark review of the cingulate cortices after meticulously questioning the validity of reported functional specializations within them. The anterior cingulate cortex is exceptionally suited to perform that integration because, on the one hand, it receives abundant input from practically the entirety of the limbic brain while, on the other, it sends output to the motor, premotor, and prefrontal cortices (Morecraft et al., 2013).

Indeed, as we will conclude in Chapter 8, the limbic and “paralimbic” regions of the prefrontal cortex are at the crossroads of the two parallel perception-action cycles that relate the organism to its environment: the cognitive cycle that courses through the sensory receptors and associative areas of the neocortex, converging on executive cortex, and the emotional cycle that collects information from the internal, visceral, and emotional receptors, and also, through the cingulate, reaches the executive cortex. At the intersection of the two, prospective values and errors would be integrated with appropriate action to increase the likelihood of reward and to minimize prediction errors to attain it.

## F. Language

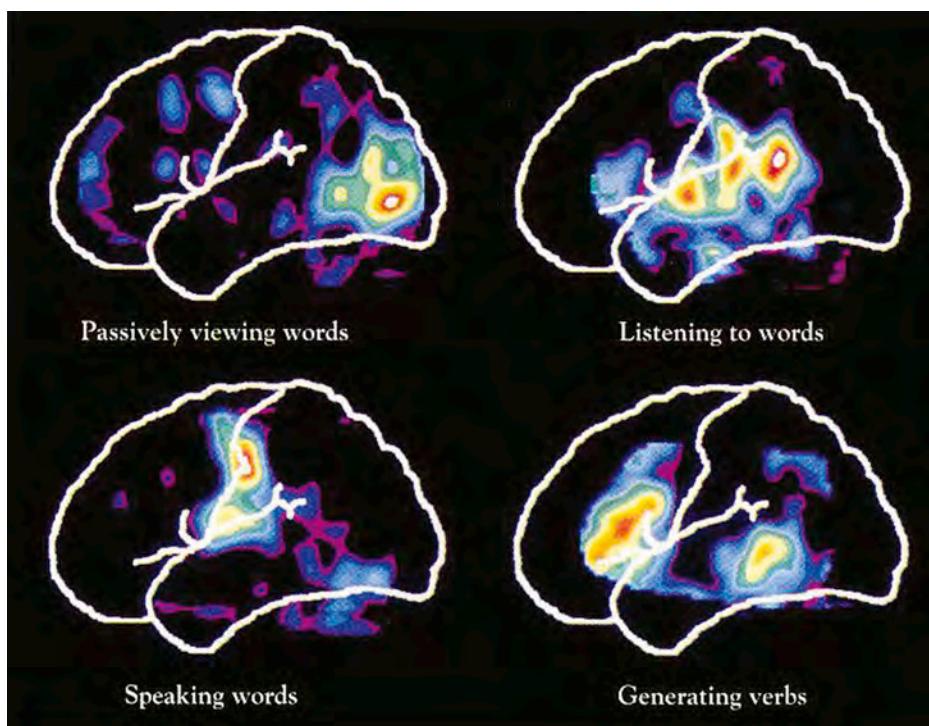
The spoken language is a special case (particular to the human primate) of temporally organized behavior. As such, it mobilizes all the cognitive processes and functions we have thus far seen to activate prefrontal regions. The more complex and novel the speech sequence, the more it will require the executive and temporally integrative functions of prefrontal cortex, and the more prefrontal activation it will induce. Here, it is appropriate to emphasize that all language is inherently to some degree *new*, for it is because of this attribute that the dorsolateral prefrontal cortex plays such an important role in language. To cite Chomsky (Peck, 1987), "language is a process of free creation; its laws and principles are fixed, but the manner in which the principles of generation are used is free and infinitely varied. Even the interpretation and use of words involves a process of free creation." The element of novelty is precisely what puts complex and original language in the purview of the prefrontal cortex.

Early imaging studies, before PET, revealed that speech is accompanied by increases in rCBF in motor cortex (mouth–larynx area), premotor cortex (especially SMA), and prefrontal cortex, especially Broca's area (Ingvar and Schwartz, 1974; Larsen et al., 1978; Ingvar, 1983; Roland, 1985). Those increases are generally larger in the dominant – commonly the left – than in the non-dominant hemisphere. The premotor and prefrontal activations are small in automatic speech with low semantic content but substantial in elaborate speech, such as reading a story aloud.

The inferences from those early studies have been confirmed, and considerably refined, with the arrival of the newer PET and fMRI techniques. It should be noted, however, that these techniques have not relieved us from several old methodological problems that remain particularly troublesome regarding language (Frackowiak, 1994). Most disturbing to the aim of localizing speech function are the close

interrelations between language and other cognitive functions, notably memory. Clearly, no task using verbal stimuli or responses can avoid the activation of memory networks that are highly distributed and idiosyncratic. The activation of these networks can impinge variably and uncontrollably upon the prefrontal cortex in its language functions. Thus, as the stimuli and response requirements of a task or test relate to hierarchically higher levels of semantic and episodic memory, the assessment of prefrontal involvement in language becomes more difficult, and so does our evaluation of the pertinent literature.

The simple discrimination of the phonetic structure of words induces the activation of left prefrontal cortex (Broca's area; Zatorre et al., 1992), whereas pitch discrimination and melodic memory activate right lateral prefrontal cortex (Zatorre et al., 1994). The mental manipulation of words and semantic memory, unlike passive listening, activates areas of the prefrontal cortex that generally include, in whole or in part, Broca's area (areas 44 and 45), areas 46, 47, 9, and 10, anterior cingulate cortex, and SMA (Penfield's speech area) (Penfield and Rasmussen, 1950), in addition to cerebellum and superior temporal cortex (Frith et al., 1991a; Wise et al., 1991; Kapur et al., 1994; McCarthy et al., 1994; Posner and Raichle, 1994; Raichle et al., 1994; Shallice et al., 1994; Tulving et al., 1994b; Bookheimer et al., 1995; Buckner et al., 1995; Menard et al., 1996; Price et al., 1996; Bookheimer, 2002; Devlin et al., 2003) (Figure 7.12). It should be noted that practically all the tests used in the relevant studies require some degree of temporal integration between material provided by the experimenter (including test instructions) and retrieved semantic material; they require the construction of some kind of verbal gestalt, whether that gestalt is implicit or explicit. Hence, in the construction of such verbal gestalts, the linguistic activation extends to areas beyond those predicted by the classical picture of language areas. To sum up, it

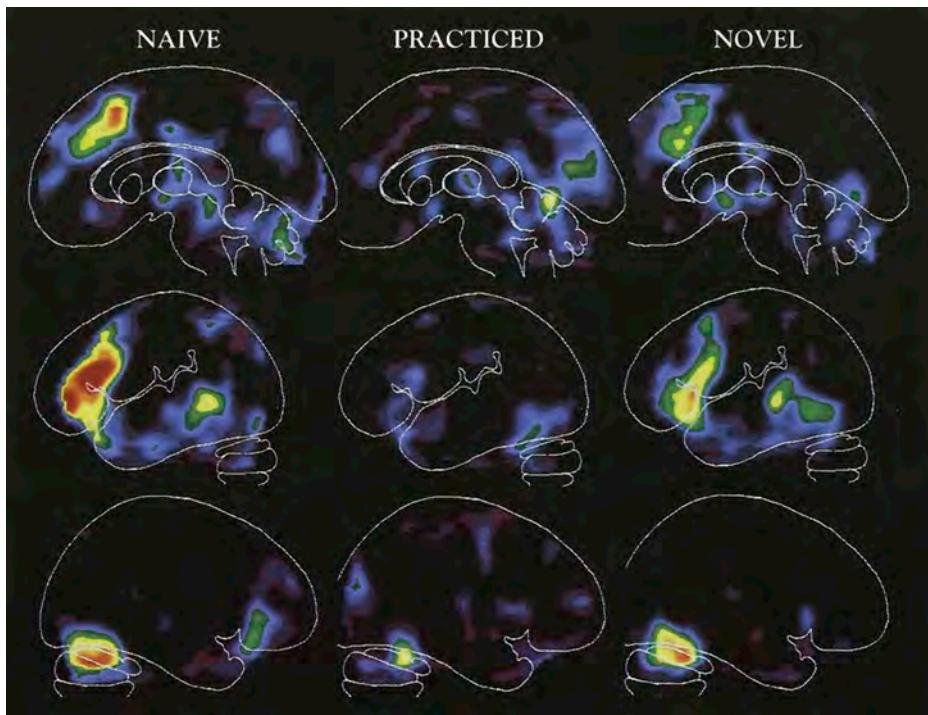


**FIGURE 7.12** Activations of the left hemisphere cortex (positron emission tomography) during four linguistic tasks. (From Posner and Raichle, 1994, with permission.)

can be argued that the prefrontal activation in word generation derives from task demands, that is, from the processing of words, not from their specific content or meaning (Gelfand and Bookheimer, 2003).

As the verbal construction becomes complex, with a substantial load on memory processes (i.e., acquisition or retrieval), the prefrontal activation becomes bilateral or shifts somewhat to the right (Squire et al., 1992; Grasby et al., 1994; Shallice et al., 1994; Tulving et al., 1994a, 1994b; Buckner et al., 1995). The studies just cited focus on the activation of prefrontal cortex in the encoding or retrieval of semantic or episodic memory (the first constituted by items of the subject's general knowledge, the second by items of information provided to the subject before the test). Based on relative

interhemispheric differences in prefrontal activation by the processing of the two types of memory, as determined by the subtraction method, Tulving, Buckner, and their colleagues have proposed that left prefrontal regions are predominantly involved in the encoding/retrieval of semantic memory, whereas the right ones are involved in the retrieval of episodic memory (Kapur et al., 1994, 1995; Tulving et al., 1994a, 1994b; Buckner et al., 1995). The proposed explanatory model has been called hemispheric encoding/retrieval asymmetry (HERA). In the light of the results, which have been replicated, at least in part, by others (e.g., Demb et al., 1995; Fletcher et al., 1995), the proposition sounds plausible. However, semantic and episodic memories are extremely difficult to isolate experimentally. Any "new" information is encoded



**FIGURE 7.13** Activation (positron emission tomography) during performance of a verb-generation task. The subject is given a series of nouns by the investigator and required to produce a verb appropriate to each. The control task was simply the reading aloud of the names as they appeared on a television monitor. Subtractive scans of three brain slices in three different conditions (*left to right*): performance by naive subject, subject practiced with the same list of nouns, and subject presented with a new list of nouns. (*From Posner and Raichle, 1994, with permission.*)

in the context of the old, any episodic memory in the context of semantic memory. Thus, it is possible that the observed left-right dichotomy is due not only to the semantic-episodic dissociation but also to quantitative differences in the load of a given test on verbal or non-verbal memory processing: the more of the former or of the latter, the higher the role of left or right prefrontal cortex, respectively. In accord with the noted dissociation, and with our tentative interpretation, is the finding of right prefrontal hypometabolism in transient global amnesia (Baron et al., 1994).

As already mentioned, the anterior cingulate region has been seen to be prominently

activated in a verb-generation task, which is a semantic retrieval task (Petersen et al., 1989; Raichle et al., 1994; Tremblay and Gracco, 2006). The attention factor has been emphasized as a likely source of that activation. The study by Raichle and colleagues (1994) validates this assumption, for they observed, as others also have (Demb et al., 1995), that as the subjects become practiced in performance of the task the activation subsides (Figure 7.13). A practiced verbal task, similarly to a practiced motor task, places fewer demands on set and memory than does a novel one. Besides, it is possible that, as with any overlearned and automatized behavioral sequence, the practiced verbal task has been

relegated away from the prefrontal cortex to lower levels of the hierarchy in the perception-action cycle (see Chapters 6 and 8).

In the light of the results obtained using more advanced imaging methods, it is time to redefine, as Bookheimer (2002) does in her excellent review on the cortical organization of semantic processing, the structure and functions of that portion of the prefrontal cortex that, on neuropsychological grounds, came to be called Broca's area. Traditionally, Broca's area (Broca, 1861) was deemed to be circumscribed to areas 44 and 45, notwithstanding the neuropathological evidence, later revealed, that the lesion of Broca's case extended into surrounding areas. Also traditionally, Broca's area was deemed to be specialized in the phonological processing of words. On anatomical and physiological grounds, however, that degree of specialization became counterintuitive, as that area is exceedingly well connected with other regions of the prefrontal cortex, which is itself, as a whole, a highly integrative structure. Furthermore, language itself – even phonological processing alone – is a highly integrative function.

Two basic facts stand out from most recent neuroimaging literature: (1) the IPC, which encompasses the inferior frontal gyrus with Broca's area in its *pars opercularis* and areas 44, 45, and 47, constitutes the prefrontal integrative domain for language; and (2) the integrative domain for language, in charge of the temporal organization of speech production and speech comprehension, works in intimate relationship with other lateral (areas 9, 10, and 46) and medial prefrontal regions, as well as with the associative areas of posterior cortex.

Because it is in that crucial integrative position, reciprocally connected with posterior and anterior cortex, as well as limbic structures, the IPC is subject to a multitude of inputs from the somatic as well as the affective sphere, from semantic as well as executive memory. This explains its involvement and activation in both semantic and phonological language (Poldrack

et al., 1999; Bookheimer, 2002; Delvin et al., 2003). The critical position of the IPC in that mesh of connectivity also explains the activation of the IPC in a variety of integrative cognitive functions related to language: selective semantic attention (Dapretto and Bookheimer, 1999; Badre et al., 2005), working memory (see above, under Working Memory), and execution – even semantic gesture (Willems et al., 2007) – as well as reception of speech.

In summary, a word about the much-debated semantic function of the IPC, which many find at odds with its supposed expressive role. Time and again, in this monograph, we have remarked on the futility of trying to separate the executive from the receptive functions of the frontal lobe. Here, as in the cortex at large, the two are thoroughly intermixed, which explains the paradox of "command cells" in parietal cortex and perceptual cells in frontal cortex. The answer to the paradox lies in the simple dictum, "no input without output, no output without input." Physiologically, in dynamic terms, the answer lies in the perception-action cycle (Chapter 8). The IPC is a crucial node of the linguistic perception-action cycle. It is at the crossroads of semantic networks from posterior cortex and executive networks from other parts of the frontal cortex; it receives also abundant inputs from both the internal and the external milieu. It sends feedback to all of them while, by enacting executive action, it closes the cycle through the environment. That environment consists, *inter alia*, of the interlocutor and the written page.

Since the last edition of this book, several studies have been published that require the modification or reinterpretation, if not rejection, of some of the imaging material discussed thus far in this section. The new data impact on three important issues related to language: (1) the influence of language development on the topography of areas involved in language processing, especially with regard to the prefrontal cortex; (2) the wide cortical distribution

of semantic contents; and (3) the hierarchical organization of semantic material and processing in frontal cortex.

As predicted by neuropsychology, imaging reveals the activation of several cortical areas in the left hemisphere during the processing of language, whether this consists of the production or comprehension of speech, the translation across languages, the naming of sensory associates, or the verbal evocation of memories and dreams. At the same time, imaging is unleashing a veritable revolution more generally in our conceptualization of the neural substrate of language. Remarkably, the distinction between brain structures dedicated to the representation and to the processing of language is disappearing. The imaging evidence falls increasingly in line with the identity of neural substrates for the representation and the expression of language. It is a concept that Jackson applied to motor cortex and movement (1882) and we have found eminently applicable to prefrontal cortex and goal-directed action.

In addition to supporting the identity of the representational (semantic) and processing substrates of language in the cerebral cortex, modern imaging has demonstrated that that substrate is (1) eminently plastic; (2) more extensive than conventionally believed; and (3) hierarchically organized, structurally and dynamically. Let us briefly review the literature in support of these tenets.

The plasticity of language networks can be easily inferred from that of cortical networks dedicated to any other cognitive function, especially if we assume that those networks are the very same for all cognitive functions (see Chapter 8). One striking example of language network plasticity exposed by imaging is that of congenitally blind people who develop language function in their visual cortex (Bedny et al., 2011). Apparently, the BOLD signal in that cortex is higher during sentence comprehension than during linguistically degraded controls, and is modulated by phonological as well

as lexical semantic information. Furthermore, in those blind individuals, their functional connectivity with language regions in the left prefrontal cortex and thalamus is increased relative to that of sighted individuals. Indeed, as a result of early experience, regions that had evolved for vision can take on language processing. Visual networks evidently turn into language networks, with the local and remote synaptic changes that this implies.

Another, more conventional, expression of the plasticity of language networks is the change in the functional imaging profile that the monolingual person exhibits with the learning of a second language. This change is dependent both on genetics and on the exposure to the new language. Japanese twins who are exposed to English as a second language as teenagers show remarkable correlations in brain activity related to the new language, as well as their proficiency in it (Sakai and Passingham, 2004). After months of classroom English exposure, pairs of twins were tested on the conjugation of English verbs, specifically the transition from present to past tense. The members of each pair showed a closely correlated activation of the left inferolateral prefrontal cortex. The correlation extended to the ability to perform the test.

Studies of bilingual and multilingual individuals challenge the concept of a well-delimited left hemisphere system exclusively devoted to language. Most of those individuals are shown to use somewhat different areas in the comprehension of different languages, although generally with a common core of classical areas in the left hemisphere (Hervais-Adelman et al., 2011; Bradley et al., 2013; Jasinska and Petitto, 2013). Kovelman et al. (2008) speak of a “signature” distribution for each language. Several studies point out the correlation between prefrontal activation and the effort or difficulty of a linguistic task, a fact in accord with the general role of prefrontal cortex in executive functions. Thus, Hernández et al. (2001), in bilinguals, note the heavy involvement of the dorsolateral

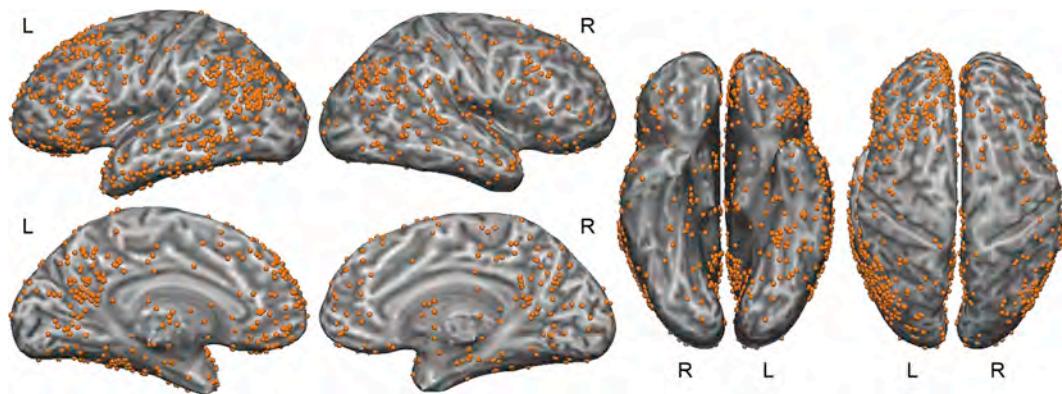
prefrontal cortex in rapid language shifting. Conversely, Chee et al. (2001), also in bilinguals, note that prefrontal activation diminishes with proficiency in the new language. In fluid bilinguals, right prefrontal activation correlates with proficiency in the pronunciation of a third language (Videsott et al., 2010).

All primates show a degree of hemispheric lateralization of functions and an expansion of the mass of the prefrontal cortex that reach their maximum in the human brain (see Chapter 2). These two facts by themselves would seem to contribute to the extraordinary evolutionary development of higher cognitive functions, especially language, in the human. But, as we have argued repeatedly in this volume, and discuss in more depth in Chapter 8, neither the increase in the anatomical mass of the cortex nor the hemispheric lateralization is sufficient to explain the emergence of the language in the human. Rather, it is the immense increase in cortical connections, now functionally substantiated by fMRI of functional connectivity in several primates (Wey et al., 2013), that explains the exponential increment of the language code, which is a relational code, as are all cognitive codes in humans. Thus, for good reason, some studies of neurolinguistics emphasize the importance of an exponential growth in subcortical white matter containing local and long-distance connections (Golestani and Pallier, 2007; Nielsen et al., 2013).

If we accept the premise that cortical connectivity is the base of all cognition, as the cognit model does (see Chapter 8), then it follows that language utilizes the same cognitive networks (cognits) that all other cognitive functions utilize. This would explain the enormous proliferation of cortical areas and networks that can be potentially used by the brain in the comprehension and production of language. In other words, all the memory and knowledge networks existing in the cortex are the infrastructure of language, as they are of attention, perception, memory, and intelligence.

It is against that background and with those premises in mind that, to understand the infrastructure of language, one has to approach the scholarly meta-analysis by [Binder and his colleagues \(2009\)](#), which they knowingly entitle: “Where is the semantic system?” Theirs is an in-depth analysis of 120 imaging studies of language, which they performed with strict inclusion criteria. The result is quite remarkable. They identify numerous areas of cortex and outside the cortex, along with their subareas, that have been seen activated in some aspect of language: inferior parietal lobe, middle temporal gyrus, fusiform gyrus, parahippocampal gyri, dorsomedial prefrontal cortex, inferior frontal gyrus, ventromedial prefrontal cortex, and posterior cingulate. A look at their Figure 2 ([Figure 7.14](#) in this chapter) shows that the cortical components of the putative semantic system practically cover the entire cortex. There is left dominance and a concentration of activated sites in Broca’s and Wernicke’s areas. But the figure conveys the unmistakable impression that the “semantic system” is nowhere and everywhere. The likely reason for this is that we are looking not at the semantic system, but at the cortical cognitive system, an immense array of networks and their nodes that serves language as well as any other cognitive function.

Functional imaging in language substantiates the hierarchical organization of executive knowledge and memory in the dorsolateral frontal cortex. Like plans and rules (above), abstract verbs, concepts, and categories of late formation have generally a more anterior, rostral, representation than concrete ones ([Jeon and Friederici, 2013](#); [Bahlmann et al., 2014](#)). This caudorostral hierarchy of knowledge is organized in the opposite direction to the cascade processing of behavior and speech that we have noted in a previous section (Executive Set and Motor Control). On the other hand, some imaging studies suggest that the caudorostral hierarchy of organized cognition in the prefrontal cortex is orthogonally intersected (see [Figure 7.4](#)) by dorsoventral



**FIGURE 7.14** Projected on an inflated view of the cortical surface, 1135 language-activated foci, from the published studies scrutinized in a meta-analysis. (By [Binder et al., 2009](#), with permission.)

gradients of sensory-modality specific cortico-cortical processing pathways ([Wendelken et al., 2012](#); [Bahlmann et al., 2014](#)).

Beyond language, by probably making use of the same cognitive networks, reasoning has an essential base of operation in the lateral prefrontal cortex ([Kroger et al., 2002](#); [Christoff et al., 2009](#); [Cho et al., 2012](#); [Ackerman and Courtney, 2012](#); [Watson and Chatterjee, 2012](#); [Donoso et al., 2014](#)). Many of the relevant studies use relational or analogical reasoning; together with prefrontal activation, most of them show, during reasoning, the concomitant activation of one or several posterior cortical areas. This finding most probably reflects the participation of extensive corticocortical networks in the process. Two studies ([Christoff et al., 2009](#); [Krawczyk et al., 2011](#)) are especially noteworthy because they demonstrate the hierarchical organization of reasoning in the lateral prefrontal cortex. In those studies, the subjects are submitted to reasoning tasks of increasing complexity and abstraction. Both studies show that the rational use of progressively more abstract representations activates progressively more anterior prefrontal areas. It is a caudorostral gradient from the concrete to the abstract that we have encountered already

in the prefrontal cortex in the organization of most sequential goal-directed actions, from simple behavior to language. As we will see in Chapter 8, that gradient matches the organization of executive knowledge and memory in the lateral prefrontal cortex.

#### IV. PREFRONTAL IMAGING IN NEUROPSYCHIATRIC ILLNESS

A number of genetic, pharmacological, physiological, and neuropsychological studies implicate the prefrontal cortex in several of the most prevalent mental disorders. Some of these studies have been addressed to some extent in previous chapters. In several respects, neuroimaging complements the findings of those studies. Below are the newest and most significant contributions of neuroimaging to the field since the last edition of this book.

##### A. Attention Deficit/Hyperactivity Disorder

In the past two decades, the attention deficit/hyperactivity disorder (ADHD) has been the subject of intensive study by neuroimagers,

some using structural and others functional methods. Especially noteworthy are the contributions using MRI by a large group of investigators at Harvard University (Bush et al., 2005; Seidman et al., 2006; Makris et al., 2007; Valera et al., 2007). The conclusions of their studies, as well as those of other investigators of ADHD, can be summarized as follows.

The ADHD syndrome is accompanied by a global reduction of cortical gray matter, adjusted for age, sex, and total cerebral volume. This has been substantiated by several studies, some of which have shown that the deficient development of gray and white matter in ADHD extends to subcortical structures, including the basal ganglia, the hippocampus, the amygdala, the cerebellum, and the frontostriatal loops (Shaw and Rabin, 2009; Castellanos and Proal, 2012; Kasperek et al., 2013). Functional connectivity studies (DTI) demonstrate that the white matter deficit is especially marked in cortical regions (Silk et al., 2009). All deficits appear to be more pronounced in the right than in the left hemisphere, although some studies differ in this respect (Proal et al., 2011; Hart et al., 2012). A cortical volumetric study reports cortical reductions in all three major association cortices (frontal, temporal, and parietal) (Sowell et al., 2003), while yet another (Mostofsky et al., 2002) reports reduction circumscribed to the frontal lobe and affecting both gray and white matter in prefrontal and premotor cortex.

In all probability, the reported volumetric deficits in certain brain regions, notably the orbitomedial and lateral prefrontal cortices, the parietal cortex, the basal ganglia, and the cerebellum, have an adverse impact on attention functions, as well as on general motility and impulsivity. It is not difficult to envision those deficits at the foundation of the ADHD dysfunction. Particularly troublesome in patients with ADHD can be the disorders in inhibitory control resulting from deficiencies in the prefrontal mechanisms responsible for that kind of control. In Chapter 3, we mentioned the possibility that

ADHD may result from a lag in the maturation of the prefrontal inhibitory system, and that the disappearance of the disorder with age could be ascribed to the laggard attainment of that maturation. fMRI studies of ADHD children and adolescents provide evidence of the hypoactivation of prefrontal inhibitory regions (Rubia et al., 1999, 2005, 2006). In autism, another disorder of childhood, the observation of affective faces induces less prefrontal activation than in healthy children (Dapretto et al., 2006).

Longitudinal studies confirm what has been inferred from neuropsychological studies: that ADHD is attributable to the delayed maturation of several structures that are critically involved in attention and the control of motility (Shaw and Rabin, 2009). That delayed maturation is manifest not only in cortical surface area but also in cortical gyration (Shaw et al., 2012). Morphological deficits may persist into adulthood (Proal et al., 2011). The spontaneous, age-related remission of the ADHD symptoms in some cases of early ADHD has been attributed to the compensatory maturation of prefrontal, cerebellar, and thalamic circuitry (Shaw and Rabin, 2009; Proal et al., 2011).

By the judicious combination of behavioral tasks and brain imaging in ADHD, Rubia and her colleagues have succeeded in establishing an interesting double dissociation. This dissociation is demonstrable between areas ("domains") with subnormal activation and two aspects of attention, both altered in the ADHD child: the inclusive, selective aspect (the focus of attention) on the one hand, and the exclusionary aspect (the inhibitory control of interference) on the other. A review by those investigators of their own work, as well as that of others, summarizes as follows the relevant dichotomy of brain domains (Hart et al., 2013). The first is a corticostriate domain including the right hemispheric frontobasal ganglia networks, the inferior frontal cortex, the SMA, and the anterior cingulate cortex. This domain is subnormally activated in situations demanding inhibition of distractions or

interference, that is, the exclusionary component of attention. The other domain, which is essential to the focus of attention, also subnormally activated in ADHD, is chiefly constituted by dorsolateral prefrontal and parietal cortex.

There is considerable evidence indicating that psychostimulants, such as methylphenidate (Ritalin®), are beneficial symptomatically in ADHD by upregulating activity in those two neuroanatomical domains (Rubia et al., 2011; Wong and Stevens, 2012; Kasperek et al., 2013; Smith et al., 2013). That drug, in particular, seems to exert its beneficial effect primarily by acting on the frontostriate system, therefore by inhibiting interference and impulsivity (Cubillo et al., 2011; Rubia et al., 2011).

## B. Schizophrenia

In early rCBF studies, patients with chronic schizophrenia were reported to have failed to exhibit "hyperfrontality," that is, the normal overactivity of frontal areas in the resting state (Ingvar and Franzén, 1974; Franzén and Ingvar, 1975); that abnormality, especially conspicuous in older patients, was characterized by not only relatively low frontal rCBF but also relatively high rCBF in occipital and temporal areas. It was further noted that these patients failed to show the activation of frontal areas that is normally induced by visual, haptic, or noxious stimulation (Franzén and Ingvar, 1975; Ingvar, 1980). Generally speaking, it was found that poverty of thought, low motivation, flat affect, inactivity, and catatonia – the so-called negative symptoms of schizophrenia – were correlated with low frontal rCBF. On the other hand, "positive symptoms," such as hallucinations, delusions, and certain thought disorders, were correlated with high rCBF in posterior cortex.

The issue of "hypofrontality" in schizophrenia has remained controversial ever since. An apparent frontal dysfunction was confirmed by later rCBF and PET studies even in young schizophrenics (Buchsbaum et al., 1982, 1984a; Ariel

et al., 1983; Farkas et al., 1984; DeLisi et al., 1985; Wolkin et al., 1985). Other studies, however, failed to confirm this (Mathew et al., 1982; Gur et al., 1983, 1985, 1987; Sheppard et al., 1983). There are probably several reasons for the discrepancies in the findings of the various studies, the most important possibly being: (1) the difficulty in defining and ensuring a steady "resting state"; (2) the polymorphous character of the schizophrenic syndrome; (3) the unreliability of certain diagnostic criteria of schizophrenia; (4) the technical and methodological differences between studies (resolving power, analytical procedures, etc.); and (5) the confounding effects of antipsychotic medication.

Weinberger and his colleagues (Berman et al., 1986; Weinberger et al., 1986) addressed the issue with a more direct neuropsychological rationale than others before them. Assuming in schizophrenia a dysfunction of dorsolateral prefrontal cortex, and in the light of the deficits that subjects with lesions of that cortex show in performance of the WCST (see Chapter 5), they tested schizophrenic patients on an automated version of the test and measured rCBF ( $^{133}\text{Xe}$ -inhalation procedure) during performance. The researchers found that, whereas the patients' rCBF at rest might be normal in all cortical areas, their dorsolateral prefrontal rCBF failed to increase, as it did in healthy subjects, during performance of the WCST. They further showed, by appropriate controls, that the absence of prefrontal activation in schizophrenic patients was not attributable to medication or failure to attend to the task. Although the main difference between schizophrenics and normal subjects was relatively small and obscured by variability, it was highly significant. The authors concluded that the dorsolateral prefrontal cortex of the schizophrenic patient is indeed functionally deficient, since it does not metabolically respond, as it does in the healthy subject, to the challenge of the test.

Hyporeactivity of frontal rCBF (on PET) in people with schizophrenia has also been reported (Andreasen et al., 1994) in performance

of the Tower of London, another test of prefrontal function which challenges planning ability. Imaging attempts to assign hemispheric laterality to the schizophrenic syndrome or its functional deficits have been thus far inconclusive. It would appear that whatever lateralizations of hypofunction have been observed are attributable to the clinical picture of each particular patient (Berman and Weinberger, 1990; Dolan et al., 1993). For example, patients with poor verbal expression tend to show left prefrontal deficits.

Studies using more modern imaging methods have approached the issue by resorting to the prefrontal activation by tasks that challenge more specifically the attentive functions most directly controlled by the prefrontal cortex, such as executive attentional set and working memory. Under these conditions, schizophrenics show poor lateral prefrontal activation in working memory (Quintana et al., 2003; Cannon et al., 2005; Honey and Fletcher, 2006; Altamura et al., 2007; Schneider et al., 2007; Walter et al., 2007) and continuous performance (Salgado-Pineda et al., 2007).

Many questions remain unanswered concerning the specificity of the reported activation deficits in terms of the pathogenesis of schizophrenia, the critical region affected, and the psychological tests used to expose the deficits. In any event, those deficits are congruent with what is known regarding the cognitive abnormalities (Kolb and Whishaw, 1983; Levin, 1984b; Nuechterlein and Dawson, 1984; Taylor and Abrams, 1984; Goldberg et al., 1987) and oculomotor abnormalities (Mialet and Pichot, 1981; Levin, 1984a) of the schizophrenic patient. All these abnormalities, including deficits of attention, working memory, thinking, and pursuit eye movements, are consistent with dysfunction of the lateral prefrontal cortex. Indeed, one of the cardinal, pathognomonic symptoms of schizophrenia is the loosening and disruption of associations in the thought process. Schizophrenic patients are clinically

distinguished by their failure to construct logically coherent temporal configurations (gestalts) of thought, and consequently of speech and behavior. The ability to form new temporal gestalts of action, even internal action, is, in the author's opinion, the essence of prefrontal function (see Chapter 8).

The functional activation disorders observed in schizophrenia and briefly reviewed here are congruent with the notion of an imbalance in neurotransmitter systems of which prefrontal circuits are a part. Apparently most prominently involved, as discussed in Chapter 3, is the prefrontal dopamine system. A disorder of this system would explain not only the negative symptoms of the disease but also at least some of the positive ones. Both positive and negative symptoms could possibly result from the disruption of connective relationships of the prefrontal cortex with subcortical and limbic structures (Bannon and Roth, 1983). One manifestation of prefrontal dopamine dysregulation may be hypertrophy or overproduction of D<sub>2</sub>-type dopamine receptors in the basal ganglia, as demonstrated in a PET study (Wong et al., 1986). Another may be the abnormal sensitivity of the anterior cingulate cortex of the schizophrenic patient to the chemical manipulation (by apomorphine) of the dopamine system, as revealed by PET (Dolan et al., 1995).

In parallel with functional imaging, morphological imaging has been used to explore the neuropathology of schizophrenia, continuing a long tradition of anatomical studies of the illness that dates back to the time of Kraepelin (1919). For many years, reports of anatomical abnormalities related to schizophrenia have appeared sporadically in the medical literature. For a variety of reasons they have been generally considered minor, inconsistent, and non-specific. In more recent years, however, largely owing to the advent of structural MRI, the subject has attracted renewed attention. It seems generally well established (see review by Antonova et al., 2004) that brain volume is to some degree

subnormal in people with schizophrenia. Furthermore, a cognitive deficit correlates with subnormal brain volume, although this is true also in some non-psychotic individuals.

Using current imaging techniques, several investigators have shown, in schizophrenics, atrophic malformations of varying degree that are particularly conspicuous in prefrontal regions, although not circumscribed to them (Weinberger et al., 1979; Nasrallah et al., 1983; Oxenstierna et al., 1984; Breier et al., 1992; Raine et al., 1992; Andreasen et al., 1986, 1994). The abnormalities are especially common in male patients with negative symptoms (Andreasen et al., 1990a, 1990b). Particularly noteworthy are the studies that demonstrate – often already in first episode schizophrenia – deficits of prefrontal gray matter (Miyakawa et al., 1972; Hirayasu et al., 2001; Hulshoff Pol et al., 2002; Arango et al., 2003; Wiegand et al., 2004; Fornito et al., 2009; Levitt et al., 2010).

Another microscopic abnormality in the prefrontal cortex of the schizophrenic patient lies in the reduced number and malformation of dendritic spines, which is especially conspicuous in the anterior cingulate cortex (Benes et al., 1986, 1987; Benes and Bird, 1987) but can also be discerned in other prefrontal regions, especially in cortical layer 3 (Glausier and Lewis, 2013). At a higher level of connective disorder, some studies indicate deficits in the structural (Spalletta et al., 2003; Mitelman et al., 2005) as well as functional (Schlösser et al., 2007; Wolf et al., 2007) corticocortical connectivity. Connectivity issues, therefore, seem to be at the foundation of schizophrenic pathology. On the basis of these issues, especially at corticocortical level, Friston and Frith (1995) speculated that schizophrenia is a disconnection syndrome.

Whereas a corticocortical connectivity disorder may help to explain the cognitive disorders of schizophrenia, along with its negative symptoms, it falls short of explaining its emotional disorders, the other major component of the psychopathology of the illness. Here is

where we need to consider the faulty connectivity of the prefrontal cortex of the schizophrenic patient, with several subcortical structures known to play a major role in the experience and expression of emotion.

Indeed, the morphological abnormalities of the schizophrenic brain revealed by imaging extend to parts of the prefrontal cortex that, as we now know from previous chapters, have much to do with emotion. They include, most prominently, its orbital areas and the anterior cingulate cortex (see reviews by Fusar-Poli et al., 2007; Nagai et al., 2007; Fornito et al., 2009). Other parts that are also frequently found to be abnormal in schizophrenia (see the same reviews) include a collection of structures of limbic or “paralimbic” character, such as the hippocampus, the amygdala, and the insula. All of these structures, added to the cingulate cortex, form a massive hub of circuits at the crossroads of the prefrontal interface between cognitive and emotional processing. In fact (see Chapter 8), these structures are at the intersection of the cognitive and the emotional perception–action cycles. Disorders in these structures could certainly be at the center of a schizophrenic disconnection syndrome.

### C. Obsessive–Compulsive Disorder

Baxter and his colleagues (1987, 1988, 1989) were the first to examine brain glucose metabolic rates by PET in patients with obsessive–compulsive disorder (OCD). In comparison with normal controls and patients with unipolar depression, patients with OCD showed markedly increased metabolic rates in orbital prefrontal areas. This finding was shortly thereafter replicated by other investigators (Nordahl et al., 1989; Swedo et al., 1989). In OCD patients, Swedo and collaborators (1989) also found hyperactivity bilaterally in anterior cingulate cortex. Today, with the additional evidence from fMRI, these findings are generally accepted facts, though, as we shall see, with qualifications.

The observation of orbitofrontal and cingulate hyperactivity in OCD raises interesting theoretical issues regarding prefrontal functions and the pathogenesis of the illness. Clinically, OCD is characterized by tenaciously persistent patterns of thought and behavior that are beyond the control of the patient and are generally accompanied by great anxiety. We might say that the patient's cognitive function and behavior have fallen hostage to excessively focused attention to unfounded sources of fear. The patient suffers from the opposite of distractibility; the patient is hyperattentive, but to the wrong things. OCD patients differ somewhat from one another, but all present with one or several of the following symptoms: excessive preoccupation with cleanliness, order, and symmetry, and with the likelihood of illness or contamination. Thus, the patient is incessantly driven by the need to check and recheck actions and events for order and safety, as well as performing hand-washing, and undoing actions that might, in the eyes of the patient, result in some harm to the self or others. People with OCD often also exhibit an exaggerated moral sense and are internally tormented by scruples, guilt, and regret.

These clinical manifestations, combined with the evidence from neuroimaging, suggest that in OCD the orbitomedial areas of prefrontal cortex, which are so important for attentional mechanisms, are overactive to avert dangers, real or unreal. Does the overactivity of these areas reflect the pathological exacerbation of that interference-control (exclusionary) function that normally supports the temporal integration of behavior and that animals or humans with orbitomedial lesions are missing? Defying this interpretation is the observation, in OCD patients, of reduced orbitofrontal activation on a reversal-learning task (Remijnse et al., 2006). Does the orbitofrontal pathology reflect a broader pathogenesis that affects the neural circuits connecting the prefrontal cortex to the basal ganglia; in other words, the frontostriatal system (Baxter et al., 1996)? Further research is

needed to answer these questions. In all likelihood, however, the abnormal activation of the anterior cingulate cortex, which is part of those circuits, reflects anxiety and effort, both of which are excessive and wasteful in the OCD patient (Friedlander and Desrocher, 2006). This could be the basis for the beneficial effects that orbitofrontal and anterior cingulate psychosurgery were reported in the past to have achieved in some severe cases of the disorder (Pippard, 1955; Knight, 1969; Bridges et al., 1973; Rees, 1973).

In recent years, those functional imaging data have been backed up by additional studies. In addition, morphometric imaging has expanded beyond orbitofrontal and cingulate cortices, the brain structures that are principally affected in OCD. Furthermore, functional imaging has attempted to relate specific OCD symptoms to malfunction in particular structures.

Extensive volumetric studies of OCD have shown structural deficits, that is, subnormal volume in several cortical and subcortical areas in addition to cingulate and orbitofrontal cortex (Shin et al., 2007; Rotge et al., 2009): the inferior and middle dorsolateral cortex, the superior temporal cortex, and the lingual cortex. Sizeable gray-matter volume reduction has been substantiated in these areas (van den Heuvel, 2009; Togao et al., 2010). White matter also shows reductions in some of these areas (Togao et al., 2010; Lázaro et al., 2014). However, functional connectivity in orbitofrontal and anterior cingulate cortices is increased in OCD (Harrison et al., 2009; Sakai et al., 2011).

In general, despite volumetric reductions in gray and white matter, it appears that the cerebral structures that harbor the circuits of the orbitofrontal-striatal-thalamic-cingulate complex are hyperactive in the OCD syndrome, especially in view of the increased functional activity and connectivity in those circuits in the syndrome (Sakai et al., 2011; Piras et al., 2013). Considering that the syndrome is heterogeneous and made up of symptoms that vary from patient to patient, some studies have

attempted to relate regional abnormality to specific aspects of the syndrome (Mataix-Cols et al., 2004; Gu et al., 2008; Ursu and Carter, 2009; van den Heuvel et al., 2009). The results from these attempts, however, are short of being conclusive.

One of the most common characteristics of the OCD syndrome is the exaggerated moral sense, an abnormal preoccupation with what is right and what is wrong in one's behavior. It is at the root of the patient's compulsion to come out clean morally, which in many cases is symbolically expressed by repeated hand-washing. The physiological abnormality at the root of the keen moral sense of the patient with OCD has been explored in at least one functional imaging study (Harrison et al., 2012). Experimental subjects were required to make decisions as they were presented with difficult hypothetical moral dilemmas. In that situation, OCD patients showed a greater activation of orbital prefrontal cortex than subjects without OCD, and the severity of the illness predicted the degree of activation.

The opposite of moral sense is moral insensitivity. This is a common observation after orbitomedial prefrontal lesions (see Chapter 5). On that basis, it was inferred that that part of the prefrontal cortex plays the important role that it seems to play in the control of impulsivity and antisocial behavior. Indeed, the OCD patient suffers from excessive control of that impulsivity and, congruently, his or her orbital and medial prefrontal areas are hyperactive in functional imaging. In that light, the reported orbitomedial prefrontal hypoactivity of criminal offenders and antisocial psychopaths becomes apparently understandable (Raine et al., 1994; Yang and Raine, 2009; Crowley et al., 2010; Marsh et al., 2011).

## D. Depression

Depression is a psychiatric syndrome of variable etiology and manifestations. The endogenous or "constitutional" forms of depression,

unlike the exogenous or "reactive" forms, have a well-recognized genetic origin and characteristic patterns of clinical evolution when untreated. Like schizophrenia, however, the symptomatology of any depression, of whatever form, varies considerably from patient to patient. For example, anxiety may or may not accompany the depressed mood, which otherwise may alternate with manic affect, which is the opposite of depression, or with obsessive-compulsive symptoms. Psychotic symptoms may be present in severe forms of depression. In sum, "pure" depression is relatively rare, in bipolar as well as unipolar cases.

In several studies using PET-FDG, major depression – whether unipolar or bipolar – was found to be accompanied by low metabolism in the frontal lobe (hypofrontality) or even the whole brain (Buchsbaum et al., 1984b, 1986; Baxter et al., 1985, 1989; Cohen et al., 1989; Martinot et al., 1990). The situation resembled that of schizophrenia (Cohen et al., 1989). Because the prefrontal hypofunction of the depressed patient did not result in hypometabolic reactions to tests such as the WCST, Berman et al. (1993) argued that the two syndromes must have a different frontal pathophysiology.

Drevets et al. (1992), however, obtained different results in a group of patients suffering from a pure and familial form of unipolar depression. It is important to note that, unlike most other researchers who preselect the cerebral areas of interest, these investigators let the data from a first group of patients determine those areas, or volumes of interest. In this manner, they discovered a circumscribed, data-defined area of prefrontal cortex that showed consistently *more* metabolic activation than in controls. This area extended from the ventrolateral aspect of the left prefrontal cortex, through its anterior convexity, into its medial surface. In addition, the left amygdala was found to be hyperactive. Hyperactive areas were not seen in a group of clinically remitted patients with the same syndrome. The authors explained the differences

between their results and those of others on the basis of the exceptional homogeneity of their group of depressed patients and their method for selecting the volumes of interest.

Two other studies found mediofrontal, orbitofrontal, and anterior temporal activations in depression (Pardo et al., 1993; George et al., 1995). On close examination of the literature, the different sets of results are not as incompatible as they first appear. As Drevets et al. (1992) point out, some earlier investigators (Buchsbaum et al., 1986; Baxter et al., 1987) had observed, along with the more global hypoactivations noted above, some hyperactivity in orbital areas that, at least in part, overlap their area.

The group of investigators led by Drevets has contributed considerably to further clarifying the matter (Drevets, 2000a, 2000b; Nugent et al., 2006). In major depression, whether part of the bipolar mood disorder or not, there is a cluster of prefrontal structures that show morphometric abnormalities primarily characterized by a diminished volume of gray matter. These structures include the orbitofrontal and posterior cingulate cortices. The volumetric abnormalities are accompanied by functional abnormalities that persist even under symptom remission (e.g., under medication), and even in the presence of normal activations under conditions of cognitive or emotional challenge. Other studies (Kanner, 2004; Lacerda et al., 2004; Lavretsky et al., 2007; Foland et al., 2008) confirm the orbitomedial abnormalities and correlate them with symptoms of mood disorder, such as depression, psychomotor retardation, apathy, or anxiety.

Neuroimaging has contributed also to substantiating the genetic factors in depressive and bipolar affective syndromes. So far, the most likely genetic factors impacting the major depression phenotype are those that regulate the expression of serotonin (5-hydroxytryptamine, 5-HT), more specifically the 5-HT transporter gene (SLC6A4). According to PET data, 5-HT<sub>1A</sub> receptor binding is decreased in

the raphe nuclei, the medial temporal lobe, and the medial prefrontal cortex of patients with major depression (Savitz and Drevets, 2009). As discussed in Chapter 3, a dysregulation and deficit in the serotonin system is at the foundation of bipolar and depressive syndromes, and is presumably severe in cases leading to suicide (Mann, 2013). Therein is the rationale for the use of selective serotonin reuptake inhibitor (SSRI) medication, especially in patients with major depression. Consequently, in such patients, the effects of such medication on brain structures normally rich in serotonin, namely the dorsolateral prefrontal cortex, the anterior cingulate, and the amygdala, have been monitored by neuroimaging for exposing the normalization of serotonin levels (Bellani et al., 2011; Meyer, 2012). Another imaging study focuses on the monoamines and glutamate levels (Meyer, 2012). It points particularly to elevated monoamine oxidase binding in the prefrontal and anterior cingulate cortices of patients with or at high risk for major depression.

A review by Price and Drevets (2012) correlates animal studies with human studies on the pathophysiology of mood disorders. Concentrating on anatomical and imaging studies, the authors point to the mood-related dysfunction in an extended network that encompasses the medial prefrontal cortex and anatomically related limbic, striatal, thalamic, and basal forebrain structures.

Several neuroimaging studies and reviews note that the crucial problem in affective disorders is the abnormal functional connectivity in the emotional sensing and expressing circuits that comprise the ventromedial prefrontal cortex, anterior cingulate cortex, and amygdala (Townsend and Altshuler 2012; Groenewold et al., 2013; Wen et al., 2014).

Myers-Schulz and Koenigs (2012) conducted an extensive critical review of the animal and human neuroimaging literature on affect and its representation in the ventromedial prefrontal cortex, a crucial component of the emotional

perception-action cycle (see Chapter 8). Their review covers a vast literature that, according to them, identifies two separate regions within the ventromedial prefrontal cortex signaling two large categories of affective experiences: a posterior region signaling negative affects and an anterior region signaling positive affects. As the authors of the study readily admit, however, their dichotomous representation of affects in ventromedial prefrontal cortex is merely suggestive, for it is based on studies of widely differing methodologies. Nonetheless, the abnormal activation of a portion of the orbitomedial prefrontal cortex in depression seems quite consistent.

### E. Dementia

The arrival of imaging methods revolutionized the diagnosis of all the dementias of old age. Using procedures that are much more accurate and less traumatic than those formerly employed, we are now able to confirm or deny what is commonly a tentative diagnosis based only on neuropsychological assessment. The new methods allow an earlier and more reliable diagnosis. On matters of pathogenesis, however, progress has been slower.

In the past three decades, there has been a gradual recognition that patients with dementia tend to have a general exacerbation of the structural and functional deficits exhibited by the general population in the normal process of aging. The advent of dementia simply precipitates those changes. In certain individuals the disease, whether it is Alzheimer's or frontotemporal dementia, is preceded by what has been called mild cognitive impairment; on statistical grounds, such individuals are considered at risk for dementia. These are important considerations that bear on the clinical and imaging characteristics of dementia, especially in view of the fact that these characteristics may vary widely in normally aging individuals as well as in those with mild cognitive impairment.

It is now generally agreed that in normal aging, and much more in dementia, there are: (1) volumetric decrements in both gray and white matter throughout the neocortex, which is particularly strong in prefrontal areas (Raz et al., 2000; Bartzokis et al., 2001; Salat et al., 2001; Tisserand et al., 2002; Rosen et al., 2005); and (2) functional deficits in several cognitive functions commonly ascribed to the prefrontal cortex, notably working memory, interference control, and the retrieval of episodic memory (Thompson-Schill et al., 2002; D'Esposito et al., 2003; Elgh et al., 2003; Rajah and D'Esposito, 2005). As mentioned in Chapters 2 and 3, the concomitant neurotransmitter or modulator losses that accompany these changes are also generally prominent in the prefrontal cortex. The same may be said of metabolic changes. The normal age-related decrements of cortical metabolism and rCBF that have been found to occur in prefrontal areas (Kuhl et al., 1982; Pantano et al., 1984; Shaw et al., 1984; Smith, 1984; Martin et al., 1991) are accelerated and accentuated in Alzheimer's disease (Benson et al., 1983), as well as in cerebrovascular disorders common in old age that also tend to affect severely the prefrontal cortex and its cognitive functions (Mamo et al., 1983; Shaw et al., 1984). Judging from metabolic studies, however, the pathological involvement of the prefrontal cortex in these conditions may not necessarily precede that of other neocortical areas (Benson et al., 1983; Haxby et al., 1986). Furthermore, the degree of involvement of the prefrontal cortex may vary widely from individual to individual, as it does in normal aging. We will end this section with a brief comment regarding the possible reasons for that variability.

In 2005, Rajah and D'Esposito wrote a comprehensive and insightful review of the PET and fMRI literature available to date on the region-specific changes that occur in the prefrontal cortex as a function of age. The review consists basically of a qualitative meta-analysis of a large number of studies. The reviewers draw the

following conclusions: (1) the morphological and functional changes of the prefrontal cortex in the course of aging are far from uniform in all areas and individuals; and (2) the process of aging is accompanied by what has been called dedifferentiation of areas (Li et al., 2001, 2004). According to this view, the age-dependent changes in neurotransmission result in a secondary rearrangement of prefrontal areas and their functions. Some change their specialization, while in general specialization becomes more diffuse and less localized. At the same time, some areas take over the functions of others that lose their own. That is reflected in the compensatory, seemingly paradoxical, activation of areas taking over certain functions (e.g., in working memory).

The end result of the aging of the prefrontal cortex is one of spotty deficits and compensations that are unpredictable from classical modular views. In the author's estimation, the overall age-resulting rearrangement is a product of the neurobiology and network dynamics of the prefrontal cortex. Executive cognitive functions result from interactions within and between innumerable overlapping and interactive networks of the frontal lobe (see Chapter 8). What defines a function here, and its specificity, is the associative composition of those networks, not their precise location in certain action domains, which are profusely interconnected by the networks. The idiosyncrasy and plasticity of those networks are at the root of the rearrangement of the functional architecture of the prefrontal cortex occurring in normal aging as well as at the beginning of dementia.

These views have been reinforced and complemented by new neuroimaging evidence.

1. In healthy aging and in individuals affected by mild cognitive impairment, there is a gradual, however subtle, atrophy of several brain structures, including the hippocampus and parts of the neocortex, notably parietal, temporal, prefrontal, and posterior cingulate

cortex; this atrophy, which affects gray as well as white matter, and may include the cortical deposition of  $\beta$ -amyloid (Sojkova et al., 2011; Sepulcre et al., 2013), is accompanied by correlated deficits in memory functions, including encoding, recognition, and working memory (Clément et al., 2009; Fjell et al., 2009; Kuczynski et al., 2010; Wang and Morris, 2010; Back et al., 2011; Han et al., 2012; Lithfous et al., 2013; Bakkour et al., 2013). Although in most cases the volumetric decreases are accompanied by prefrontal hypoactivation, in some cases the morphological change is accompanied by hyperactivation, presumably reflecting a compensatory mechanism (Gigi et al., 2010; Clément and Belleville, 2012; Maillet and Rajah, 2013).

2. In Alzheimer's disease, these changes undergo an accelerated increase (Frisoni et al., 2009; Fouquet et al., 2009; Meulenbroek et al., 2010; Zhang et al., 2010; Teipel et al., 2012; Bakkour et al., 2013; Hornberger et al., 2014). Any part of the prefrontal cortex can be affected at one time or another, although the orbital prefrontal cortex is usually more affected in frontotemporal dementia than the dorsolateral prefrontal cortex, which is more affected in Alzheimer's (Wong et al., 2014). DTI and other kinds of functional connectivity analysis indicate that connectivity and white matter are affected first, and more so than gray matter (Kuczynski et al., 2010; Gili et al., 2011; Zhang et al., 2010; Lo et al., 2010; O'Dwyer et al., 2011; Shao et al., 2012; Zaidel et al., 2012). This is in line with the network concepts of cognition to be discussed in Chapter 8.

## V. SUMMARY

Computerized scanning and tomography methods allow the visualization of changes in regional blood flow and metabolism related to neuronal activity. Thus, functional

neuroimaging provides indirect records of activity simultaneously in various regions of the brain; in other words, functional maps of the brain. Neuroimaging is still subject to unresolved methodological problems that basically stem from the uncertain relationships between neuronal firing and the imaged variables, especially blood flow (neurovascular coupling). Despite these problems, decisive progress has been made with neuroimaging toward unravelling by essentially non-invasive methods the functions and dysfunctions of the human prefrontal cortex.

Because the cognitive functions of the prefrontal cortex are intimately intertwined, it is difficult to determine their spatial (topographic) and temporal distribution by either of the two prevalent methods of neuroimaging: PET and fMRI. A common and effective procedure is the subtraction method. Activity is measured during performance of two tasks that are identical in all respects except with regard to the cognitive function being tested; one task requires that function and the other does not. Statistical comparison of regional activity in the two tasks yields a reasonable measure of the activity related to that function.

Since the last edition of this volume, decisive progress has been made by neuroimaging in the study of the anatomical and functional connectivity of the prefrontal cortex. Based on the magnetic image produced by the spatial orientation of water molecules, the DTI method has become invaluable, especially for the tracing of nerve fibers with high water content, such as myelinated axons. Consequently, DTI is extremely useful for tractography, thus for the tracing of fascicular connections between prefrontal and posterior cortices, as well as interhemispheric commissures such as the corpus callosum. Its use in the tracing of intracortical unmyelinated fibers, however, is more limited. The study of functional connectivity in the cortex is aided by the analysis of temporal correlations of blood-flow activity between areas.

Neuroimaging during sensory stimulation of various modalities substantiates the convergence of cortical sensory pathways upon prefrontal cortex revealed by anatomical and physiological studies. The activation and its distribution depend on the degree of attention that the subject concentrates on the stimuli. Tasks requiring heightened attention, such as the Stroop task or a verb-generation task, activate regions of medial – anterior cingulate – and dorsolateral prefrontal cortex that have consequently been ascribed to a hypothetical “anterior attentional system.” Appropriately, it has been noted that this system is engaged, above all, in attention *for action*.

The cortical neuroimaging at rest provides the background on which the cognitive functions of the prefrontal cortex operate. Functional imaging in the rest state reveals the prevalence of slow-frequency oscillations in widespread areas of the cerebral cortex, including some prefrontal areas, which demarcate what has been called a “default network.” As imaging and electrical methods indicate, when the cortex enters some form of organized activity at the service of cognition, parts of that “default network,” together with other areas of prefrontal and posterior cortex, engage in the dynamic activation and behavioral intervention of cognitive networks. These networks appear to have two fundamental characteristics: (1) a widespread and mutually overlapping distribution; and (2) a hierarchical organization. The serial or parallel, and orderly, activation of cognitive networks or cognits in the pursuit of goal-directed actions, under prefrontal control, is at the foundation of all the cognitive functions of the prefrontal cortex. One common characteristic of all of them, as recent neuroimaging studies emphasize, is their prospective, future, and orientation.

The conceptualization or planning of an action elicits activation at the highest levels of the prefrontal executive hierarchy. At those levels, action is represented in its most abstract form. As the subject prepares to execute the

action, lower levels of the hierarchy become engaged, representing more concrete aspects of the action, such as rules or strategies, in prefrontal and premotor cortex. The action-related activation becomes greater in those lower cortices and their networks as they mobilize motor set or attention to prime effector systems in advance of the action.

Attentional sensory-perceptual set is the priming or preparation of sensory systems in the expectation of sensory input in the context of a behavioral task. It is a top-down, prospective function of the prefrontal cortex that in functional imaging manifests itself by the anticipatory activation of a prefrontal area and, concomitantly, the activation of the sensory areas involved in the processing of the expected stimulus.

Attentional executive set is the mirror image of sensory-perceptual set. It prepares motor systems for the anticipated action(s). The cingulate cortex and the SMA, both largely in the medial frontal lobe, and especially the prefrontal cortex, are heavily activated in preparation for movement and are presumably critical for motor control. In the temporal organization of goal-directed behavior, as actions are integrated at progressively more concrete and automatic levels of the executive hierarchy of the frontal lobe, functional imaging provides evidence of a cascade of processing downward in that hierarchy, from prefrontal to premotor to motor cortex. At every stage, executive networks link with subcortical structures and with perceptual networks of posterior cortex. All those relations form interactive and reciprocal loops within the perception-action cycle, which links the organism with its environment.

The working memory for the performance of any action, whether the memorandum is visual or auditory, spatial or non-spatial, activates a portion of lateral prefrontal cortex. To some degree, that portion varies with the content or modality of the memorandum. The activation is most prominent on the left if the memorandum is verbal. Regardless of the memorandum, the

degree of activation depends on the memory load contained in it.

In addition to activating a portion of lateral prefrontal cortex, working memory activates a cortical area in posterior cortex related to the modality of the memorandum. Thus, if the memorandum is visual, the posterior cortex activated is the inferotemporal cortex; if it is spatial, the posterior parietal cortex; if it is auditory, verbal or not, the associative cortex of the temporal and parietal lobes. In this monograph it is assumed that working memory is maintained by reverberant re-entry within a large updated network of long-term memory that represents the memorandum with all its associative attributes: the executive attributes in prefrontal cortex and the perceptual attributes in posterior cortex. Functional imaging during working memory reveals the almost simultaneous activation of the two in tandem, as both are needed in the process.

Decision-making results from the confluence of neural influences from several brain structures upon the prefrontal cortex. Some of these influences come from other cortical regions and include sensory processing, long-term memory, and ethical discernment. Imaging in working-memory tasks, before and during decisional choices, provides evidence of the activation of cortical areas that influence decision. Other influences come from several limbic and diencephalic structures that are activated in proportion to the positive or negative value of external events and stimuli. These structures form part of the emotional perception-action cycle, which in goal-directed behavior interacts with the cognitive perception-action cycle. That interaction takes place in orbitomedial and cingulate cortices.

The insula, a transitional structure between limbic cortex and orbital prefrontal cortex, is consistently activated by the consequent frustration from error. Further forward, the ventrolateral and orbitomedial prefrontal areas are involved in the prediction of errors as well as in their avoidance. Both functions are most clearly

attributed by imaging studies to the cingulate cortex, in the medial aspect of the frontal lobe, which, under inputs from the insula and orbital prefrontal cortex, interfaces emotion with the cognitive integration of action.

As a special case of temporally organized behavior, complex speech activates lateral prefrontal cortex, especially on the left. However, because semantic activities engage large cortical networks of long-term memory, the generation of any configuration of language usually activates also extensive areas of posterior cortex, both on the left and on the right. The retrieval of episodic memory induces a relatively strong activation of the right dorsolateral prefrontal cortex. The inferior lateral cortex on the left constitutes the highest executive link of the linguistic perception-action cycle. It is involved in both phonological and semantic aspects of linguistic integration. At the same time, because of its connections with higher prefrontal and posterior semantic cortex, it is involved in higher cognitive functions (e.g., working memory) that take part in the integration of elaborate language.

Modern imaging studies attest to the plasticity of the cortical areas involved in language. The most explicit evidence in this respect is that obtained from activation of new areas in bilingual or multilingual individuals acquiring a new language. Evidence has also been forthcoming to show the correlation between cortical (especially prefrontal) activation and the effort required to learn a new language. Imaging studies, some of them cross-species, point to the enormous increase in cortical connectivity that accompanies the evolution of language in the human brain.

A most important fact revealed by imaging is the language involvement of cortical areas that formerly were not implicated in language. A highly trustworthy meta-analysis shows that practically any part of the neocortex can potentially participate in language. This reinforces the concept, repeatedly mentioned in these pages, that (1) the cortical networks (cognits) are widely dispersed and overlapping one

another throughout the neocortex; and (2) any of those networks can serve not only language but also any other cognitive function. This does not challenge the concept that certain networks and cortical areas – especially in the left hemisphere – are more likely than others to be engaged by language.

Imaging also reveals that both the cognitive structure of language and its function are hierarchically organized. This is consistent with the view of the hierarchical organization of the representation as well as the execution of complex, goal-directed actions. Also consistent with that view is the evidence that analogical reasoning takes place along patterns of descending, hierarchically organized, areas of frontal cortex, beginning with abstract constructs or plans of action in the rostral polar prefrontal cortex.

Children and adults with ADHD show volumetric deficits of gray matter in practically all brain structures. This gray-matter deficit is generally accompanied by an even more marked deficit in white (connectivity) matter. Longitudinal imaging studies indicate that these deficits tend to diminish with age, thus giving credence to the hypothesis that ADHD results from defective maturation of assorted brain structures. The deficit in cortical areas – especially right dorsolateral prefrontal cortex – has been considered to lie at the root of the problem that ADHD subjects have in focusing attention. Imaging demonstrates the hypoactivity of these areas. On the other hand, the deficits in right prefrontal cingulate cortex and in several subcortical structures (e.g., basal ganglia, cerebellum) have been deemed to be the cause of the impulsivity and distractibility that characterize the syndrome. Drugs such as methylphenidate help to restore attention by assisting the maintenance of focus as well as the suppression of distractibility and interference.

Morphometric studies in schizophrenic patients show reductions in prefrontal gray matter, and also a number of abnormalities in cell-contact processes, such as dendritic

arborizations and corticocortical connections. Deficits in prefrontal morphology are already present in first episode patients. The prefrontal cortex of schizophrenic patients shows a tendency toward low metabolic activity ("hypofrontality"). This tendency seems to be most evident when the cognitive functions of that cortex are challenged. Such is the case during performance of a temporally integrative task such as the WCST or a task that challenges the ability to plan actions (Tower of London). Schizophrenic patients show deficient activations in attentional set and working memory.

In general terms, and on the basis of the noted morphological abnormalities, in addition to neurochemical disorders, schizophrenia seems to be, as proposed by some, a "disconnection syndrome." Defective corticocortical connectivity, as well as the connectivity between prefrontal and brainstem structures, would explain the negative symptoms of the disease (thought disorder, flat affect, catatonia, disconnection from reality, etc.). On the other hand, disorders in the connectivity between cortical and limbic structures would explain many if not all of the positive symptoms (delusions, hallucinations, affective ambivalence, emotional decontrol, etc.). The two disorders of connectivity, cognitive and affective, would disrupt the cognitive and the emotional perception-action cycle, respectively.

Several volumetric abnormalities have been found in the brains of patients suffering from OCD. The most consistent are subnormal volumes of gray and white matter in orbitofrontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex, and temporal cortex. Paradoxically, hyperactivity in these structures has been revealed in the OCD syndrome or some of its clinical components. It would appear that the OCD patient puts on "overdrive" diminished structural resources. This is most apparent in tests of moral sense, which OCD patients possess to an exaggerated degree.

Endogenous depression, the kind of depression with a definite genetic component at its root, is one of the most extensively investigated neuropsychiatric disorders with imaging methods. Morphologically, a deficit in cortical gray matter has been identified in prefrontal areas of the depressed patient, including orbital, medial, and lateral cortex, especially on the left. Functionally, however, whereas early studies reported the hypoactivity of those areas, more recent studies reveal their hyperactivation. PET imaging has contributed to the elucidation of genetic factors in depression. This research has exposed in prefrontal cortex and subcortical related regions (e.g., raphe nuclei) a gene responsible for serotonin receptor binding. This ties depression to serotonin dysregulation, which is a target of effective antidepressant medication.

Neuroimaging shows that normal aging is accompanied by a generalized reduction in cortical gray and white matter. That reduction affects somewhat disproportionately the prefrontal cortex. Along with those morphological changes, there is an age-related decline in cognitive functions, notably executive functions such as working memory. This decline is moderately evident in the mild cognitive impairment of old age. Both the morphological changes and the cognitive decline accelerate precipitously in dementia. The cortical patterns of pathological change and functional decline, however, are far from uniform, either in normal aging or in dementia. In Alzheimer's disease, temporal, parietal, and dorsolateral prefrontal areas are rapidly but not uniformly affected. Frontotemporal dementia is more circumscribed to the temporal pole and the prefrontal cortex, especially its orbitofrontal component. In both conditions, especially Alzheimer's, functional neuroimaging reveals at first a compensatory rearrangement of the functional commitments of prefrontal areas. That rearrangement, which varies to some degree from individual to individual, involves deficit as well as exacerbated compensatory changes.

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# Overview of Prefrontal Functions: *E Pluribus Unum* – Coordinating New Sequences of Purposeful Action

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## I. CONCEPTUAL INTRODUCTION

This chapter develops a conceptual synthesis of the material reviewed in the preceding chapters. As the reader has undoubtedly noticed,

I have tried to place the various facts and observations regarding the prefrontal cortex within a functional model that has become progressively more explicit during the course of the review. Now, 7 years after the last edition of this book,

and largely because of decisive recent advances in electrophysiology (see Chapter 6) and neuroimaging (see Chapter 7), the model has acquired considerable resilience. It is essentially based on seven general propositions for which there is now sizeable empirical support:

1. The entirety of the cortex of the frontal lobe is devoted to the representation and production of action at all levels of biological and behavioral complexity, including language.
2. The neuronal substrate for the representation of any action in the cortex is identical to the substrate for the production of that action.
3. That substrate for action consists of a complex array of widely distributed, partly overlapping and interactive neuronal networks of the frontal lobe, some of which extend into posterior cortex.
4. Networks in the dorsolateral convexity of the frontal lobe are chiefly in charge of the cognitive aspects of action; networks in the ventral (orbital) and medial frontal cortex are in charge of its emotional (affective and reward-related) aspects.
5. Frontal cognitive networks interact with other cortical networks in the frontal lobe and in other cortices; cognitive and emotional networks interact with one another in ventromedial prefrontal cortex.
6. All goal-directed actions, especially if they are new and complex, are processed in the perception-action cycle, the adaptive biocybernetic interface between the cortex and the environment. Two parallel components of that cycle, one cognitive and the other emotional, interact with each other in ventromedial prefrontal cortex.
7. Cognitive networks, as well as the cortical levels of the perception-action cycle, are hierarchically organized, from the most concrete to the most abstract adaptive action: simple actions in lower levels (motor cortex and striatum) and global actions and plans in the prefrontal cortex.

The model does not provide a topographic map of prefrontal functions. Such a map would be largely antithetical to the model itself, at least with regard to higher cognitive functions, which are essentially integrative and therefore not localized. However, the model goes a long way toward providing a useful *explanation of the principles* of prefrontal function, as enumerated above. That explanation reconciles the two most prevalent and competing views on the subject. One of these is the modular view, with roots in sensory and motor physiology and suggested by lesion data; it divides the prefrontal cortex into a finite number of areas specializing in discrete cognitive or emotional functions.

The other is the network view, based on the principle that prefrontal representations, that is, executive memories or *cognits*, are widely distributed, spread over and unite various combinations of modular-like action and perception cell groups. These networks are made of associations that are dynamically established and modified by learning and experience. All prefrontal functions, executive and emotional, rely on the orderly activation of these networks in the organization of goal-directed, purposeful actions. In the past two decades, this view has gained substantial support from physiological and imaging studies.

Therefore, in the light of the available evidence, the debate about the functional homogeneity or heterogeneity of the prefrontal cortex becomes idle, for both hold some validity depending on the level of analysis. At the level of neuroanatomy, the different connectivity of prefrontal areas suggests that these areas serve different functions. As we have seen, data from neuropsychology and electrophysiology also point in that direction. However, several of the functions that these data support (e.g., monitoring, working memory, error correction, or set shifting) can be rightfully viewed as components of a more global function, that is, the temporal organization of behavior (hence the title of this chapter).

At the level of particular behaviors and motor domains, some topographic specificity of prefrontal function is apparent. That kind of specificity is even apparent for certain cognitive functions, such as working memory. These functions, however, serve a wide range of motor and cognitive activities, from eye movement to speech and reasoning, and cannot be localized anatomically. In practically all instances they serve the more general purpose of ordering sequential actions toward a goal, whatever that goal may be.

In a broad sense, the prefrontal cortex is “action cortex,” “doer cortex,” like the rest of the cortex of the frontal lobe. This does not mean that we can assume, as has been frequently done, that the prefrontal cortex is the highest doer cortex, the central executive, the ultimate decision-maker or the causal initiator of action, and even the center of will. For one thing, this approach leads inevitably to an infinite regress, as does the assumption of any form of high-level executive agency anywhere in the brain. Indeed, such an approach raises inevitably the question of what other entity supervises that putative executive and, in turn, what other entity supervises that other one, and so on.

A more reasonable approach is to place the prefrontal cortex and all its areas in the parallel and circular paths of the perception-action cycle, where there is no true origin, cortical or subcortical. In that position, the prefrontal cortex works as an integrator of current inputs from cortical and subcortical sources, capable of feeding signals forward to effectors as well as receiving feedback from them. The prefrontal cortex therefore operates under continuous constraints from experience (long-term memory), from the neural substrate of instincts and emotions, from current sensory input and motor output, and from feedback of both receptors and effectors.

In any case, the organism cannot produce any sustained series of goal-directed actions, except the most automatic and routine, without

mediation by the temporal integrative functions of the prefrontal cortex. Consequently, it is justifiable to attribute to the prefrontal cortex the cognitive infrastructure of goal-directed action. This infrastructure is made of distributed, overlapping, and interactive neuronal networks. At low levels of their hierarchical organization, these networks are innate (phylogenic memory); at higher levels, they are formed by associative synaptic modulation through life experience. To understand the neurobiology and properties of these networks it is indispensable to understand the temporal-integrative functions of the prefrontal cortex.

This chapter deals with the anatomical and physiological nature of these functions, not only in the prefrontal cortex but also in the neocortex at large. This comprehensive treatment of cortical cognition is essential, because all cognitive functions of the prefrontal cortex are dependent on its close interactions with other cortices, as well as several subcortical structures. That interdependence is a direct consequence of the widely distributed and interactive character of cortical cognitive networks. Thus, the first objective of this chapter is to describe these networks in terms of their neurobiology, distribution, and hierarchical organization, and the associative character of the memory that they contain, represent, and enact.

Following a line of reasoning substantiated elsewhere (Fuster, 2003, 2009; Fuster and Bressler, 2012) and here further (see Section II), it is maintained that all five essential cognitive functions of the human brain, that is, attention, perception, memory, intelligence, and language, consist of neural transactions between and within the cognitive networks of the cortex, which I call cognits. The concept is further explained in Section II. Here follows a brief précis.

Cognits are units of knowledge and memory. (In the ensuing text the terms “cognit” and “cognitive network” will be used interchangeably.) They are formed by the strengthening of synaptic connections between neuronal groups

that are stimulated by temporally coincident inputs from sensory or proprioceptive receptors. A cognit is therefore a network of cortical neurons formed by connective association between the sensory and/or motor constituents of a given experience. The main characteristics of cognits, which distinguish them from "Hebbian assemblies" (Hebb, 1949), are as follows: (1) cognits have a wide distribution – a cognit can extend widely over large areas of cortex that are not necessarily contiguous; (2) cognits are hierarchically organized; and (3) cognits overlap and interact profusely, sharing nodes of association. An individual cognit, encoding a percept, a memory, or an action, is defined by a network made of relatively solid and stable synapses, established by repetition and usage. It is surrounded, however, by a penumbra of weak and unstable associations with other cognits, overlapping with one another or far apart. The reinforcement of that penumbra may be of definite value in the rehabilitation of cognits impaired by age, trauma, or illness.

The executive functions of the prefrontal cortex are variants, components, or combinations of temporal-integrative cognitive functions using these networks or cognits to serve the organization of novel goal-directed action. Because the objective of goal-directed actions is largely in the future, it follows that cognitive prefrontal functions devoted to that organization should have a prospective aspect; hence the general inference that the prefrontal cortex is a predictive and preadaptive structure (Fuster and Bressler, 2015): it proactively adapts to predicted changes.

From the empirical evidence gathered in this volume, the following executive functions emerge as cardinal for the temporal organization of new behavior or of old behavior in a new context. The first is planning; the second, attentional set (both perceptual and executive); the third, working memory; the fourth, decision-making; the fifth, the dual function of error monitoring and avoidance; and the sixth,

inhibitory control. All have excitatory as well as inhibitory components (the last by definition). As we have seen in previous chapters, none can be safely localized in any particular area of prefrontal cortex, although there is a certain area of dominance for each. That dominance depends not so much on the function itself as on the particular cognitive content (the cognit or cognits) with which it operates at any given time. Thus, for example, a dominant focus of electrical or metabolic activity in the lateral prefrontal cortex during a spatial working-memory task is not a sign of the localization of that memory function in that cortex, but rather a sign of an active net that in its associative ensemble encodes the task and its spatial content.

None of these temporally organizing functions of the prefrontal cortex, however, which mainly involve cortex of the frontal convexity, is exempt from influences from the brainstem and the emotional or limbic brain. At all times, the level of alertness and motivation, as well as the exigencies of the biological drives, modulate these cognitive functions as they engage in coordinating behavior. Furthermore, in the temporal organization of any behavior, the cognitive and the emotional "inform" each other about risks and values, and interact with each other principally in orbitomedial prefrontal cortex, which is the crossroads of both cognition and emotion.

In general, it is the generic, action-related character of executive and emotional prefrontal functions that, despite the obstacles in localizing them, allows us to draw inferences about them that appear valid for several animal species. Indeed, although the discussion in this chapter is centered on the prefrontal cortex of primates, it stands to reason that the basic functional principles discussed below also apply to other kinds of mammal.

One biological principle that applies to all higher species and which the prefrontal cortex supports is that of the perception-action cycle, a principle that regulates the organization of all

goal-directed actions in the temporal domain. The perception–action cycle, as we will see, is the circular flow of information between the organism and its environment in any sequence of actions toward a goal. The prefrontal cortex is the supreme temporal integrator of action at the summit of the cycle.

Nevertheless, there are valid reasons to conclude that the various frontal functions described here are not equally shared by different species, as the anatomy differs, homologies become uncertain, and behaviors are to a high degree species specific. That specificity is most evident in two forms of activity that are characteristic of the human and in which the prefrontal cortex is profoundly involved: language and creative intelligence. After discussing them in separate sections, this chapter closes with a few neurophilosophical reflections on two other subjects that are key to the human “agenda” and thus germane to prefrontal physiology: consciousness and free will.

## **II. HIERARCHICAL ORGANIZATION OF COGNITIVE NETWORKS (COGNITS)**

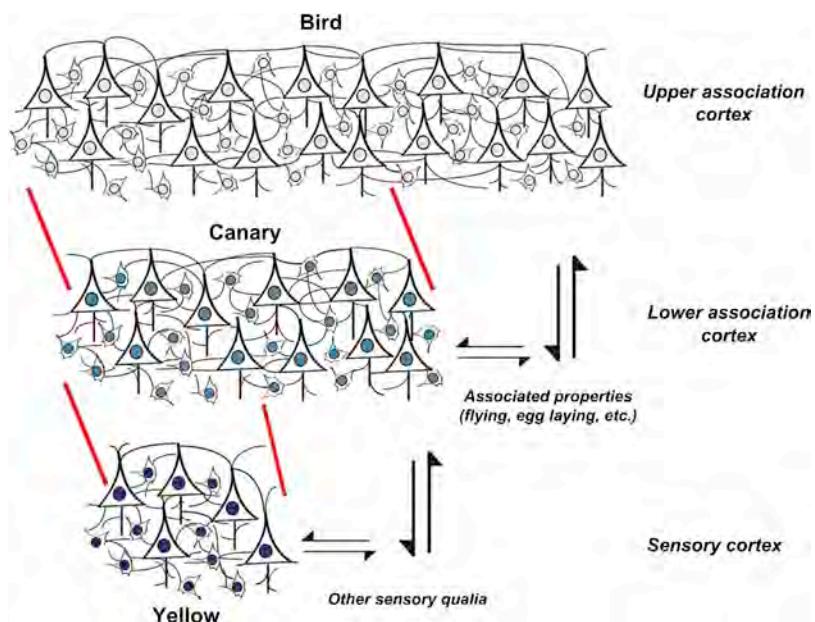
In all mammals, the nerve axis is divided lengthwise into two major moieties, each devoted to one of the two quintessential functions of the nervous system: a posterior moiety for *sensing* and an anterior one for *acting*. This dichotomy prevails at all levels, beginning at the lowest, in the spinal cord. (Arguably, the cerebellum is an exception, although it has both sensory and motor functions.) As first noted by [Betz \(1874; see Chapter 6\)](#), the dichotomy extends upward into the cerebral cortex where, in primates, the areas behind the central sulcus (rolandic fissure) are dedicated to sensation and those in front to movement. This applies to cognitive functions as well, for the cortex of the parietal, temporal, and occipital lobes (PTO cortex) largely supports perception

and perceptual memory, while the cortex of the frontal lobe supports action and executive or motor memory. Indeed, the frontal cortex is “motor cortex” in the broadest sense of the expression. It supports the actions of the organism and the cognitive and emotional processes that mediate them.

### **A. Perceptual Cognits in Posterior Cortex**

Most of our behavior is anchored in experience. Much of it consists of learned habits, that is, sequences of more or less automatic responses to internal and external stimuli. Some of it, however, most characteristically in our species, depends not only on habit but also on educated choices, and leads to the purposeful creation of new changes in the environment and new relationships between that environment and ourselves. This form or part of behavior can be appropriately called deliberate, for it is guided by the cognitive deliberation of alternatives, expected risk and value, and deliberate purpose. Most certainly, it requires the proper function of the cerebral cortex, because it is in the cerebral cortex that the representations of individual sensory experience and behavioral action reside – after acquisition through intervention, still unclear, of the hippocampus.

In humans and other primates, the postcentral (postrolandic) cortical areas are largely devoted to perceptual memory and processing and to the representation of sensory images and constructs of the external world. There is substantial evidence that the memory storage and processing of perceptions are functions of large networks of interconnected neurons of posterior cortex. These perceptual networks or cognits ([Fuster, 2009](#)) transcend anatomical areas and modules by any structural definition. They are, however, hierarchically organized ([Figure 8.1](#)); that is, depending on their sensory content, their complexity, and their level of abstractness, perceptual memories are



**FIGURE 8.1** Highly schematic diagram of the architecture of a perceptual cognit with three arbitrary levels of hierarchical categorization (abstraction).

represented by neuronal networks at various levels in orderly hierarchies of interconnected areas. The development of these hierarchies begins at the bottom, in sensory cortices, and progresses upward into cortices of association (see Chapter 2).

How are perceptual networks formed? Based on the experimental evidence reviewed elsewhere (Fuster, 1995, 2003, 2009), it can be concluded with considerable certainty that these networks are made by association, in accord with Hebbian principles (Hebb, 1949), especially the principle of synchronous synaptic convergence (Hebb, 1949; Fuster, 1995), which Hayek (1952) also postulated in his seminal book "The Sensory Order". In other words, perceptual memory is made of neuronal assemblies of the cortex representing sensory inputs that are associated with one another by temporal coincidence. The co-occurrence of these inputs enhances the synaptic connections between assemblies, thus forming new

relationships between them. Therefore, a new memory represents not so much the aggregate of the assembly representations as the relationships between them: the memory code is a relational code in cortical space. Consequently, one neuron or group of neurons in the cortex can be part of many memory networks. The idiosyncrasy of our memories derives from the practically infinite combinatorial power of our innumerable cortical neurons.

Genetic factors play a critical role in the formation of cognitive networks. Both genotype and phenotype provide what we could call the cognitive infrastructure on which these networks, our cognits, are formed. Edelman (1987) aptly articulates the process of cognitive network formation in his theory of *group selection*. According to him, the interactions of the organism with its environment lead to a selective reduction and specialization of certain groups of neurons (network nodes) out of the primordial oversupply of neuronal elements available at

birth. Both the oversupply and selective reduction (pruning) of formal neuronal elements are well documented in neurobiology. The selection, according to the theory, would occur as a result of the “Darwinian” competition for inputs between neuronal groups as the organism dynamically adjusts to its environment. From that theoretical construct it is reasonable to infer the plausible corollary that the process takes place, at least in part, by intervention of Hebbian principles of memory formation, especially the principle of synchronous convergence.

Whereas new cognits are largely made of co-occurring sensory inputs, internal inputs from pre-existing memories also participate in the making of these new cognits. These are inputs from long-term memory networks that have been evoked and reactivated by the sensory inputs; in this manner, the incoming sensory inputs will establish new associative links with old established ones. Thus, new memories, or new networks, are expansions of old ones. For example, the making of a new acquaintance with a person in a familiar environment will incorporate the memory of that new person into an old memory network that contains the memory of that environment. The memory of the new person, with all its perceptual and semantic components, will also contain the memory of the familiar environment in which we have met her, with its perceptual and semantic components. The two will reinforce the associations within each and with each other. Thus, the memory retrieval of either will be made easier by the presence of the other, and conversely more difficult in its absence. That is the reason why sometimes we encounter difficulty in recognizing a person out of the context in which we met her or commonly see her.

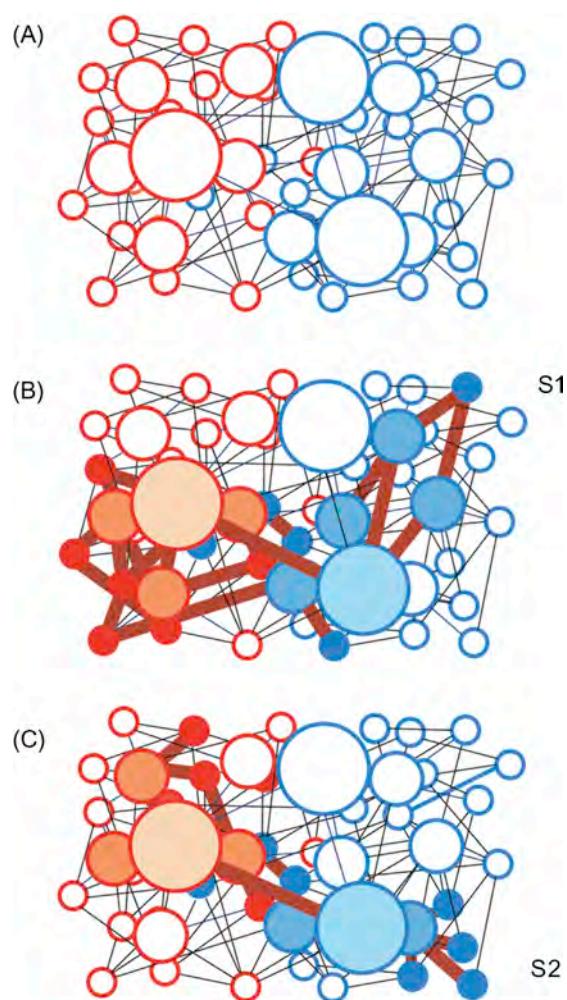
The formation of memory networks in the cerebral cortex follows rather definite gradients or directions. These are basically three: phylogeny, ontogeny, and connectivity. All three follow the direction from primary sensory to association areas of the cortex. By mechanisms

that are still unclear, the hippocampus, through connections with associative cortices, seems to play an essential role in the process of memory formation (Fuster, 1995; Albouy et al., 2013; Pezzulo et al., 2014; Takehara-Nishiuchi, 2014). The formation of new memory networks on top of older ones, from primary to associative cortex, leads to the “stacking” of broader networks representing progressively more abstract and more categorical knowledge and memory in hierarchically higher areas of posterior cortex. Consequently, in that hierarchy, unimodal sensory memories lie at the bottom, just above primary sensory areas, which themselves constitute a form of memory: sensory phyletic memory or “memory of the species.” The latter is simply the physical structure of primary sensory cortices. It is inborn structural “memory,” genetically acquired, that has been formed in evolution with adaptation of the organism to its environment. Phyletic sensory memory, that is, the structure of primary sensory cortices, is a kind of memory that is rehearsed during certain critical periods at the beginning of life and is later retrieved with every perceptual act.

Phyletic sensory memory, the network structure of sensory cortices, is at the base of the perceptual memory hierarchy. All other forms of perceptual memory networks grow on that base. At successively higher levels lie the networks of unimodal and polysensory memory, episodic memory, semantic memory, and conceptual memory (Figure 8.1). Thus, the progressively higher layers of the perceptual hierarchy accommodate progressively more widespread networks that represent progressively more abstract and complex information acquired through the senses. In other words, individual memories diverge and overlap with one another, forming net-like structures that are antithetical to the absurd concept of the “grandmother cell.” (We could in theory speak of “grandmother networks,” except that such networks would contain associations with all conceivable aspects of a personal or generic grandmother.)

Perception and memory share to a large extent the same networks. Thus, perceptions are processed through pre-established memory networks. This is the neural foundation of the intimate relationship between perception and memory at the phenomenological level. We not only remember what we see, but also see what we remember. We see the world the way we know it, the way we have learned to see it (Helmholtz, 1925; Hayek, 1952; Bruner, 1973). In a similar manner to the formation of memory networks by association, their retrieval in perception is an associative phenomenon. At its root is the processing of sensory information through the hierarchically ordered areas of posterior cortex and the neuronal networks (memories) that they harbor.

Certain percepts elicit the representation of behavioral acts that in previous experience have become associated with them. Action has become part of representative cortical networks much as other associated properties of any sensory stimulus or group of stimuli. This is probably made possible by associative connections formed through basically the same processes of co-occurrence and synaptic facilitation that form perceptual memory. However, whereas perceptual memory mainly resides in posterior cortex, motor memory – that is, the representation of action – involves the anterior (frontal) regions of the cerebral cortex. The extension of a perceptual network or cognit to represent action may occur when, by way of collateral and terminal connections, neural impulses from posterior cortical areas reach and recruit neurons in frontal regions. Just as in posterior cortex, where the areas involved in sensory analysis are also involved in perceptual representation, frontal areas are responsible for the representation as well as the organization and execution of action. Figure 8.2 illustrates schematically the structure and dynamics of perceptual and executive cognits in the retrieval of memory or knowledge (which is semantic memory) for cognitive function.



**FIGURE 8.2** Structure and dynamics of perceptual and executive cognits in the retrieval (activation) of hierarchically organized memory/knowledge. (A) Hierarchies of perceptual (blue) and executive (red) cognits of different sizes and hierarchical levels (three sizes and levels are arbitrarily chosen; thin lines indicate bidirectional connections; blank circles represent cognits of long-term memory in resting state). (B) Stimulus 1 (S1) activates a large distributed cognit made of smaller, more localized cognits connected by excitatory pathways (large maroon lines). (C) Stimulus 2 (S2) activates another large cognit and its nested components. Cognits 1 and 2 are partly heterarchical and share common nodes.

## B. Executive Cognits in Frontal Cortex

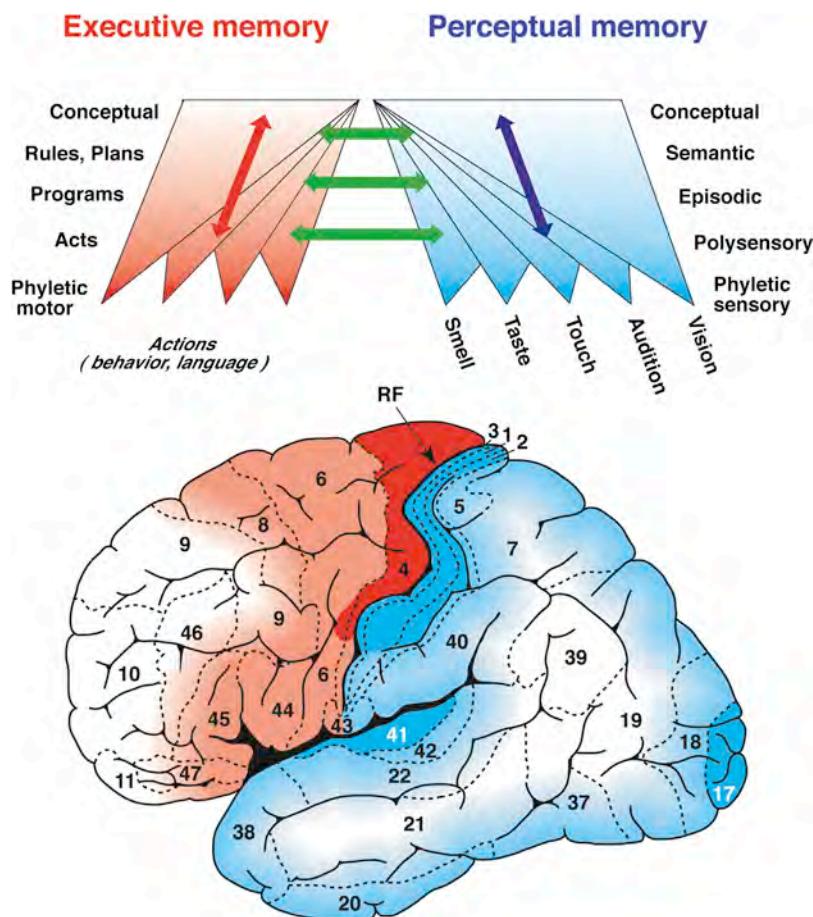
As in posterior cortical areas, frontal areas are hierarchically organized along connective and ontogenetic gradients (see Chapter 2), and so are the cognitive networks that they harbor. At the lowest stage of the frontal hierarchy for representation and processing of action is the primary motor cortex. Above it lie the premotor areas, 6a and 6b, including the supplementary motor areas, and above these are the lateral areas of the prefrontal cortex. As discussed later in this chapter, motor memory is also hierarchical, like perceptual memory, and motor memories are represented in order in that hierarchy of frontal areas. Moreover, in a similar fashion to perception being processed hierarchically in the posterior cortical sector, so is action processed in the frontal sector hierarchically. The execution of motor actions results in large part from the retrieval (“recall”) of motor memories, that is, of executive networks or cognits in the frontal lobe, and from their role in preparing the motor apparatus for their re-enactment.

Despite the noted similarities, there are differences between the two cortical hierarchies, posterior and frontal, that support perception and action, respectively. Whereas in posterior cortex the main connective flow departs from primary (sensory) processing areas, at the lowest cortical level of the perceptual hierarchy, and proceeds through association areas, in the frontal cortex the trend is in the reverse direction. Here, the main connective flow departs from associative (prefrontal) areas, the highest cortical level of the motor hierarchy, and proceeds through premotor cortex toward a primary (motor) processing area. Both pathways contain, and necessitate for proper processing, reciprocal feedback connections between the successive stages that constitute them. This feedback may play an essential role in the correction of prediction error (see Error

Monitoring and Avoidance, in Section IV) and the formation of new executive networks.

Indeed, theoretically, the formation of executive cognits in the frontal cortex requires the associative co-occurrence of inputs from the effectors of movement. Some of these inputs may come, through the thalamus, from proprioceptors at muscles and joints. In addition, however, other contributing inputs come from the neural structures of the motor system itself (e.g., motor cortex) in the form of what has been termed “efferent copies” or “corollary discharge.” These are collateral monosynaptic or polysynaptic outputs from pyramidal cells that, when a movement is produced, are directed to other motor and sensory structures to prepare them for further actions and their consequences. [Teuber \(1972\)](#) hypothesized that corollary discharge is the essence of prefrontal function. As we will see later in this chapter, corollary discharge is an important component of the perception–action cycle, regulating the relationships between current and expected input and output.

Thus, the formation of executive networks in the prefrontal cortex probably follows the same Hebbian principles ([Hebb, 1949](#); [Hayek, 1952](#)) as that of perceptual networks in posterior cortex. The key principle, in this author’s view ([Fuster, 1995](#)), is that of synchronous synaptic convergence. As noted earlier with regard to sensory memory, the hippocampus plays a critical role in the synaptic modulation at neocortical sites that mediates the formation of memory networks. From the anatomical evidence of hippocampal efferent connections to the prefrontal cortex (see Chapter 2), it is reasonable to infer that the hippocampus acts in similar fashion on frontal networks to mediate the formation of executive cognits. Presumably, hippocampal inputs mediate the formation of executive cognits in the prefrontal cortex on the basis of the co-occurrence of proprioceptive



**FIGURE 8.3** Schematic diagram of the hierarchical organization of memory networks (cognits) in the human cortex, lateral view of left hemisphere. Bottom: Brodmann's cytoarchitectonic map. Abbreviation: RF, rolandic fissure. The posterior cortex is shaded blue to white from primary sensory to association areas, the frontal cortex red to white from primary motor to prefrontal cortex. Top: Gradients of development and of organization of cortical cognits, with the same color code as in the map below. Bidirectional arrows symbolize: blue, perceptual corticocortical connectivity; red, executive corticocortical connectivity; green, reciprocal connectivity between posterior and frontal cortices. Note the increasing span and overlap of networks as they develop from the bottom up. As they grow upward in the hierarchy, nets become more widespread and represent progressively more abstract memory and knowledge.

inputs, efferent copies, and corollary discharge. In this manner, motor and executive networks or memories of various degrees of complexity and abstraction are acquired and deposited at various levels of the frontal hierarchy. Furthermore, as in posterior cortex, the incoming inputs interact and associate with established long-term networks, in this case

executive memory networks that are retrieved, activated by these inputs. Thus, here too, we have new memory expanding old memory at all levels of the hierarchy.

In a broad sense, the frontal hierarchy is the mirror image of the posterior hierarchy (Figure 8.3). In both hierarchies, simple representations lie at the bottom, the most abstract at the top.

However, also in both hierarchies, our stacking of cognit categories, while heuristically useful to establish a general principle of organization, cannot be taken too rigidly, in either structurally or functional terms. In reality, as is most apparent on phenomenological analysis, there is no clear-cut separation between cognit categories. Their networks are mixed; they contain component neuron populations at several hierarchical levels. This is in part understandable if we consider how cognitive networks are formed, from the bottom up. At any level, networks maintain ties with lower level, simpler, networks that contributed to their formation and stay nested within them. As a result, there is no pure memory of any category. Semantic memory, for example, is made from the bottom up by instantiations of lower level experiences (e.g., episodic, polysensory); the contributing lower level memories will become an inextricable part of the higher networks. In fact, the reactivation of lower level cognits will serve as associative access for the retrieval of the higher ones. Similarly, in the executive hierarchy, simple movements and their representations will contribute to the formation of larger (higher) motor-action representations. They will also become an integral part of their enactment. In other words, the hierarchical organization of memory networks is a solid general principle with a solid neurobiological base, but in both the representational and functional content of these networks, perceptual as well as executive, there is a considerable degree of what we may call *heterarchy*, that is, interaction between hierarchical layers.

The representational and functional symmetry of the two large cortical regions separated by the central sulcus in the primate brain is undoubtedly of deep biological significance. It has a deeper phyletic root than the functional differences between the two anatomically symmetrical cortical hemispheres in humans. The evolutionary development of ever-higher areas of association, in posterior as in anterior cortex, reflects the opening up of

ever-greater possibilities for abstract (i.e., symbolic) perception and for elaborate and deliberate goal-directed action. These possibilities reach a maximum (or, we might say, infinity) in the human, where the development of two large associative regions, one posterior and the other prefrontal, provides the cortical substrate for logical reasoning and for the understanding and expression of language. This evolutionary expansion of possibilities extends into the temporal domain. This is most apparent if we consider the temporal integrative functions of the prefrontal cortex that derive, as we have repeatedly stated, from its representational capabilities; that is, from the richness of its cognitive networks, its executive cognits. Part of that richness lies in the capacity to represent the future.

Arguably, in functional terms, nothing distinguishes the prefrontal cortex from other cortices, and especially the prefrontal cortex of the human from that of other animals, as much as its capacity to represent the future and prepare the organism for it; to preadapt to it, proactively (Fuster, 2014). As we will see in the ensuing pages, it is probably correct to say that all of the cognitive prefrontal functions “look to the future”; the future is implicit or explicit in all of them. It would probably be even more correct to say that every identified function of the prefrontal cortex has a past perspective and a future perspective. Every one of these functions is based on representations of the past for an action sometime in the future, however proximate or remote. It is that future perspective that imparts teleology to prefrontal functions. At variance from conventional scientific methodology, it is practically impossible to understand causality in frontal physiology without teleological reasoning. Such reasoning calls for cognitive networks representing actions that will or could occur; in other words, prospective or potential cognits. This is where the concept of the “memory of the future” (Ingvar, 1985) comes in. We will encounter it repeatedly in the course of this chapter.

### III. FRONTAL ACTION DOMAINS

Whereas it is not possible to ascribe any emotional or cognitive function to any discrete portion of the frontal cortex, it is possible with current knowledge to ascribe cognitive network *content* to the hypothetical hierarchy we have traced on the lateral surface of the human frontal lobe. By this we mean that there are relatively well-defined domains within that hierarchy that appear to specialize in one or another aspect of emotion or motility. Therefore, we can do some tentative mapping of the frontal cortex, not in terms of specific functions or processes, but rather in terms of the nature of the cognits or memories that these non-localizable functions use. If we do that, then the monolithic executive hierarchy depicted in [Figure 8.3](#) for heuristic purposes becomes fragmented into component hierarchies for one or another category of actions. Each of these hierarchies, like the general one depicted in the figure, is oriented upward and expands from primary motor areas toward prefrontal cortex. Thus, a degree of topography is compatible with both the hierarchical organization and the associative networking of executive content. In any case, we must carefully distinguish cognitive content from cognitive function. In the prefrontal cortex literature, one is often confused with the other.

The evidence reviewed in previous chapters points to some separate hierarchies for separate action domains in the primate's frontal cortex. Each action domain would provide the neural substrate for the representation and processing of a different category of movements. It is even possible to trace within it the neural connectivity that supports the information flow in that hierarchy. The topographic segregation by action domain, however, does not appear to be complete; certain areas seem to be shared by different domains, suggesting functional interactions between domains. At any rate, with the evidence available, no neat borders can be

traced between them, but the principles of their organization can be inferred with confidence.

Based on the evidence in Chapters 2 and 4–7, let us attempt to outline, however coarsely, three different action domains – and hierarchies – on the lateral frontal cortex: the domains for skeletal motility, ocular motility, and speech.

*Skeletal motility* has its base in area 4 by Brodmann's terminology, that is, the precentral primary motor cortex (M1), which constitutes the anatomical substrate for movements of the head, trunk, and limbs. Right above that cortex, in the hierarchy for the representation and processing of skeletal movements, is the premotor cortex of area 6, and above this is the cortex of prefrontal areas 8, 9, 10, and 46. Whereas in area 4 there is a degree of somatotopy, in the premotor and prefrontal cortex, actions are represented at a more global level, by goal and trajectory of movement and across muscle groups. Furthermore, a corollary of this author's general tenet on how memory networks are organized is that, in these higher cortices, the represented actions are more abstract, and at the same time more personal, peculiar to the individual organism. That would apply not only to the memory of past actions but also to the "prospective memory" of planned or imagined actions.

In the premotor cortex of the monkey, Rizzolatti and his colleagues discovered the "mirror neurons" ([Rizzolatti et al., 1996](#); [Rizzolatti and Craighero, 2004](#)). These are a particular type of neurons that are activated when the subject performs a given motor action, as well as when it observes another subject perform the same action. The role of such neurons or of the presumptive system of which they are a part has been the subject of considerable speculation, much of it unfounded. To quote [Rizzolatti \(2005\)](#),

[T]he question of which is the function of the mirror neurons or of the mirror-neuron system is ill posed. Mirror neurons do not have a specific functional role. The properties of mirror neurons indicate that [the] primate brain is endowed with a mechanism for the pictorial description of actions ...

If we extend the adjective “pictorial” to include sensory modalities besides vision, that interpretation coincides with my view of the neurons that constitute a frontal executive cognit or network. These neurons, in their ensemble, encode specific actions. As such, the cells participate in both the representation and the reproduction of an action – or several actions. Thus, mirror neurons epitomize, in the premotor cortex, the Jacksonian principle of the identity of representational and executive substrates that guides the reasoning in this chapter on the functions of the prefrontal cortex, especially its dorsolateral convexity, except that in this cortex, actions are more global, more broadly defined than in premotor cortex, and extend beyond the skeletal musculature.

The hierarchical domain for *ocular motility* does not seem to have a base in M1 (conceivably its base is subcortical, in the superior colliculus, which is a cortical homolog in lower species). The lowest frontal representations of eye movements are in areas 8 and 6 (oculomotor supplementary motor area). From these, the hierarchy and the connectivity for eye movement extend upward into areas 9 and 46. In these areas of the monkey’s cortex, as the research by Goldman-Rakic (1995) and her collaborators demonstrates, the representational memory of visual locations can be found. Neurons in these areas of the prefrontal cortex take part in the working memory of visual locations for the integration of goal-directed eye movements. These neurons provide a clear indication that, in the prefrontal cortex, network representations of eye movement blend with a wider network representation of a working-memory task with all its sensory, motor, and reward components.

The frontal hierarchy for the representation and processing of *speech* has its base in the oropharyngeal subarea of M1. Above that, in uncertain hierarchical order, are some premotor areas (including the supplementary motor area) and areas 44 and 45, which constitute Broca’s area in the left hemisphere. Again, prefrontal

areas (46, 9, 10) lie above and beyond, harboring the upper stages of the speech hierarchy for the representation and organization of elaborate and abstract speech.

In each action domain, the more specific and concrete aspects of action are represented in the lower levels of its frontal hierarchy. Accordingly, area 4 represents elementary muscular movements. The neuronal networks in this area can be said to store the motor memory of the species, in other words, the motor component of what we term *phylectic memory*. This is the aggregate of cortical representations of essential movements that the species has developed in the course of evolution, possibly by similar mechanisms to those that mediate the formation of individual memory, only on a much longer timescale. Phyletic memory can be called “memory” because it is a fund of information that the species has acquired about itself and its relations with the world. It too, like individual memory, is “recalled” to fulfill the adaptive needs of the organism.

More complex actions, those that the individual has learned to perform after birth, are represented in hierarchically higher areas of frontal cortex. These are no longer defined by elementary movement but by trajectory or by goal. Some are temporally extended; they are sequential. The evidence in Chapters 4–6 places them in premotor and prefrontal cortex, whether the sequences are of skeletal or ocular movements. The same is true, within its domain, for the spoken language. Phonemes and morphemes may be represented in primary motor cortex and Broca’s area, but speech sequences are in some form, and at some time, represented in premotor and prefrontal cortex. This can be inferred from the apparent role of these cortices in the construction of speech (see Chapters 5 and 7).

In general terms, we can conclude that, in primates, the more complex and global aspects of behavioral action are represented in the anterior and lateral areas of the cortex of

the frontal lobe, that is, in the upper stages of the frontal hierarchies for the various action domains. Considerable support for this notion lies in the evidence that lesions of these sectors of cortex result in the absence or failure of temporally extended programs of behavior (see Chapters 4 and 5). Additional support lies in the electrophysiological evidence of neuronal activity patterns in these cortices, which temporally span the entirety of these behavioral structures (Chapter 6). In the human (Chapter 5), there is also evidence that lesions of the lateral prefrontal cortex result in a general constriction and concreteness of behavioral structures, as well as difficulties in their planning. Moreover, as we have seen (Chapter 7), metabolic activity has been shown to increase in prefrontal areas during the conceptual planning of complex motor acts.

Not all the constructs of action, however long and complex, are represented in the prefrontal cortex; certainly not the stereotyped instinctual routines or the sequences of automatic and well-rehearsed acts. Animals without prefrontal cortex can perform both. Thus, such routines and sequences are not represented there. In Chapter 4, we have seen that animals with prefrontal lesions have difficulty learning delay tasks, but with extensive training they do eventually learn them, although they can never perform them with long intratrial delays. The fact that they learn one such task, however, indicates that the basic construct of the task, the procedural memory of it, is stored in other structures, not in the prefrontal cortex. Neuroimaging evidence (see Chapter 7) indicates that the prefrontal cortex intervenes in the representation and performance of a sequential task only during the initial stages of learning. Afterward, we are led to assume, other structures take over. The engram of the task, the procedural memory of it, seems to have migrated elsewhere, possibly to hierarchically lower structures (e.g., premotor cortex, basal ganglia).

What seems, therefore, to be represented in prefrontal areas are the relatively *novel*

variants of old structures of action, in whatever the domain. The novelty of a structure may be determined by the need to adapt to changes in the environment, or it may be generated by the individual in creating the mental image of a new program of action, a new plan. Therein probably lies the role of the frontal lobe in creativity (see *Imagination and Creative Intelligence*, in Section VII, below). It should be noted, however, that a behavioral structure formed by the agency of prefrontal cortex, and presumably represented in it, need not be all new; in fact, most of its component acts and context are, most likely, pieces of old repertoires. What makes the structure novel and puts it under the purview of this cortex are the new contingencies and uncertainties it contains. This is what makes the organism treat it as new, even though its components may be old and familiar.

A structure of action is a *temporal gestalt*, like a melody. Temporal gestalts obey the same laws that govern spatial gestalts ([Koffka, 1935](#); [Wertheimer, 1967](#)). One of them is the law of proximity: close or contiguous elements are treated as parts of the same configuration, whereas distant elements are not. Here, what gives cohesion to the gestalt of action is not only the temporal proximity of the individual acts that constitute it, but also their goal. Furthermore, the temporal gestalt we are dealing with is a composite of sensory percepts as well as motor acts. Perceptual and motor acts are intertwined in the perception-action cycle (see section later in this chapter) to form together the gestalt.

The central representation of that gestalt of action is the equivalent of what many writers call the *schema*. The schema stands for the plan or program of action. It does not represent all of its elements and steps, however. It is an abridged, abstracted, representation of that plan or program, which may contain some of its components and also contains, in some manner, its goal. The schema here is nearly identical

to Piaget's "schema" (1952) or Neisser's "anticipatory schema" (1976). It is what some cognitive psychologists have called a "script" or "memory organization packet" (Schank and Abelson, 1977; Grafman et al., 1995). It is reasonable to assume that novel schemas, plans, and programs are represented in executive cognits, that is, in large-scale networks of premotor and prefrontal cortex that cross over several domains of action. Further, it is reasonable to assume that their frontal representation is a precondition for their enactment, as they are to guide actions to their goal. As mentioned in Chapter 5, Luria proposed that the schemas of action consist of linguistic commands or syntheses ("presyntheses") that are located in prefrontal cortex and from there regulate behavior (Luria, 1973). This ascribes to the schema the symbolic and abstractive power of language, something which is conceivable in the human but not in other animals.

There is a biologically critical action domain in the prefrontal cortex that does not appear to be hierarchically organized: the domain for emotion. From the evidence in previous chapters, we know that this domain extends mainly through the medial and orbital aspects of the prefrontal cortex. There are two major foci of representation within it. One is the orbital cortex, which is intimately and reciprocally connected with limbic structures, especially the amygdala, the hypothalamus, and the monoaminergic systems of the brainstem. Through these structures, orbitofrontal networks collect diverse visceral inputs (see Chapter 6), as well as inputs conveying information related to basic drives, general states of the organism, and the motivational significance of sensory stimuli. It is mainly in orbitofrontal cortex that information about actual and expected rewards is collected – through the dopaminergic system – and funneled to the rest of the prefrontal cortex to drive and shape behavior. Thus, the orbital action domain is critically involved in emotion in two major ways: (1) by

acting on the cognitive networks of the cortical convexity to promote reward-seeking behavior; and (2) by acting on subcortical structures (nucleus accumbens, hypothalamus, striatum, etc.) and the autonomic and endocrine systems to support and control the major drives of the organism.

The other major focus of the prefrontal emotional domain is the anterior cingulate cortex. Lesions, electrophysiology, and imaging point to this area as an important node in a cortical network that is involved in attention, especially effortful attention, reward, and the success in obtaining or failure to obtain a reward. These three types of neural involvement are consistent with the assumption of a monitoring function in that cortex (see below). The medial prefrontal cortex, anterior cingulate in primates, would be at least a part of a network monitoring the success or failure of challenging performance toward rewarding goals. In the light of our principle to attribute operational functions to representational frontal networks, it is reasonable to further assume that this monitoring network in medial cortex also takes part in error correction. The electrical evidence of error-correction potentials in anterior cingulate cortex supports that inference (see Chapter 6).

## IV. EXECUTIVE FUNCTIONS

The executive functions of the prefrontal cortex are commonly assumed to control the cognitive aspects of organized action through influences over other cortical and subcortical structures. For this reason, they are generally placed under the rubric of "cognitive control" functions. These functions, however, are not localized either in particular action domains or in networks or cognits within them. Again, it is necessary to distinguish a cognitive function from its representational content, and this distinction is not always easy. For example, because working memory can best be exposed

in sequential actions – skeletal or oculomotor – that are represented and integrated in the lateral prefrontal convexity, we may feel inclined to localize working memory, a major temporal integrative function, in that part of the prefrontal cortex. This ignores the evidence that (1) working memory integrates inputs from many cortical and subcortical regions; and (2) working memory is at least as widely distributed as those inputs in prefrontal cortex. Nonetheless, there is no denying that, whether by virtue of the type of information they ordinarily process or the behavioral paradigms most commonly used to test them, executive functions appear to have certain foci of dominance within the prefrontal cortex. We will deal with these foci as we discuss the functions one by one.

In any case, it is not possible to separate executive functions completely from one another, either on anatomical or on functional grounds. Again, as with the major cognitive functions (attention, perception, memory, intelligence, and language), failure to recognize the interrelatedness of executive functions leads almost inevitably to a frontal “phrenology.” For heuristic and operational reasons, we will describe executive functions separately, although in neurobiological terms the separation is largely artificial, and in anatomical terms only somewhat permissible by the presence of these apparent functional foci.

Nevertheless, there is one physical parameter, other than brain space, that to some degree separates and also unifies the executive functions of the prefrontal cortex: time. In the course of behavior or speech, there is a time at which one function takes precedence over the others, as that function is then especially critical and necessary for temporal integration. Thus, each function is preferentially deployed at a particular time.

On the other hand, there is a particular aspect of time that all executive prefrontal functions, without exception, “observe” and are oriented to: *the future*. All executive

functions are prospective: planning, attentional set, decision-making, and working memory by definition; the others (error monitoring, inhibitory control) by implication. Although all of them are based on past experience of one kind or another, the prospective feature is common to all and is what characterizes the prefrontal cortex as essentially a prospective and predictive part of the brain ([Fuster and Bressler, 2015](#)).

## A. Planning

As we ponder the evident importance of the prefrontal cortex in planning (see Chapter 5), we are struck by an apparent teleology in the physiology of this cortex. Indeed, its involvement in the formulation and implementation of plans of action seems to be dictated by future objectives and events. This apparent inversion of causality in the temporal domain, however, can be explained by the pre-existence in frontal cortex of executive cognits or representations of plans and rules that are associated with the plan formulated and executed at a give time. Their apparent location, according to imaging (see Chapter 7), is the frontopolar cortex.

However, plans are not conceived *de novo* in a vacuum. New plans are thoroughly anchored in established executive memory. A new plan is a rearrangement of that memory with a new set of objectives, a new order, a new timetable, and possibly a new ultimate goal. In any case, that plan is essentially based on old experience of prior actions. In a way similar to the way a new perceptual memory is formed in posterior cortex on a base of old memory (phylectic, episodic, semantic, or other), so is the prospective memory of a new plan formed in frontal cortex on a base of established executive memory. By current means, we have no way of knowing how that plan is represented in frontal cortex, least of all how its attributes of time and order are represented. Considering the organization of memory in the cortex, however, we are

compelled to assume that the plan is represented in the form of an executive frontal network or cognit that incorporates the schema of the plan, its essential action components, and its goal. We can further assume that the network representing the plan, as well as its components, is organized in hierarchical fashion. The abstract schema of the plan would be represented in higher prefrontal (perhaps frontopolar) regions and its more concrete elements of action in lower, premotor, and motor levels. Some of these concrete elements of action may not be represented in the cortex at all but, instead, in the lower levels of the executive hierarchy, such as the cerebellum and the basal ganglia. All in all, the plan is for the organism a way of imagining or creating the future by means of a new or reconstituted neural network. That network, like those that serve the other executive functions, can be appropriately considered a “memory of the future.”

In humans, lesions of the lateral prefrontal cortex cause deficits not only in the making of plans but also in their execution (see Chapter 5). As we have seen, these deficits are so characteristic as to be almost diagnostic of substantial lesion of that cortex. Based on what we know about prefrontal functions, we can conjure several reasons for the deficit in the enactment of a plan. The most apparent is a failure in temporal integration (see below). The frontal patient has difficulty in ordering actions toward a goal – or any of the subgoals under it – and, most conspicuously, in mediating cross-temporal contingencies. Temporal integration critically depends on these contingencies for the implementation of new extended goal-directed plans. There are many kinds of contingency within a plan. All are part of the perception-action cycle and as such will be discussed later. They include the dependencies between temporally separate elements, such as the formulated plan, the goal, the sensory inputs in the course of performance, and the individual acts in the pursuit of the goal.

As we have seen in Chapter 7, neuroimaging in the normal subject provides evidence of the activation of the prefrontal cortex and its networks in the formulation and execution of plans. Especially activated in motor planning are large portions of right and left lateral frontal cortex, as is the anterior cingulate cortex. Nonetheless, it is unclear how a plan of goal-directed actions, however represented in a hierarchy of frontal networks, unfolds in its enactment precisely in the order it does. Clearly, the prefrontal cortex is not needed, nor does it intervene, in all aspects of the execution of a plan. Many, probably the great majority of acts in a plan or script of action, are automatic, well rehearsed, and possibly part of daily routine. Others, however, including novel subroutines for the attainment of critical subgoals, undoubtedly necessitate the lateral prefrontal cortex.

In sum, the unfolding of the sequence of acts toward its goal engages the perception-action cycle, with the orderly intervention of its feed-forward, feedback, and monitoring mechanisms at all levels. The prefrontal cortex, at the highest level of the cycle, only intervenes whenever there is ambiguity of alternatives, uncertainty, or a difficult cross-temporal contingency to be mediated. In any case, the organism utilizes the same prefrontal substrate for the representation of a plan as for its enactment. Thus, the plan is another instance, on the grand scale, of how the same network that represents an action or a set of actions is in charge of its implementation; this highlights the validity of extrapolating that basic Jacksonian principle from motor cortex to the prefrontal cortex. Here, however, the action is much more complex, extended in the time domain, and widely distributed in a hierarchically organized frontal network.

## B. Attentional Set

To lead behaviors to their goal, the cortex of the frontal lobe makes use of a fund of general neural activation, largely of subcortical

origin, that can best be characterized as basic *drive*. Drive is the source of alertness or general attention, and of interest in the world and in the self. Drive determines the initiative and vigor with which the organism performs behavioral actions. It is provided to the frontal cortex in the form of modulating activity from the subcortical and limbic structures that have connective access to it, as well as other cortical regions (see Chapters 2 and 3). These structures include, most prominently, the reticular formation of the mesencephalon, the amygdala, the thalamus, the hypothalamus, and the monoaminergic systems of the brainstem.

Most voluntary and deliberate behavior is made of simple and automatic acts, old habits integrated at hierarchically lower cortices and basal ganglia. If the behavior is new and elaborate, however, its most critical constituents are the attentive acts that palpate the environment in search of significant clues, the intentional and elaborate movements, the continuous monitoring and updating of relevant information, and the referring of that information to the schema of the action and its goal. The arguably most rapid of the cognitive functions controlling these operations is attention, which on psychological and neurobiological grounds can be appropriately considered a specialization of basic drive.

In phenomenological terms, attention was aptly defined by [William James \(1890, pp. 403–404\)](#) as “the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought ... It implies withdrawal from some things in order to deal effectively with others.” In neurobiological terms, matching James’s definition, attention is the selective allocation of limited neural resources to the optimal processing of neural information. That selective allocation is accompanied by the inhibition of resources that not only are alien to, but also possibly interfere with, what is in the focus of attention at any given time. That focus may

be in the sensory sphere or in the motor sphere. There is sensory attention and motor attention; at higher levels, perceptual attention and executive attention. Consequently, the attentive preparation for expected sensory input is called perceptual set, whereas the attentive preparation for action is called executive set. They are the most nimble cognitive functions of the prefrontal cortex.

### **Perceptual Set**

Perceptual set is the selective anticipatory priming of a sector of the sensory system(s) for an expected sensory percept at the onset or in the course of goal-directed behavior or language. With the exception of automatic correction of prediction error (see Error Monitoring and Avoidance, below), perceptual set is the most agile prospective function of the prefrontal cortex. Its neural manifestations can best be recorded by electrophysiological (Chapter 6) and imaging (Chapter 7) methods just before discrete stimuli that are expected in a cued-attention or working-memory task.

As in any form of attention, perceptual set consists of two complementary brain mechanisms: one facilitatory and inclusionary, with the focus on the expected stimulus; and the other suppressive and exclusionary, inhibitory of irrelevant material. The first, equivalent to what [Shallice \(1988\)](#) calls the “supervisory attentional system,” is thought to be primarily based in the lateral prefrontal cortex, the second in the inferior and orbital prefrontal cortex ([Bari and Robbins, 2013](#)). Both act in a top-down manner on the substrates of perception and action as part of cognitive control ([Desimone and Duncan, 1995](#)) and anticipated attentive perception ([Dentico et al., 2014](#)).

The neuroimaging manifestations of attentional set can be recorded from the prefrontal cortex immediately before an anticipated visual stimulus. Anticipatory blood oxygen level-dependent (BOLD) activations (see Chapter 7) are observed in a portion of the prefrontal

cortex (the frontal eye field) and in the visual cortex when subjects anticipate a visual percept (Sylvester et al., 2009; Dentico et al., 2014). Expectation of sensory stimuli improves their use in working memory as well as in long-term memory (Bollinger et al., 2010).

### **Executive Set**

Executive set is the preparation for action. It is attention focused on the action that is to come, thus focused on the preparation of executive networks for the execution of that action. If the action is skeletal or oculomotor, the set is *motor attention*, and entails the priming of a sector of the motor apparatus for a goal-directed movement. In addition, however, the action may involve executive cognits of high order, in the form of schemas, temporal gestalts, scripts, or rules. The preparatory set may then involve the anticipatory coordination of actions for the attainment of the main goal of the action and the subgoals toward it.

The evidence for executive set in the prefrontal cortex comes from human neuropsychology (see Chapter 5), electrophysiology (Chapter 6), and neuroimaging (Chapter 7). As we have seen, there are cells in lateral prefrontal cortex that, in the delay before a motor response, accelerate their discharge until that response is produced. Furthermore, the magnitude of that accelerating discharge is usually related to the direction (e.g., right or left) of that response, and the slope of acceleration is proportional to the certainty with which the animal can predict that direction in advance. Since the cells anticipate the response with some specificity, it is reasonable to assume that they engage in the encoding of the response and the preparation of lower stages of the motor system for it.

From the surface of the lateral frontal cortex of the primate, human and monkey, the contingent negative variation can be recorded. This slow negative potential emerges after a sensory signal and commonly grows in amplitude in anticipation of the motor response or cognitive

decision that is contingent on that signal. It has also been called the “expectancy wave,” and its last component, just before the response, has been called the “readiness potential.” These field potentials can be best understood as phenomena of cross-temporal contingency (see Section V) and of the role of the underlying prefrontal neurons in the preparation for the action.

From executive set or motor attention derives the intention to act, although the latter may appear to precede the former. The conscious intention to perform an act, whether at the start of a sequence of actions or in the middle of it, may in fact precede the preparatory set of the motor apparatus for the act. However, in the neural logistics of the behavioral structure, preparatory set can take place before and even without intention. Support for this view is provided by the experimental results of Libet and colleagues (1983), who demonstrated the start of the frontal readiness potential a few hundreds of milliseconds before the intention to move (see Chapter 6). Conscious operations in general may be secondary to neural operations.

The attentional set for the coordination of actions within a large goal-directed schema involves in all likelihood the top-down processing through successive layers of cognits in the frontal executive hierarchy. Set begins at high, prefrontal, levels of the hierarchy that encode rules, plans, and long-term goals. It then progresses through lower, premotor, and motor levels that encode more concrete actions for the attainment of partial goals toward major goals. Like the goals and cognits in the hierarchical organization of actions in frontal cortex, partial sets are functionally nested within larger sets. Thus, in the organization of complex, goal-directed behavior, it is plausible to postulate a cascade of activation from higher frontal networks to lower ones, with monitoring and correction acting at every step (see Chapter 7); based on BOLD imaging data, Koechlin and colleagues (Koechlin et al., 2003; Koechlin and Hyafil, 2007) and Badre and D’Esposito (2007)

argue persuasively for that cascade. The operations of monitoring and correction at every step (see below) would ensure that the action stays on course, congruent with the ultimate goal and in accord with the prevailing rules.

When rules or external conditions change, preparatory set may have to change. This may happen at any time before the action begins or when it is already underway. As the evidence in Chapters 4 and 5 amply illustrates, monkeys and humans with lateral prefrontal lesions have considerable difficulty performing set-shifting tasks, such as the Wisconsin Card Sorting Test. A set-shifting problem, however, may be secondary to a deficit in another aspect of executive attention in which the lateral prefrontal cortex is deeply involved: working memory. Indeed, if the subject loses the working memory of the prevailing rule or set, he is unlikely to be able to appropriately shift either rule or set. Conversely, the subject may fail to do so because of inappropriately sticking to an old rule or set; in other words, to prevent failure of another aspect of attention, inhibitory control, in which the prefrontal cortex also plays a decisive role, is essential (see Inhibitory Control, below).

### C. Working Memory

In neural, as well as phenomenological terms, working memory can be best understood as attention focused on an internal representation. The term originated in cognitive psychology, but with a different meaning. [Miller et al. \(1960\)](#) first used it to characterize a transient and operant form of memory for provisional use. [Atkinson and Shiffrin \(1968\)](#) used it to refer to a dynamic state of short-term memory in their two-stage memory model. [Baddeley \(1986\)](#) defined working memory as a temporary memory store for information needed to perform a task or to solve a problem in the short term. He placed working memory at the center of his hypothetical “central executive,” and

identified the working-memory deficit as characteristic of what he called the “dysexecutive syndrome.” Working memory, according to his theoretical construct, had several components or slave functions, such as an “articulatory loop” and a temporary “sketch-pad,” that were only applicable to the human, at least insofar as they assumed language. In all three notions of working memory mentioned so far, the content of working memory is, at least in operational terms, new and generally sensory or linguistic.

It was Baddeley himself, however, who first saw and emphasized the close relationship between working memory and attention. From the inception of the concept, he and his colleagues placed working memory at the center of supervisory attentive control ([Norman, 1968](#); [Norman and Shallice, 1986](#); [Shallice, 1988](#)). Trouble in working memory was at the root of what he called the “dysexecutive syndrome.” In one of his writings, he suggests that working memory and attention are not only inseparable but to some degree identical ([Baddeley, 1993](#)). Some of the neuroimaging evidence in Chapter 7 clearly points in that direction.

In my view, working memory is indeed a form of attention: sustained attention focused on an executive cognit for the processing of prospective action. That prospective aspect makes working memory a prospective executive function by definition, like the three already discussed in this section. The cognit in its content may be an item of long-term memory that has been updated by a new but associated item that is critical for the best outcome of the action a few seconds or minutes hence. However, the content of working memory is not limited to that new item but extends to its entire associative context, which includes the representation of the action itself. The focus, the center, of the sustained attention, nonetheless, is in the new item, the memorandum (the Latin gerund emphasizes the *to-do* feature of working memory), and the associated prospective action

it evokes. Insofar as the sustained attention of working memory incorporates percepts and actions, working memory operates intimately with attentional set. Insofar as the content of working memory consists largely of updated long-term memory, working memory can be legitimately called *active memory*, as it was in previous editions of this book.

Two distinctive characteristics of working memory mentioned above deserve further emphasis because they bear decisively on its neural substrate and mechanisms. One is its associative character. The content of working memory is associative and elicited by association. That content, the memorandum, is an item of information that, before it is perceived for retention in working memory, has been associated with many others in its context; in formal testing, for example, it is associated with a set of prior instructions from the experimenter. It may also be associated with a previously acquired lexicon or behavior. In any case, only a portion of the associated information is in the focus of attention of working memory at any given time. The rest, which is just as critical for the pending action, is a mass of information in associative long-term memory elicited by the memorandum. The point here is that, whereas the focus of working memory is a discrete item of lexicon or sensorium, that item is couched in a constellation of associated items that provide it with meaning and purpose. In other words, the item is part of a vast associative neural network, a large cognit in long-term memory with perceptual and executive components, which is activated not only to retain that special item but also to provide it with historical and behavioral context. Only with that context will the working memory in focus serve its purpose. Therefore, working memory may be viewed as largely consisting of the temporary activation of updated long-term memory. Supporting this assertion are unit data from the primate cortex showing that the cells that participate

in working memory belong to widely distributed networks attuned to multiple associated features of the memorandum, even if these features pertain to different sensory modalities (Fuster et al., 2000; Zhou et al., 2007; Mante et al., 2013; Wang et al., 2015).

The second crucial characteristic of working memory is its future perspective. It must be emphasized that working memory always has a purpose in the more or less distant future; the purpose may be a biological goal or the solution of a problem. That future perspective is what distinguishes working memory from other forms of short-term memory. Insofar as the action and the set for it are part of that perspective, working memory may be called "memory of the future" (Ingvar, 1985). Of course, that characterization applies not only to working memory but also to the longer term perspective of planning, another prefrontal function. Both functions are distinctive elements of the fundamental teleology of prefrontal mechanisms. As discussed earlier, the apparent paradoxical causality of the future upon the present can only be understood in the context of the participation of the prefrontal cortex in the renewal of old memory and in the perception-action cycle (Fuster and Bressler, 2015).

As already mentioned several times, the content of working memory may be old material that is given renewed timeliness and term by the action at hand. With the attainment of the goal, however, that content outlives its usefulness and has to be discarded. In fact, its retention beyond that point may interfere proactively with ensuing behavioral structures. The suppression of influences from obsolete material (i.e., obsolete in terms of current action) is part of the prefrontal role of inhibitory control of interference (see Inhibitory Control, below). Because of these considerations, the *ad hoc*, operational character of working memory is more important to its definition than either its specific content or its duration by the clock.

The evidence for the role of the prefrontal cortex in working memory is threefold: (1) prefrontal lesions induce deficits in the performance of delay tasks, temporal ordering tasks, and other tasks that rely on the mediation of cross-temporal contingencies by working memory (see Chapters 4 and 5); in primates the deficits ensue mainly from lesions of lateral prefrontal cortex; (2) sustained activation of neuronal populations is seen in this cortex during the active retention of sensory information, such as during the delay of a delay task (Chapter 6); particularly demonstrative are the neurons that during that time show temporally decaying activation specifically related to a memorandum; and (3) activation of lateral prefrontal cortex is observed on positron emission tomography or BOLD during the performance of working-memory tasks in humans (Chapter 7).

The topography of working memory is the topography of its contents and, therefore, of its activated executive networks. The anatomy of prefrontal functions is the anatomy of the neural networks in which these functions process information; thus, the anatomy of prefrontal functions coincides with the anatomy of the neural cognitive networks that store the information in long-term or recent memory. If working memory appears to be localized in lateral prefrontal cortex, it is because that cortex contains executive cognits commonly activated in working-memory tests, notably delay tasks. These cognits include gestalts of instructed eye movements, skeletal movements, and language, all of which contain temporal delays to be bridged with working memory and are at least in part represented in the cortex of the prefrontal convexity. Nonetheless, the ventral and medial prefrontal cortex cannot be excluded from working memory. On the one hand, there is abundant evidence of delay activity in these regions; on the other, these regions contain neural associations of cognitive networks with reward and reinforcement. They are likely to be

activated to some degree in whatever process activates these networks to bridge temporal gaps with working memory.

As noted in Chapter 6, the neural mechanisms behind the process of working memory are still a matter of debate. The most plausible basic mechanism is reverberation through re-entrant circuits within the confines of a memory network that associates all the elements of the memorandum. That network is likely to include perceptual components in posterior cortex as well as executive components in frontal cortex. Working memory, according to that view, is maintained by reciprocal re-entry between neuronal assemblies and networks that represent the multiple associations of the memorandum; in other words, the global network that defines the memorandum as it has been formed by prior experience. That includes perceptual as well as executive networks extended throughout the cortex, especially association cortex. As we have seen in Chapters 6 and 7, the multiplicity of re-entry (i.e., associative) paths within and between perceptual and executive cortices gives rise to a multiplicity of activated areas and frequencies, some of these oscillatory. Whereas the focus of working memory, that is, the focus of internalized attention, may be circumscribed to a discrete portion of the activated memory network, it is unlikely that such activation dominates the entire period of delay in a delay task. We have seen abundant evidence that the dominant focus shifts throughout that period between different network components, perceptual and executive. That apparently leads to the fragmentation of the “attractor” frequencies that one can identify in cortical neurons during the memory period (Bodner et al., 2005).

Is working memory conscious? Does it need to be conscious to perform its time-bridging function? These questions become especially pertinent if we consider working memory a form of attention, as we do here. The content of perceptual attention is limited; there is a limit

to what is in the focus of attention at any given time. In the human, that content is conscious; it varies with the needs of the moment, as does the flow of consciousness. The focus of working memory is the memorandum, which is conscious – the “remembered present” of Edelman (1989). However, conscious awareness cannot be ascertained in animals, which are fully capable of using working memory. Furthermore, as in the case of perceptual attention, some working memory may be unconscious and still be used in the processing of information. We process much perception of which we are not aware, unconsciously. Whereas what is in the focus of attention is conscious and processed in series, the rest, in the periphery of attention, is unconscious and processed in parallel. The same may be true in working memory. We may be fully aware of the memorandum, but not of what is in the penumbra of attention, which may be processed unconsciously and is just as important as the memorandum for the temporal-integration role of working memory. Here, in that penumbra belong innumerable associated features of the memorandum that have been acquired with experience and are essential to the integrative process, yet processed or retained in unconscious obscurity.

## D. Decision-Making

In psychological parlance, a decision is the formulation of a course of action with intent to execute it. It is another executive prefrontal function with a perspective into a future that is more or less immediate. This broad definition applies to plans, which we have just considered, as well as to discrete actions. In either case, a decision, like any other cognitive operation in which the prefrontal cortex participates, requires the basic drive to make it. Deciding is predicated on the presence of a minimum level of that drive, and the strength of the decision is a function of that level. The choice of decision, however, is an attentive act that is determined

in frontal cortex after analysis and evaluation of assorted items of sensory perception, memory, and motive. Many of them may be unconscious. Ultimately, any decision depends on the evaluation of risks and benefits of its potential outcome. For these reasons, the decision is in most cases probabilistic and Bayesian, founded on the updating of established hypotheses and expectations (Jaynes, 1986). Decision-making and the role of the prefrontal cortex in it are subjects within the field of neuroeconomics.

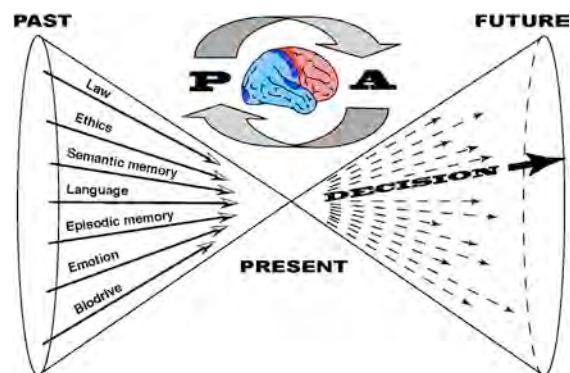
Simply on anatomical considerations it is reasonable to infer that the making of a decision is a multidetermined event and does not come down from any hypothetical “center of decision,” let alone “center of will.” Aside from the absence of any neural evidence for such a center, we should take into account that the “central executive,” as the anterior frontal cortex has sometimes been called, is the best connected of all neocortical regions (see Chapter 2). To various parts of the prefrontal cortex come, directly or indirectly, inputs from practically everywhere else in the brain: inputs from the brainstem and diencephalon bringing information on the internal milieu, from limbic structures on affective state and motivational significance, from myriad cortical locations on past memory and experience, and from the prefrontal cortex itself. Among the latter, we should single out the input from the anterior cingulate cortex, which brings critical information resulting from the monitoring of the results of prior decisions taken under similar circumstances (see Chapters 6 and 7).

With regard to decision-making, no other region of the prefrontal cortex has received as much attention in recent years as the orbital prefrontal cortex. There are three obvious reasons for this. The first is that this region is an important collector of dopamine terminals from subcortical locations that are endowed with abundant dopamine receptors; thus, it is evidently involved in the encoding of reward signals (see Chapter 3). The second is that the

orbitofrontal cortex is the recipient of visceral signals ("somatic markers") from many points of origin in the internal milieu (see Chapters 2 and 5). The third is that the orbitofrontal cortex is part of a complex system of neural, mostly limbic structures, especially the amygdala, that are heavily involved in emotional behavior (see Section V) and in the evaluation of the motivational significance (valence) of internal as well as external inputs. For these three reasons the orbitofrontal cortex is deemed a crucial center for the integration of emotional behavior and, at the same time, a provider of emotional and visceral information that is destined to weigh heavily in the process of decision-making.

Given the richness of inputs to the frontal cortex, it is reasonable to view any decision as a vector of converging neural influences upon it, as the resolution of competition or conflict between numerous motives and items of internal and external information. That resolution is bound to involve some selection, which in the nervous system means selective facilitation and usually also exclusionary inhibition. We should add that many of our decisions are determined by higher values, which are the product of education and good example and probably represented in cortical networks of unknown distribution. These high-level "procedural memories" undoubtedly prime many of our decisions unconsciously. **Figure 8.4** depicts schematically the categories of inputs that may impinge on a decision.

An important point, in conclusion, is that a superordinate deciding agency such as a central executive most probably does not exist, nor is it needed, in frontal cortex or anywhere else in the brain. To postulate one such agency in the frontal lobe leads to a regress on to precursor structures that feed into it. All the executive functions are phenomena of the processing in neural networks of the frontal lobe, and this applies to decision-making as well as the other functions.



**FIGURE 8.4** Schematic diagram of various categories of cortical and subcortical cognitive or emotional information converging on the present in the making of a decision with prospective impact. *Inset (top):* The perception–action (PA) cycle enclosing an image of the human brain.

## E. Error Monitoring and Avoidance

The evidence from electrophysiology (see Chapter 6) and neuroimaging (Chapter 7) clearly indicates the presence in the prefrontal cortex of mechanisms dedicated to obtaining and generating signals of the success or failure of an intended act after it has been performed. Inasmuch as success means the attainment of a reward (arguably success in itself is its own reward), it is not surprising that these signals would originate in the dopamine-rich region of the orbital prefrontal cortex (Chapter 3), within the "reward axis" of the paralimbic basal brain. Furthermore, neuroeconomic research substantiates the presence, in the same region, of mechanisms to measure and evaluate a particular reward or the consequences of its absence. If the result has been failure, the measure will estimate the degree to which the intentional action missed its goal. The prefrontal cortex will use that information to restructure or correct future actions to ensure success. Every goal-directed action carries with it the implicit prediction that it will succeed. For this reason, the failure to attain an expected goal or reward

has been called *prediction error*. The avoidance or minimization of that error has emerged as one of the chief preadaptive, future-oriented, executive functions of the prefrontal cortex. In any case, human neuroimaging (Chapter 7) shows the activation of orbitofrontal cortex by negative reward, that is by prediction error, as well as by positive reward.

While several brain structures, including the orbital and medial (anterior cingulate) prefrontal cortex and the amygdala, receive prediction error signals, it is not clear exactly by which mechanism an error is corrected and avoided in subsequent actions. Nonetheless, based on certain anatomical features of the fine structure of the pyramidal motor system and the role of sensory feedback in perception, Friston and colleagues (Friston, 2003; Shipp et al., 2013; Adams et al., 2013) propose that the descending output to the musculature in a motor act essentially carries a “predictive code,” anticipating proprioceptive feedback from movement and thus minimizing prediction error. Similarly, Clark (2013) argues that the brain is essentially an adaptive “machine” which, through its motor apparatus, projects to the periphery “action-oriented predictive coding.” Both Friston and Clark place the narrow concept of prediction error at the core of their theories, and adopt the concept of the hierarchical organization of action, as we have done above. Both also adopt the idea that action processing takes place in cascade fashion down an executive hierarchy of frontal cortex, as also proposed above.

In an extensive review of cingulate functions, Shackman et al. (2011) come to the conclusion that the cognitive and emotional contributions of anterior cingulate cortex to goal-directed behavior cannot be dissociated from each other, as they are intimately interrelated, anatomically and physiologically. This agrees well with the model proposed by Alexander and Brown (2011) and with the concept of the orbitomedial prefrontal cortex as an integrative hub for both a cognitive and an emotional perception-action

cycle. As we see below, the two cycles serve the coordination of preadaptive actions to minimize error and secure reward.

## F. Inhibitory Control

Inhibition plays an important role in frontal physiology; this can be readily inferred from the fact that  $\gamma$ -aminobutyric acid (GABA) is the most abundant neurotransmitter in the frontal lobe. Inhibition is there not simply to prevent the brain from seizing, but also to support some of the finest and most discriminatory functions of the prefrontal cortex. All executive functions require inhibition to enhance contrast or to prevent interference. This is true for all the functions discussed so far in this section, and most conspicuous in those most demanding of attention, that is attentional set, decision-making, and working memory.

In addition to its inclusive (selective focusing) component, attention has an exclusionary component that protects what is in focus from interference by perceptual or mnemonic material that is not germane to the present task. It protects the structure of behavior, speech, or thought from interfering influences that may conflict with it and lead it astray. This attentive function of interference control is essentially inhibitory and based to a large extent, but not exclusively, in the orbitomedial aspects of the prefrontal cortex. The evidence for this and for its cortical topography derives almost entirely from animal and human neuropsychology (see Chapters 4 and 5); some evidence also comes from electrophysiology (Chapter 6) and neuroimaging (Chapter 7). Let us briefly consider the behavioral conditions in which this function operates.

A large variety of interfering factors can disrupt a behavioral structure from progressing toward its aim. Some may be external, others internal. Extraneous sensory stimuli may distract the organism from the currently active memory or from the action in preparation.

Unexpected stimuli, or stimuli that are similar but not equivalent to the stimuli being used for the task, may compete with working memory, and thus distort or block the task. The memory of the memorandum in a delayed-response or delayed-matching trial is most vulnerable to external interference during the delay, the retention period.

Internal influences can also interfere with memory or set. Such influences include the mnemonic traces of previous behavioral structures with which the animal may be familiar and which may contaminate and distort ongoing behavior; old habits may also compete with it. Especially disruptive are the central representations of stimuli and motor reactions that have similar characteristics and, in the current context, have almost equal probability of occurrence as the current stimuli and reactions. Because the inappropriate stimuli and responses are similar to and just as probable as the appropriate ones, the former are likely to interfere with the latter. Similarity and equal probability produce confusion. Traces of previous memories interfere with the present one (proactive interference). Finally, impulses toward immediate gratification, another internal source of interference, may abort a temporal synthesis of behavior at any time before its completion.

There is substantial evidence in the last four chapters that the control of interference is carried out by inhibitory counterinfluences originating in orbital and probably also medial prefrontal cortex. Thus, with regard to memory, orbitomedial cortex may perform a function opposite to, yet complementary of, that performed by lateral cortex. The retention of the memory of the relevant elements of the behavioral structure in lateral cortex is complemented by the orbitomedial role of suppressing interfering memories. I call this reciprocal action on memories the "Lebadea principle" of prefrontal function. (At Lebadea, before being admitted to the Oracle of Trophonius, the visitor had to drink the miraculous waters of two nearby

springs. He drank from the source of forgetfulness, Lethe, to forget the past, and from the source of remembrance, Mnemosyne, to remember the revelations about to be made to him.)

As already mentioned, motor attention, or set, also has inhibitory control at its disposal, and this seems to originate in the anterior cingulate areas of medial prefrontal cortex (see Chapters 6 and 7); again, this is an exclusionary role of attention, based in orbitomedial cortex, complementing the selective and intensive role in lateral cortex. Both help the animal to direct and maintain the proper conduct of the behavioral sequence. In orbitofrontal dysfunction from lesion, some behaviors are impaired primarily, if not exclusively, for lack of inhibitory protection from interference. Such is the case in reversal tasks, delayed alternation – a form of place reversal – and successive discrimination. In all of them, the ultimate casualty of prefrontal damage is a temporal structure of behavior that is distorted or pre-empted by a similar but untimely structure or by an untimely impulse. The usual result is fragmentation of the behavior and *perseveration* in one of its constituent acts (Mishkin, 1964). Outside task performance, the lack of inhibitory control has manifestations in certain pathological conditions. As we have seen in Chapters 5 and 6, both animals and humans with prefrontal, especially orbital, damage show a marked tendency to distractibility, hyperreactivity, and impulsivity, all symptoms of poor control of external or internal influences (as in attention deficit/hyperactivity disorder).

Because the possible sources of interference are many, some coming from inside and some from outside the organism, they may be represented in various cerebral locations, cortical and subcortical. At present, it is not possible to ascertain precisely the mechanisms by which the prefrontal cortex exerts its control over them. Nevertheless, we can plausibly view the inhibitory prefrontal role as a form of "lateral inhibition" on neural representations

that detract from current behavior, resembling a similar phenomenon in sensory physiology. Whereas much of the lateral prefrontal cortex is primarily active in the short-term retention and preparatory set that the current behavioral sequence demands, the orbitomedial prefrontal cortex may be primarily active in inhibiting the neural structures that represent extraneous and distracting material. It is difficult to construe a single inhibitory area in orbitomedial cortex suppressing such diverse contents as one may reasonably postulate that the prefrontal cortex must suppress (sensory, motor, mnemonic, motivational, etc.). Thus, we must suppose that there is more specificity in that part of the prefrontal cortex than neuropsychological evidence would seem to suggest. As for the targets of inhibition, interfering sensory stimuli and memory representations may be suppressed by orbitofrontal inhibitory impulses upon posterior cortical regions, possibly through the medial thalamus (see Chapter 6). Motor representations may be suppressed by comparable inhibitory impulses upon cortical and subcortical motor structures, notably the basal ganglia. Other internal influences and drives may be suppressed by inhibitory efferents from orbitomedial prefrontal cortex to the hypothalamus and other parts of the limbic system.

## V. EMOTIONAL FUNCTIONS

For heuristic reasons, the executive functions of the prefrontal cortex have been described separately, even though, as we will see later, they all blend dynamically into one another in both time and brain space. The description of prefrontal emotional functions must be less distinct, for one thing because to some extent they impact on each of the executive functions described above. There is, however, a region of the frontal lobe, the orbitomedial or ventromedial cortex, that is the receptor and origin of emotional impulses, both excitatory

and inhibitory, which modulate the cognitive activity of the cortex at large as well as that of visceral and autonomic centers of the diencephalon and lower brainstem.

Anatomically (see Chapter 2), the orbital and medial cortex of the frontal lobe is closely connected with limbic structures, especially the amygdala. The cellular architecture of much of that cortex deviates from the six-layered and granular-cell pattern. For this reason and because of its proximity and connectivity to limbic brain, it has been called "paralimbic" prefrontal cortex. Through the amygdala, the hypothalamus, and the anterior and dorsomedial nuclei of the thalamus, the ventromedial frontal cortex receives information from the internal milieu: information of humoral and visceral origin, some of it arriving in the brain via the autonomic system (see Chapters 2 and 6). Furthermore, the ventromedial cortex reciprocates the inputs from these structures with corresponding outputs to them. There is substantial electrophysiological evidence indicating that, by way of these outputs, the orbital prefrontal cortex has powerful influences upon viscera and regulates a variety of emotional behaviors (Chapter 6).

Furthermore, from the point of view of neurochemistry (see Chapter 3), the orbitomedial prefrontal cortex occupies a critical position, at the crossroads of several neurotransmitter systems that are involved in drives, motivation, valence, and the assessment of the emotional significance of sensory stimuli. These inputs to orbitomedial cortex come mainly from the hypothalamus and the amygdala. For these reasons, and those adduced in the previous paragraph, it is appropriate to consider the amygdala, the orbitomedial cortex, the basal paralimbic cortex – including the insula – and some striatal structures (e.g., nucleus accumbens) as forming a massive structural complex devoted to encoding emotions and emotional responses.

Many questions remain unanswered regarding the prefrontal initiation and regulation of

emotional behavior. As alluded to above, emotions and motives enter cognitive functions, notably decision-making. They constitute one of the important sources of neural information on the value of actual or expected rewards, on which the lateral frontal domains base the pursuit of goal-directed actions. The mediating connections are probably those that come to these domains from limbic structures and from the orbital prefrontal cortex (see Chapter 2). It is probably through these connections that visceral and emotional information enters cognition.

There is also, however, a presumptive role of ventromedial frontal cortex in the conduct of emotional behavior that would parallel the role of lateral cortex in the cognitive processes. This ventromedial role can be reasonably postulated from three lines of evidence: (1) the reciprocal connectivity of ventromedial cortex with the basolateral amygdala and the hypothalamus (see Chapter 2), both of which are major recipients and effectors in emotional behavior; (2) the emotional disorders of patients with ventromedial lesions (see Chapter 5); and (3) the abnormal metabolic activation of orbital cortex in certain mental disorders (e.g., obsessive-compulsive disorder) with severely disturbed emotional behavior (see Chapter 7). These interconnected structures – basolateral amygdala, hypothalamus, and orbital prefrontal cortex, among others – constitute an emotional perception-action cycle parallel to the cognitive one that circulates through lateral prefrontal and posterior cortex.

Emotional behavior has many variants, and there is no evidence that would allow us to allocate different orbitofrontal areas to different emotional representations, as we have done with action memory in lateral cortex. We may, however, hypothesize that this cortex is a depository of emotional memory, possibly together with the amygdala and other limbic formations (LeDoux, 1993). Emotional memory could be stored in frontal networks in the form of what Damasio (1996) has called “somatic markers.” These are

hypothetical neural indicators of autonomic, endocrine, and visceral concomitants of emotion. According to Damasio, somatic markers actually play a major role in decision-making, consistent with the view presented in Section IV.

However they are encoded in orbital frontal cortex or subcortical centers, emotional engrams would determine and guide behavior much like the motor engrams (executive cognits) of lateral cortex, and perhaps in functional conjunction with them. Emotional behavior leads to changes in the internal and external environments, and these changes lead to new inputs – new markers – into orbital cortex, which in turn will modify the emotional response of the organism, and so on. Is this the circular exchange that shapes the emotional interactions of two animals or humans with each other? Indeed, as suggested above, we see a perception-action cycle emerging in the emotional sphere to match, or rather complement, the one in the cognitive sphere that plays such a crucial role in the temporal organization of behavior, as we see below. It is proposed that orbital cortex regulates the emotional cycle much as dorsal cortex regulates the cognitive cycle. The two, working in parallel and in close interaction with each other, guide the organism to its biological and cognitive goals.

## VI. TEMPORAL ORGANIZATION OF ACTION

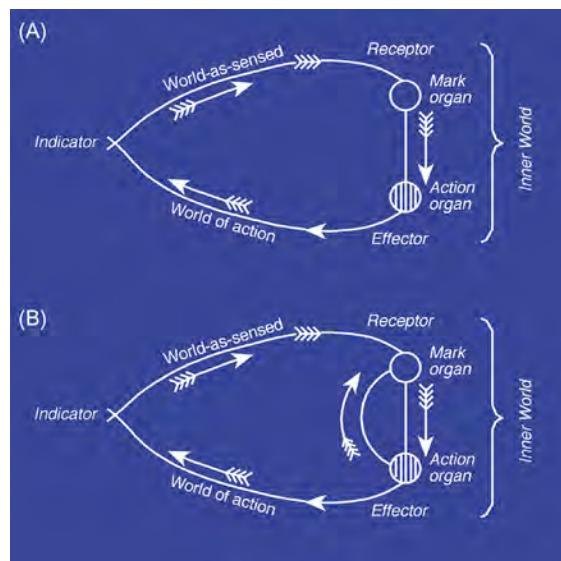
Thus far, this chapter has dealt with the principles of structural organization of cortical networks, with special emphasis on frontal executive networks and domains. We have also dealt with the major executive and emotional functions of the prefrontal cortex, and described the essentials of these functions as we can gather them from the empirical evidence in animals and humans. We have come to the conclusion that cognitive and emotional functions are distributed over the prefrontal cortex,

although each of them is primarily, not exclusively, based in a certain broad region of lateral or orbitomedial prefrontal cortex. We have also examined some of the neural mechanisms at the foundation of these functions. What we have not done yet is to examine with a broad view the joint dynamics of these functions in the organization of goal-directed sequences of actions. As we have seen, there is growing evidence, especially in the human, that the most critical and characteristic role of the prefrontal cortex as a whole is the goal-directed sequencing of new actions in behavior, reasoning, and speech. The neural dynamics of that kind of sequencing is the next subject of this chapter.

To understand prefrontal dynamics it is necessary to keep in mind two basic principles. First, a structure of goal-directed sequential actions is a *temporal gestalt* defined by its goal and the *relations* (including order) between its component actions. That temporal gestalt, therefore, obeys similar rules to spatial gestalts (e.g., the whole is more than the sum of the parts and defined not only by them but also, most critically, by the relations between them). Second, a structure of goal-directed sequential action results from a continuous cybernetic interplay between the organism and its environment that we call the *perception-action cycle*. The prefrontal cortex sits at the top of that cycle, controlling temporal integration and the sequencing of actions.

## A. The Perception–Action Cycle

In all forms of behavior, from the most automatic to the most deliberate, motor action is not only initiated or triggered by sensory signals, but also regulated by sensory feedback generated by changes that the action itself induces in the external environment. Thus, a circular pattern of influences is at work in behavior: from the environment on the organism through sensory receptors, from the organism on the environment through motor effectors, from the environment back on the organism



**FIGURE 8.5** Uexküll's diagram of the organism's relationship with its environment. He describes that relationship as follows. (A) "As the diagram shows, the inner world is divided into two parts; one, which receives the impressions, is turned toward the world-as-sensed, and the other, which distributes the effects, is turned toward the world-of action." (B) "In the highest animals, however, the creature's own action-rule penetrates further into the world-as-sensed, and there assumes direction and control ... A new circle is introduced within the animal's own central organ, for the support of the external function-circle, and this connects the action organ with the mark-organ." (From Uexküll, 1926, pp. 155–157.)

again through sensory receptors, and so on. The biologist Uexküll (1926) was the first to formulate this circular pattern, which he identified in many animal species (Figure 8.5). It was later called the "gestalt cycle" (*Gestaltkreis*) by Viktor von Weizsäcker (1950), a neurologist who recognized with it the principle of the indissoluble union of perception and movement in the nervous system. More recently, that principle and its operational aspects have been characterized as the "action–perception cycle" (Arbib, 1981; Friston, 2013) or, where the emphasis is not so much on motor behavior as on cognition, simply as the "perception cycle"

([Neisser, 1976](#)). I call it the perception–action cycle. Whatever the term used to designate it, the principle is unquestionably of critical biological significance. It is the implicit or explicit subject of a vast body of literature dealing with the psychophysics and neural mechanisms of sensory–motor interaction; it is the basis of neuromybernetics, robotics, and the adaptation of the organism to its environment.

In the nervous system of higher organisms, the perception–action cycle has an important new feature that Uexküll had already pointed out ([Figure 8.4](#)): internal feedback from effectors to sensors. That feature allows the representations of current action to feed back upon sensory structures to modulate further sensory input. Clearly, this type of feedback is at the root of what, at higher neural stages, have been called “efferent copies” ([McCloskey, 1981](#)) and the “corollary discharge” ([Teuber, 1964, 1972](#)). At cognitive levels, in the execution of complex action sequences, feedback from prefrontal upon posterior cortices is probably at the root of what has been termed the cognitive control of attention. Working memory depends on it too (see Chapters 6 and 7).

By applying Jacksonian concepts to what is known about the connective structure of the central nervous system and its receptive and motor functions, a sensation–action cycle can be recognized at every level of the neural hierarchies for sensation and movement, from the spinal cord upward. At each level of either hierarchy, sensory or motor, there is communication with the environment through a corresponding level of the other hierarchy. This order of connectivity extends to the cortex, where the cycle becomes the perception–action cycle and where the reciprocal connections between the two cortical hierarchies serve the cognitive functions of the cycle at its highest level in the steering of action sequences toward their goal.

In the human, where objectives reach further into the future than in lower animals, and where short-term objectives are nested in and

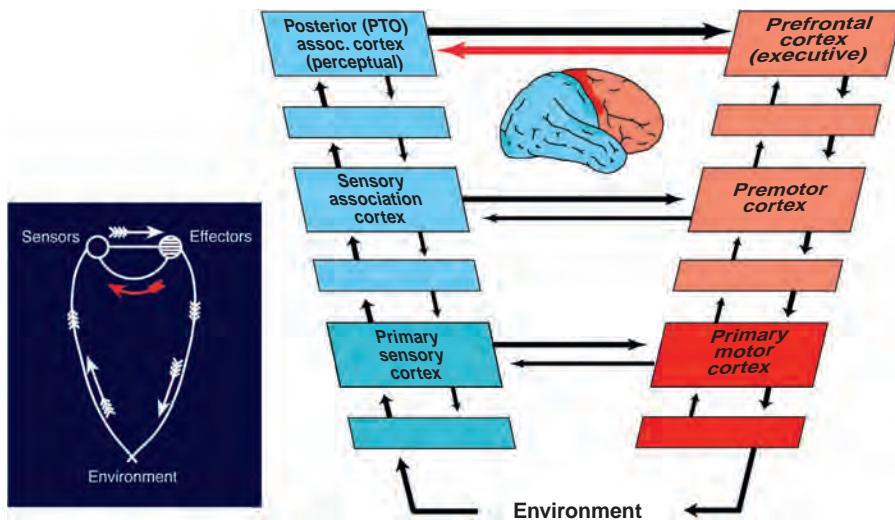
serve higher and longer term objectives, it can be easily inferred that multiple perception–action cycles are active at the same time. It is also easy to infer that, as indicated in the following section, the human brain must accommodate a hierarchy of perception–action cycles subserving simultaneously a hierarchy of behavioral or linguistic goals and subgoals.

## B. Functional Anatomy of the Perception–Action Cycle

In its essentials, the cortical anatomy of the perception–action cycle is made up of the two hierarchies of cognitive networks, one perceptual in posterior cortex and the other executive in frontal cortex, as described at the beginning of this chapter and depicted in [Figure 8.3](#). As we will see later, a course of goal-directed action can begin anywhere in the external or internal sectors of the cycle. Because of its structural constraints, including feedback at many levels, the system regulates the action at several levels toward its goal.

[Figure 8.6](#) illustrates schematically the cortical connective anatomy of the perception–action cycle in the primate. The diagram is based on the available evidence of fiber connections between neocortical areas; most of these connections are described in Chapter 2 and some of them have been substantiated by neuroimaging (diffusion tensor imaging). Corresponding areas of the two hierarchies, sensory and motor, on each side of the central sulcus, are connected by reciprocal connections. Each successive area in the posterior cortical pathways for three major sensory modalities – somesthesia, vision, and audition – sends collateral efferent connections to a progressively more rostral frontal area; all such connections are reciprocated by others in the opposite direction.

Thus, progressively higher stages of perceptual memory and processing reach progressively higher stages of executive memory and



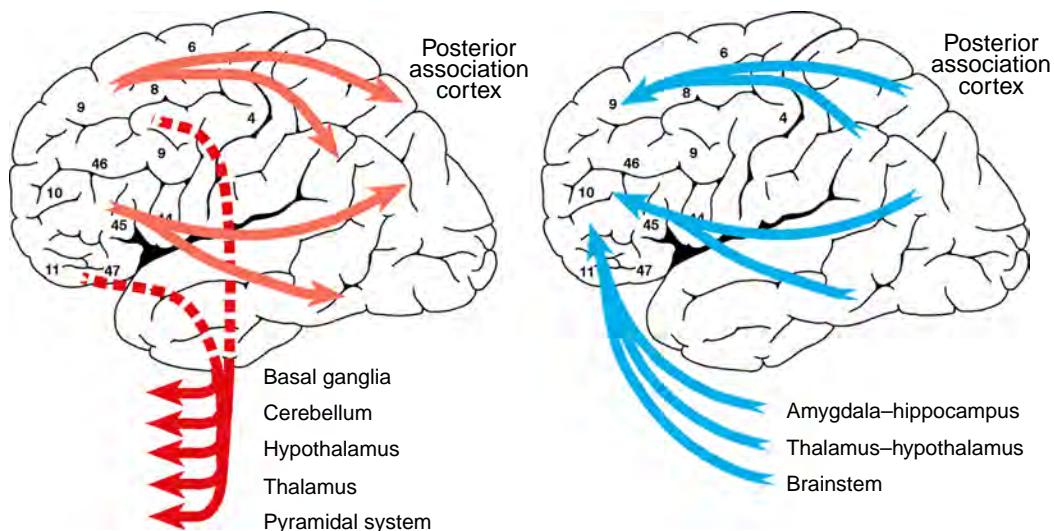
**FIGURE 8.6** Cortical circuitry of the perception–action (PA) cycle. Unlabeled rectangles represent cortical areas intermediate between labeled areas, or subareas of the latter. The perceptual hierarchies of cognits are depicted on the left, the executive hierarchy on the right of the main diagram. The top-left compartment, parietal–temporal–occipital (PTO) cortex, includes both unimodal and multimodal association cortex (Mesulam, 1998). The major connectivity of the cycle runs through thick arrows. Thin arrows mark intracortical feedback connections that play important roles in cognitive control. Bottom left: Uexküll’s internal feedback in lower animals (curved red arrow), which in the human cycle on the right is represented by the straight red arrow from prefrontal to PTO cortex.

processing. And *vice versa*, reciprocal connections flow in order from the motor to the perceptual hierarchy. Consequently, the cortical connective apparatus of the perception–action cycle is completed in both directions at every hierarchical level. At its highest levels, the cycle is closed by connections between association areas of posterior cortex and the lateral prefrontal cortex.

The cortical component networks of the perception–action cycle do not work independently from subcortical structures. To the contrary, both perceptual and executive networks receive inputs from, and send outputs to, a number of subcortical structures; these exchange information with cortical networks and aid the cycle in its operations (Figure 8.7). Some of these inputs and outputs course through the thalamus, whereas others are direct (see Chapter 2). The most critical subcortical

inputs are those that come from the limbic system and the hypothalamus, conveying to the orbital prefrontal cortex information regarding the internal environment. The most critical subcortical outputs are those flowing to the basal ganglia, the cerebellum, and lower components of the pyramidal system. Some of the subcortical inputs and outputs constitute loops of connection through the prefrontal cortex, thus forming the framework for the emotional perception–action cycle mentioned above, which is intertwined and cooperates with the cognitive cycle described earlier.

To better understand the structuring and integrative functions of the frontal cortex in behavior, and its role in the perception–action cycle, it is helpful to conceptualize all behavior as a hierarchical order of structured units of sensation and action. In the central nervous system, accommodating that order, would be the



**FIGURE 8.7** Schematic diagram of the cortical and subcortical afferents (right) and efferents (left) of the prefrontal cortex modulating and steering the perception–action cycle toward the goal of concatenated actions.

hierarchy of components of the cycle that we have described, each uniting at some level representations of sensing and acting, and all closed at the bottom in the environment. The definition of the most elementary unit of behavior is debatable but not essential to this argument. The reflex act will fit the role as a basic cybernetic unit of interaction with the environment. It is biologically adaptive, anchored in phyletic memory, and conditionable, that is, modifiable by experience. Spinal reflex arcs, at the bottom of the sensation–action cycle, may serve as an example of that basic unit of behavior.

Above reflex arcs, in higher neural levels, are the representations of learned behaviors and habits, stacked roughly by order of increasing complexity and decreasing experience of the organism with them. Still in phyletic memory, at the diencephalic level, are the complex instinctual sequences, which are also modifiable by experience and influenced from higher levels. In the basal ganglia and the cerebellum,

we encounter representations of learned and automatic actions, which at one time may have depended on the cerebral cortex but are now relegated to these lower levels of sensory–motor integration. In their execution, after they have been learned, the cycle is “shunted,” closed at a lower level of the hierarchy of the perception–action cycle than it once was.

As we reach the cerebral cortex, the representations of sensation (now perception) and of action associated with it become more complex and more dependent on new plans or recent experience. The actions integrated there are less automatic, more subject to deliberation. These trends increase as we go up the frontal hierarchy, from motor cortex to premotor cortex to prefrontal cortex. As we ascend that hierarchy, the goals of behavior, which are also hierarchically organized, are ever more distant in time, dependent on a progressively greater number of subordinate actions and subgoals. At high levels in prefrontal cortex, however, actions

need not be represented in all their complexity. Only the schema and the goal of a behavioral sequence need to be there in abstract form, except in the actual execution of complex, novel sequences. Thus, we have a hierarchy of behaviors of increasing duration and complexity serving a corresponding hierarchy of purposes. Representing and supporting the execution of these behaviors is a corresponding hierarchy of neural structures engaged together at various levels in the perception-action cycle.

At all levels of that hierarchy, the same networks that represent the action engage in its execution; this execution may engage networks at different levels of the hierarchy (heterarchically). The processing trend may zigzag between different levels as they alternate between different levels of complexity, but generally cascades down from the abstract toward the concrete, from the schematic to the detailed. Whether a structure of action is part of the perception-action cycle or has its origin in prefrontal cortex, its representational network (its cognit) will successively activate a series of subnetworks representing the component actions of that structure. The trend of processing will be generally downward, by activation of progressively lower networks in frontal cortex and through corticothalamic-striatal loops (see Chapter 2). Thus, if the processing begins with an action schema in prefrontal cortex, the activation will progress through premotor cortex and ultimately to primary motor cortex, where the “microgenesis” of the action (Brown, 1987) takes place.

The activation of a frontal network representing a behavioral structure may occur in response to afferent inputs from several possible sources. The most immediate source is the neural representation of the outcome of previous actions in the same goal-directed sequence of behaviors. The feedback signals of that representation may come from the anterior cingulate cortex or other parts of the prefrontal cortex (e.g., orbital). These signals are essential to the

monitoring of the task or behavioral sequence. Other feedback inputs, within the perception-action cycle, may come from the brainstem or the limbic system. Others may come from posterior cortical networks of perception (i.e., the sensory sector of the cycle) or from other frontal networks of higher rank.

While the processing of actions occurs generally downward and feeds forward through the executive hierarchy, it necessitates the continued *feedback* from each level to its precursor levels. That feedback allows the monitoring by higher levels of the action at lower levels, so that actions can be matched to schemas and goals. The feedback allows also the adjustment of perceptual areas – and sensory structures – to anticipated action (corollary discharge, attentional set), and allows the persistence of traces of sensory information to guide that action (working memory).

For the spoken language, which exemplifies the most highly differentiated form of the perception-action cycle, two neocortical areas appear to be critical (see Chapter 6): one postrolandic (Wernicke's area in the left angular gyrus) and the other prerolandic (Broca's area in the left inferior frontal gyrus). Nonetheless, higher frontal areas are also needed for elaborate language. In propositional language, as in mathematical or logical reasoning, the prefrontal cortex seems to play a pivotal role, in no small measure because of its demonstrable importance for the mediation of new cross-temporal contingencies in the perception-action cycle, which is our next subject.

### C. Temporal Integration: Mediating Cross-Temporal Contingencies

To fully appreciate the adaptive properties of the perception-action cycle and the critical importance of the prefrontal cortex in that cycle, it is necessary to step back to highlight with a wide perspective the global role of the

prefrontal cortex in temporal integration. This is a supraordinate role, in that it is served by all the executive prefrontal functions previously discussed (see Section IV). These functions operate seriatim or partly simultaneously in the perception-action cycle. Therefore, to outline their subordinate physiological roles it will be helpful to analyze their intervention in simplified versions of the cycle. But first we will examine the general idea of temporal integration.

In a classic paper entitled "The problem of serial order in behavior," Lashley (1951) addresses theoretically the issue of how organisms synthesize behavior in the temporal domain, using the spoken language as a prime example of "action syntax." After cogent arguments against stimulus-response links and chain associations, he postulates the necessity of central schemas controlling the action and providing it with order and unity. He concludes that these schemas probably reside in the cerebral cortex. Naturally, the schemas and plans that we have placed in the prefrontal cortex, that is, the abstract representations of temporal gestalts of action, are precisely the same construct that Lashley postulated. It is in that sense that he wrote of the *synthesizing* of structures of action and "syntax of action." This prefrontal function of synthesizing goal-directed behavioral structures can be best understood by extending to the temporal domain the concepts that gestalt psychology generally applies to the spatial domain.

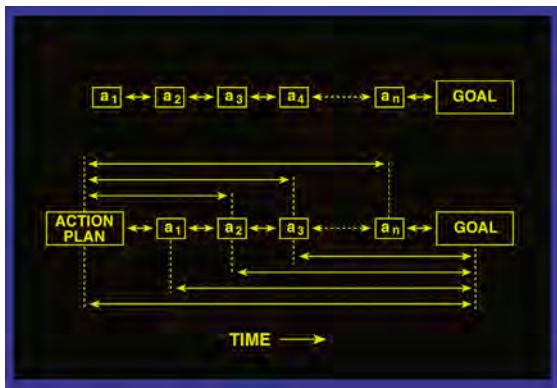
Indeed, the behavioral structures for which the prefrontal cortex appears so important consist of novel, usually complex, temporal gestalts or "melodies" of action. The biological meaning of any gestalt, spatial or temporal, lies not in its component parts but in the associative relationships of these parts to one another, which, in the case of temporal gestalts, include order and timing. My views here, however, deviate somewhat from gestalt psychology, not only in that they emphasize the temporal, instead of the

spatial, aspects of structure formation, but also in that they avoid the nativism, the assumption of innateness, that encumbers much of classical gestalt theory. The organism does not merely experience temporal gestalts; it makes them in the form of behavior with the critical assistance of the prefrontal cortex.

Once a new structure of behavior has been initiated, the perception-action cycle becomes engaged and mechanisms are set in motion for the proper choice and order of individual acts toward the goal. From then on, it is up to a properly operating perception-action cycle to ensure the orderly execution of the behavioral structure in the temporal domain. To that end, the basic processes that take place in the brain are: (1) the mediation of cross-temporal contingencies; and (2) the monitoring of the success or failure of every action. These are accomplished by the timely deployment of the six executive functions listed in Section IV.

In the course of a behavioral structure, the successive acts within it need to be carried out in conformity with past and future events in the sequence. In other words, each act is contingent on one or more of these temporally separate events. That contingency basically consists of the previously established association – by learning and memory – between the various components of the sequence, all of them constituting, by means of synaptic connections, the executive cognit of that sequence. This cognit includes the representation of the plan or schema of action, the perceptual cues, the individual acts, and the goal or reward. The script of that sequential cognit consists of the orderly execution of the sequence toward its goal. Both the order and the proper integration of the temporal synthesis are strictly dependent on the mediation of all the contingencies within that sequence across time.

The lower part of Figure 8.8 illustrates schematically a goal-directed sequence of acts according to a pre-existent plan. The most critical contingencies, those for whose



**FIGURE 8.8** Succession of acts ( $a_1-a_n$ ) constituting a behavioral structure or plan of action toward its goal. Two-way arrows represent cross-temporal contingencies. Some of them link individual acts to each other, while others link individual acts to the schema or the goal of the action, and still others link the schema to the goal. *Top:* A chain of thoroughly learned or instinctual acts, where one act is strictly contingent on the immediately previous and succeeding acts without major cross-temporal contingencies. The prefrontal cortex is needed for integration of the lower sequence, not the upper one.

mediation the prefrontal cortex is needed, are not between automatically or reflexively concatenated acts (upper figure), but for those acts between distant elements of the sequence. The more novel and complex the plan, and the longer the time that separates contingencies, the more important the intervention of the prefrontal cortex in one or more perception-action cycles of that sequence. In the execution of the plan, individual acts are contingent not only on one another, but also on the schema of the plan and on the expected goal. Furthermore, some of the acts are contingent on sensory stimuli with which they are associated but from which they are temporally separated.

Clearly, the prefrontal cortex becomes essential when mutual contingencies in a series are separated by substantial periods, especially if these contingencies are novel or complex and contain ambiguities or uncertainty. This set of circumstances is practically universal in human

behavior, language, and empirical reasoning, whether the latter is inductive or deductive. There is virtually no novel structure of behavior, speech, or reasoning that does not contain substantial temporal discontinuities between logically related items. In other words, the need for mediating cross-temporal contingencies is practically universal in any novel human activity that is temporally extended and has a goal.

How is the plan actually implemented? How are cross-temporal contingencies mediated? The empirical evidence in previous chapters strongly indicates that the answer to these questions resides in the cooperation of the prefrontal cortex with other brain structures. However, to understand how that cortex, together with these structures, mediates cross-temporal contingencies and how order emerges from it, it is necessary to decompose goal-directed sequences into their constituent perception-action cycles and apply to these the executive functions of the prefrontal cortex. Cross-temporal contingencies and the order by which these functions mediate them are epitomized by a single trial in a delay task, such as delayed matching to sample. Indeed, the logic of a delay task epitomizes the logic of mediating cross-temporal contingencies: “If now this cue, then later that action” and “If earlier that cue, then now this action.” This logic requires the dynamic process of internal transferring of information across time that is within the physiological purview of the prefrontal cortex.

Before we proceed, however, we have to dispel a blatant and deceptive ambiguity. Over and over in this volume, and again in the next section (Section VII), we claim that the prefrontal cortex is mainly if not exclusively needed to temporally integrate *new* actions, that novelty is an essential quality of these actions or of the sensory information on which they are dependent. However, novelty would not seem to be an essential property of the stimuli, the rule, or the actions of a delay task; rather, it seems that habit and familiarity characterize every trial of

such a task. That simplicity is deceptive, however, because *for that trial* both the stimuli and the actions are independent from other trials, and for the organism, at that time, they are indeed *new* (the game is old but the play is new). This means that new is the cross-temporal contingency across the delay. It also means that the animal must suppress, that is, inhibit, any memory of a stimulus or response that, although appropriate for other trials, is inappropriate for the present one.

Thus, in the monotonous succession of well-practiced acts that make up a delay task, each trial is a new configuration of events with a time-break in the middle. Most behavioral analyses of the task unfortunately miss the point. Either they consider the task one more habit that animals can learn, or they fall into the atomistic dissection of individual acts and events, thereby destroying the unique and irreducible essence of the temporal gestalt that each trial is and for which the prefrontal cortex is needed.

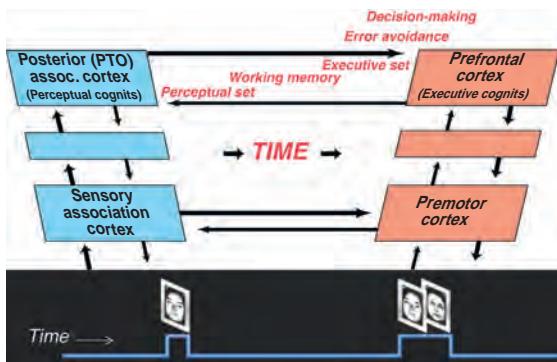
With these considerations in mind, let us view a single trial in a delayed-matching task as a new structure of behavior, a cortical cognit or set of cognits to be activated in a certain order for the mediation of a cross-temporal contingency (across the delay period). That trial is a perception-action cycle to be successfully closed through cortex and environment. Certainly, that new structure takes place within the context of an older set of rules embedded in that cognit or set of cognits. The schema of the action or plan is broadly defined by that pre-existent context, but the stimuli and the behavioral response are, for that trial, novel. Any success of the task, above random, depends on the mediation of the cross-delay contingency of every trial.

According to some modular models of behavior, each of the necessary functions to perform the task successfully is localized in a given structure or structures of the brain

dedicated to that function, whether it be attentional set, working memory, decision-making, error monitoring (and avoidance), or inhibitory control. Instead, based on the evidence presented in previous chapters, each of these functions consists simply of the timely activation or inhibition of the network or networks representing the associated components, sensory or motor, of each trial. Because a network can take part in more than one cognitive function, and its activation or inhibition is poorly demarcated experimentally in time (with the exception of working memory, which can be time-bracketed by the experimenter), it is only possible to estimate approximately the time of deployment of each function in the course of the perception-action cycle of a delay trial ([Figure 8.9](#)).

The importance of monitoring action outcomes in the structuring of a sequence of goal-directed sequences of behavior (e.g., trials in a delay task) was noted above. Each sequence has certain consequences on the environment and on the organism that will inform ensuing acts in the perception-action cycle. This will occur through feedback monitoring probably involving medial and orbital regions of the prefrontal cortex (see Chapters 3, 6, and 7). The resulting integrated information about these consequences and about other contingencies will determine the timing and configuration of the next act in the series. Avoidance of errors is founded on that monitoring and so is the inhibitory control of maladaptive alternatives.

Among all the executive functions that mediate temporal integration, two are the most amenable to physiological analysis in a primate's delay task: working memory and attentional executive set. The two are temporally symmetrical functions (in the course of the delay, the first wanes while the second waxes). Both are primarily based in the lateral prefrontal cortex (see Chapters 4–7), and both have a degree of sensory or motor specificity depending on the action domain within that cortex in which these



**FIGURE 8.9** Temporal deployment of executive functions in upper, cortical, levels of the perception-action cycle during a test of working memory (see Figure 7.7). Each function is predicted and expected from the past, which is made up of the context, the instructions from the tester, and the outcome of previous trials. The trial begins with attentional perceptual set to the face presented on the screen (the memorandum). This is followed by the working memory of that face, which smoothly leads to the attentional set (perceptual and executive) for the presentation of two faces, followed by the decision to choose the memorandum. That decision is preceded and accompanied by error avoidance, which includes the suppression (inhibition) of the alternative face. All timing is arbitrary and relative to the events of the test. Just as a cortical cognit is spatially “scale free,” its activation in a cognitive function is also temporally “scale free” (quotation marks here imply the relative nature of cognits and their activation, not the strict mathematical definition of the word they enclose). Abbreviation: PTO, parietal-temporal-occipital.

functions operate. Let us recapitulate the issue as discussed in Chapter 6.

The most plausible mechanism of working memory is reverberation by re-entry. To support that mechanism, there is a profusion of connective loops and reciprocal connections that tie prefrontal areas with one another and with several other structures. It is reasonable to postulate that the sustained activation of prefrontal cells in working memory results, at least in part, from continued reactivation of cortical pyramidal cells through *re-entrant circuits*,

whether these circuits are local or they course through structures outside the prefrontal cortex. Thus, the persistent activation of cortical neurons in working memory can be explained as a phenomenon of re-entry in existing cognitive networks of long-term memory (cognits) with synaptic weights pre-established by learning. However, as some computational studies indicate (Bodner et al., 2005; Deco et al., 2005; Shafi et al., 2007), these neurons in working-memory tasks are far from shifting between only bistable states (i.e., memory versus no-memory). Instead, their behavior in working memory obeys the constraints that result from belonging to a multiplicity of attractor circuits and being subject to rapidly changing synaptic dynamics. It is highly probable, as suggested in Chapter 6, that the multiple frequency “attractors,” as well as the synaptic dynamics of cortical cells in the working-memory state, reflect the successive activation of multiple associative circuits of the activated network. These circuits or subnetworks would represent the associated attributes of the working memory currently in focus, and thus components of the *ad hoc* activated long-term memory at large in the cerebral cortex.

Attentional executive set is the other major temporal-integration function of the prefrontal cortex. It is conventionally understood as the preparation for action. In several respects, executive set is the opposite of working memory. Whereas the latter is retrospective, set is prospective. Whereas the content of working memory is commonly sensory, that of set is commonly motor or, more broadly, action oriented. Whereas working memory is attention directed to an internal representation, set is attention directed to a prospective action; it is *executive attention*. By “executive” we mean much more than movement, skeletal or otherwise; outside a delay task, we also mean speech and internal action, logical reasoning. They all need set, in addition to working memory, for temporal integration, order and timing. Thus, working

memory and, we might say, working set, are two sides of the same coin, which is temporal integration in the perception-action cycle under the prefrontal cortex.

On the executive side, the process of preparation is cognitively, and possibly also neurally, similar to that of sensorial attention. That is one of the reasons why executive set may be equated with motor attention. Just as perceptual networks, when activated, select certain sectors of sensorium and perceptual memory, so do the activated motor networks select other motor networks for preparation and outlet. Thus, the prefrontal cortex prepares the motor apparatus for forthcoming acts that are part of the ongoing behavioral structure under its control. How prefrontal networks serve motor set remains unclear, however. It seems most likely that they do so by exerting facilitating influences, in part through subcortical loops, on lower stages of the frontal hierarchy for action, ultimately on the motor cortex. Connective loops through the cerebellum may be critical for immediate action. On the whole, prefrontal influences probably prime the motor apparatus in anticipation of the action, even though its final enactment in all its specifics may hinge on yet one or more pieces of pending sensory information.

In conclusion and somewhat allegorically, the two temporal integrative functions of the prefrontal cortex, working memory and executive set, *reconcile the past with the future* of a behavioral structure. They close the perception-action cycle at the top, bridging time between sensory and motor components of that structure. Some of the integration probably takes place in the prefrontal cortex itself, where cells are found in close proximity to each other that support the two functions (see Chapter 6). Integration by memory and set is also probably achieved by interactions between prefrontal cortex and posterior cortices. The exact cortical areas involved in that integration depend on the modality of the information in working memory and on the particular action domain involved.

## VII. PREDICTION AND NOVELTY IN THE HUMAN BRAIN

The prefrontal cortex is the vanguard of brain evolution (see Chapter 2). It develops most and last in the human brain. It also develops last in ontogeny. For these reasons, the prefrontal cortex supports the most human of all human cognitive functions, namely, prediction, language, and creative intelligence. It has been argued that these functions are not new to the human, for they are already present in lower mammals, especially the great primates. This is the old "continuity" argument, which maintains that the cognitive transitions to the human are only quantitative, not qualitative. The argument has some merit on volumetric grounds; after all, the relative size of the prefrontal cortex in the chimpanzee is 17% with respect to the totality of the neocortex, while in the human it is 29%. It seems unlikely, however, that a difference of 12% in mass would justify such a large difference in cognitive capabilities to include such extraordinarily specialized functions as human language. The continuity argument can only be defended by transferring the extraordinary cognitive load from volume to connectivity, and by not simply making connectivity reducible to white matter but also extending it to the imponderable, yet enormous, proliferation of fine, unmyelinated, fibers and synaptic connections of the human brain. These would multiply the power of connectivity exponentially, in effect converting an evolutionarily continuous function into a step function and immensely incrementing the power of cognitive functions such as language, which receives and transmits information essentially by a *relational code* of words, sounds, and ideas.

Etymologically related to a quality of language is the capacity to predict (Latin *praedicere*), which also evolves extraordinarily in the human with the prefrontal cortex (Fuster and Bressler, 2015). It is a curious phenomenon that, with evolution (a postdictable science), the prefrontal

cortex opens the brain to predicting the future. This is a direct result of the future orientation of the executive functions of this cortex (see Section IV), notably planning, attentional set, working memory, and decision-making. This capacity to predict includes that of *self-predicting*, of predicting oneself doing something in the future. Prediction in the human is tantamount to purposeful preadaptation. The ability to preadapt to the future is a distinctly human ability that derives from the development of the prefrontal cortex. The prefrontal cortex makes the human brain a preadaptive system (Fuster, 2014).

All predictions are based on past memory and experience; there is no true teleology or reversal of temporal causality in the prefrontal cortex. Be that as it may, because of the predictive capacities of the human prefrontal cortex, people can plan to attain long-term objectives with long and multiple perception-action cycles. The same capacities allow a person to create new language and new structures of behavior to his or her benefit and that of others.

## A. Language

Most of the activities related to language, such as speaking, writing, reading, reasoning, or conversing, necessitate temporal integration and the integrative role of the prefrontal cortex. The degree to which they require them depends on the novelty and complexity of the material – in this case linguistic content – as well as the length of time to be bridged between contingencies. Clearly, language in all its forms of expression, except for routine, depends on the perception-action cycle to bridge contingencies across time.

The structure of the linguistic proposition is literally made with syntax. Words are arranged in sentences that for meaning require the mediation of contingencies between them. Verbs, adjectives, nouns, prepositions, and other word forms are among the elements serving that mediation. To the speaker, the

listener, or the reader, the single sentence is a structure of action that derives its meaning from the order and choice of words, much as a behavioral structure pursues its goal through the order and choice of individual acts. More complex forms of language require even more the temporal integration and mediation of cross-temporal contingencies that the prefrontal cortex can provide. A paragraph or a discourse is unintelligible without integration and cross-temporal mediation. There is a very close resemblance between language expression, that is, the structuring of language, and the structuring of goal-directed behavior.

The reason for that resemblance is that both language and behavior utilize the same perceptual and executive hierarchies of representations, and the dynamics of the perception-action cycle is essentially identical in the two. The posterior association cortex harbors the semantic representations of language, whereas the frontal cortex harbors the syntactic and grammatical representations (including action verbs). The two hierarchical orders of representations, semantic and syntactic, interact within the perception-action cycle in the production and understanding of language.

In phylogeny, as in ontogeny, the two hierarchical organizations of cortical networks, posterior and frontal, develop in correlation with the development of language. In both association cortices the maturation of connectivity (synapses, axonic and dendritic branching, myelination, etc.) comes on top of the evolutionary expansion of subcortical white matter, which is to a large extent made of corticocortical connections (see Chapter 2). The growth of cortical connectivity is at the foundation of the enormous expansion of cognitive networks in the adult human brain. Therein lies the reason for the enormous increase in representational power of the cortex and the richness of the uniquely human means of communication. These developments take place side by side with the development of cognitive capabilities

in functions other than language. With regard to the frontal cortex, it is of singular interest that the development of linguistic syntax is narrowly correlated with that of complex motor sequencing (Kimura, 1993), that is, Lashley's (1951) syntax of action. It has been suggested that the evolution of linguistic syntactic ability takes place in an area of the left frontal cortex specialized in the manipulation of tools and instruments. That area, in the human, becomes Broca's area. In more general terms, the two abilities, language and manipulation, depend on left-hemisphere dominance. It is conceivable that both derive from the evolution of a common frontal area of the left hemisphere devoted to the organization of sequential behavior (Greenfield, 1991). It is a matter of further speculation whether Broca's area and its closely associated areas (44–47) contain a "phylogenetic" neural substrate of language that would account for *universal grammar* (Chomsky, 1985).

In the processing of speech or language, the perception-action cycle becomes and stays engaged at several levels. At subcortical levels, inputs from the limbic brain modulate the cortical cycle by imparting to it the emotional influences that will color the expression and interpretation of language in terms of emphasis, affective nuance, and prosody (emotional perception-action cycle). In addition, at every cortical level of the posterior (semantic) and frontal (productive, grammatical) hierarchies, there will be continuous feedforward and feedback between levels toward assuring order, direction, and correction of language toward its goal; that is, the conveyance of intended meaning. In these general aspects of language processing, the perception-action cycle operates in a manner similar to the manner it operates in any other form of purposeful behavioral processing.

As in behavioral sequencing, feedback plays a crucial role in regulating the perception-action cycle during language. Here, it is important to distinguish the *internal feedback*

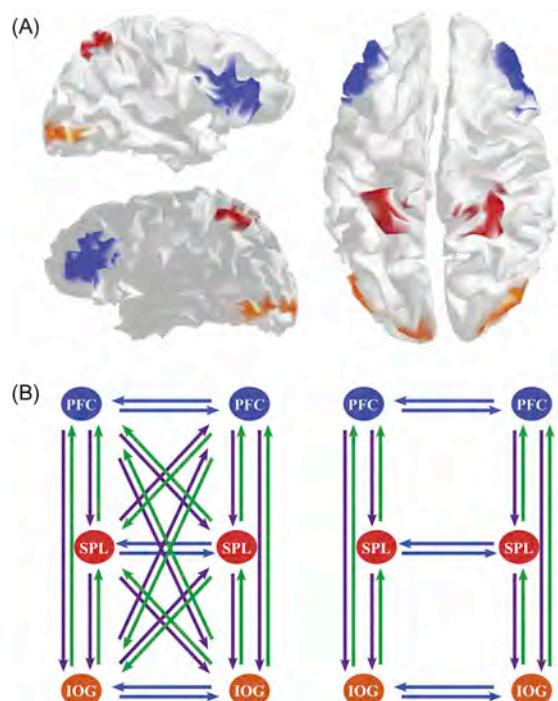
originating in effector systems from the – sensory – *external feedback* originating in the environment. The first includes efferent copy and corollary discharge from the organs and muscles of articulation. At higher levels, however, internal feedback includes signals from the prefrontal cortex, upon the posterior cortex of association, that are essential for the temporal integration of language. These signals, in the aggregate, constitute the so-called cognitive control by the prefrontal cortex upon posterior semantic networks. Such control is essential for the proper operation of the attentive processes of language. Feedback from the prefrontal cortex on posterior cortex plays a critical role in working memory; some of that feedback contributes to the recurrent reverberation between prefrontal and posterior cortex that has been postulated to lie at the foundation of working memory (see Chapter 6).

Working memory is a critical component of language understanding and production at the top of the perception-action cycle. By working memory, cross-temporal contingencies are mediated in speeches and paragraphs, in syllogisms and logical discourses, in debates and "simultaneous" translations. Nothing in the spoken or written language makes complete sense without the working memory of precedents or premises, subjects or predicates, assumptions or lexical equivalents. It is the working memory of these materials that brings closure and meaning to the argument, the document, or the discussion. Although its precise mechanisms are still unclear, linguistic working memory is most likely to be achieved by the dynamic interaction of prefrontal and posterior networks in the form of recurrent reverberation. This reverberation in working memory, which by definition includes internal feedback, would close at the summit of the perception-action cycle of language. The cycle is closed at the bottom, in the environment, by external feedback from the audience, the interlocutor, or the written page.

## B. Imagination and Creative Intelligence

"To invent the future," it has been said, is the exclusive purview of the prefrontal cortex. Yet, because in human creativity there is no future without a past, it is difficult to dissociate that presumed role of the prefrontal cortex in creativity from its role in the temporal organization of behavior, language, and reasoning. Temporal organization is based on temporal integration, which entails not only the reconciling of the future with the past, but also the building of the future on the past. More specifically, future behavior, language, or reasoning is based on a past in long-term memory. All new actions in the three domains are created out of existing representations (cognits, memories), and no new action is conceivable – literally conceivable – without precedents in the experience of the individual. The richer the experience, the richer the possibilities for new action derived from that experience.

All future action is a remaking of the past by the brain. That past is represented in myriad networks of anterior and posterior cortex. Out of these existing networks, the prefrontal cortex creates new plans and, with their enactment, new experiences. These plans and their enactment require imagination, which is the internal remaking of old percepts (perceptual cognits) in the service of new forms in the realms of the artistic, the scientific, the social, and the economic. Imagination can be construed as new perception internally generated by top-down influences from prefrontal upon sensory cortex and introduced in the perception-action cycle of new action. There is empirical evidence for this. [Figure 8.10](#) illustrates the flow of functional connectivity in visual perception and in visual imagery using the latest methods for cortical tracing of electrical signals ([Dentico et al., 2014](#)). Whereas in perception the flow of signals is bottom-up, from sensory to (lateral) prefrontal cortex, in visual imagining it is the reverse. Furthermore, signals from orbitomedial cortex have been shown to complete (predict)



**FIGURE 8.10** Study (by high-density electrical recording) of functional connective directionality of signals during processing of visual perception and visual imagery. (A) Regions of interest (according to Montreal Neurological Institute brain map): orange, inferior occipital gyrus; red, superior parietal lobule; blue, Brodmann's area 46 (BA46) in dorsolateral prefrontal cortex. (B) Representation of backward (violet), forward (green), and lateral (blue) connections in the empirical multivariate model used to compute Granger causality (left), and cross-spectral densities (right) ([Friston et al., 2012](#)). Abbreviations: IOG, inferior occipital gyrus; PFC, area BA46 in dorsolateral prefrontal cortex; SPL, superior parietal lobule. From [Dentico et al., 2014](#), with permission.

incomplete visual percepts based on prior associative experience ([Chaumon et al., 2014](#)). In sum, the prefrontal cortex appears to exert control of visual experience in cognition and possibly also in emotion. Both mechanisms can serve imagination, that is, the internal experience of percepts based on externally incomplete, absent, or emotional signals generated in frontal cortex.

In Chapter 5, we discussed the importance of the prefrontal cortex for the complex, multifaceted function of intelligence, which we define as the ability to adjust by reasoning to new changes, to solve new problems, or to create new valued forms of action and expression. In that chapter, we emphasized how much intelligence depends on other cognitive functions, notably attention, memory, and language. Here, we will re-emphasize these dependencies of intelligence, especially on language, and the novel, creative, aspects of intelligence.

Between 6 and 16 years of age, a child's intelligence undergoes an enormous change toward the independence of mental life from sensory perception. It is a change from within, in that the actions of the child become increasingly detached from the environment and governed by internal factors, among them curiosity, the fund of knowledge, and the drive toward innovation. Behavior becomes more cognitively driven, less stimulus bound, more autonomous, less reactive, and more spontaneous and proactive. This is the origin of creative intelligence. Its development takes place in close correlation with two interrelated phenomena: (1) a momentous expansion of language ability; and (2) the maturation of the prefrontal cortex, especially the cortex that covers the lateral and anterior convexity of the frontal lobe.

Some developmental psychologists attribute the explosive advent of creative intelligence to the development of language, and we might add, in the light of previous discussion, the capacity to use tools and instruments. Language development, according to [Vygotsky \(1986\)](#), is at the very essence of the development of intelligence in general, as well as of the other cognitive functions. Language stays in that pre-eminent position, at the root of intelligence, throughout adult life. Other cognitive functions, as they develop, enhance the development of language, and with it intelligence. Eventually, in that critical 6–16-year-old period, these functions transcend the stage of merely

enhancing intelligence to become its servants. Thus, creative intelligence, the "intelligence from within," emerges as the aggregate outcome of intelligent attention, intelligent perception, intelligent memory, and intelligent language. Together with them, intelligent action develops, which leads to the intelligent, innovative use of language, tools, and instruments.

All the developments on which creative intelligence is founded take place in conjunction with, indeed as a result of, the maturation of the lateral prefrontal cortex. The maturation of the prefrontal cortex of the right hemisphere seems to be especially important for the development of spatial creativity ([Luria and Simernitskaya, 1977](#); [Lezak, 1995](#)), while that of the left is important for the development of linguistic creativity, and also, arguably, for that of musical and logical creativity. Neither hemisphere, however, has exclusive control over one or another form of creativity; instead, we are dealing with a relatively great contribution to one or the other. Both hemispheres contribute to some degree to creative intelligence in general.

Furthermore, it is not the case that prefrontal maturation makes intelligence fully autonomous, independent of the perception-action cycle. Rather, prefrontal maturation adds new, higher, more conceptual layers to the cycle, opening wider cortical networks to represent higher, more novel representations – better yet perhaps, "pre-presentations" – of action. These representations result mostly from the divergence, not so much convergence, of lower level representations. Convergent representation includes both inductive and deductive reasoning, which leads to logical inferences, whereas divergent representation is free of logical constraints, leading to the free interpretations of reality from free usage of imagination.

To reiterate, the creative process is largely one of making new cognits out of old ones, that is, of making new associations within and between old cognits, under the agency of the prefrontal cortex. Because of the enormous

combinatorial power of cortical networks, the potential for new cognits or representational networks – as well as imagination – is practically infinite. Because of that open-ended potential for new representations, and their diverse make-up, their cortical distribution is subject to large variability.

In the creative process, the prefrontal cortex is influenced by three orders of inputs: (1) inputs from the brainstem and limbic structures; (2) inputs from posterior association cortex; and (3) inputs from sensory organs. The inputs from the brainstem, largely through glutaminergic and monoaminergic systems, contribute to the prefrontal cortex signals related to biological drives, attention, and reward, all essential to the creative act. Among the limbic inputs, those from the amygdala in particular signal the motivational significance of creative associations.

Both brainstem and limbic inputs affect prefrontal networks largely through orbital and cingulate prefrontal cortex. The inputs from posterior association cortex, through cortico-cortical associations, contribute to the prefrontal cortex signals from established perceptual memory networks that will aid in the formation of new executive networks. These signals will also serve the perception-action cycle at its summit in the temporal display of creative production. Included in both the old and the new networks are the representations of a variety of esthetic and ethical values, innate or acquired, that guide and constrain creative intelligence. Finally, sensory inputs will also prompt and modulate the creative production under cognitive control of the prefrontal cortex. These inputs may be essential for the initiation of that production or, at one point or another, of its course. Nonetheless, what unquestionably prompts and guides the prefrontal cortex of the artist, the writer or the composer, as well as the scientist, is not so much what comes through the senses but a wealth of influences from the internal milieu and from the internal fund of

memory and knowledge in the neocortex. Only by taking these various influences into account can we understand the power of affect, drive, memory, and imagination in the realization of an original creation.

## VIII. CONSCIOUSNESS AND FREE WILL

Consciousness is the awareness of one's self. It is the central subject of phenomenology, only amenable to study in the human by the use of introspective methods and personal inquiry. The description and classification of conscious experiences and states are of great value to psychology and psychiatry. To cognitive neuroscience, consciousness is also a valuable aid because, first, it provides subjective correlates to all cognitive functions, and second, it assists the psychophysical measurement of some of these functions, notably perception. Because of fundamental epistemic differences between phenomenology and neuroscience, however, questions such as the location or mechanisms of consciousness are to a large extent meaningless and unanswerable. The neural correlates of conscious experience, however, are a legitimate question.

The most characteristic phenomenological traits of consciousness are *unity* and *ownership*. Both are intimately related. In the conscious state, the experiences of the internal and external milieu merge to yield a spatially and temporally unitary experience that is inalienably one's own. Although unitary, however, that experience is not static, but fluid, as its content changes with time without losing its phenomenal cohesion. That fluid change is what [William James \(1890\)](#) called "the stream of consciousness." The flow or stream of consciousness does not deprive the latter of either unity or ownership. This is true whether we engage in free-floating mental activity or in conscious cognition during attention, perception, memory, language, or intellectual activity.

We can carry out many cognitive operations unconsciously, especially if their content is thoroughly familiar to us. But the operations of intentional memory recall or retrieval, speaking, reasoning, and reading, for example, are conscious. Most definitely conscious are the processes of attention, especially perceptual attention, and working memory. Because, as we have seen, the prefrontal cortex plays a pivotal role in both, this cortex has been occasionally attributed as the seat of consciousness. However, there is now substantial evidence from neuropsychological sources that consciousness is not localized anywhere in the brain, but rather is a phenomenon – in the strict sense of the word – of neural activity in several regions of the brain, especially the neocortex.

Indispensable for consciousness is a certain minimum level of tonic excitatory influences reaching the neocortex from neurotransmitter systems in the brainstem. That subcortical tonus enables the cortex to engage in whatever cognitive operations are called for at any given time. The level and distribution of activity in the cortex engaged in cognition determine the content of consciousness. Changes in that level and distribution determine the flow of consciousness. In any case, inasmuch as the prefrontal cortex controls cognition, that is, controls the activity of cortical areas involved in cognition, its role in consciousness is critical. This is especially the case in the attentive processes that lead a structure of behavior, speech, or reasoning to its goal.

Among these processes, working memory is the most closely associated with consciousness. The reason is simple: during working memory the content of attention (internal attention) remains in a relatively steady state, or “remembered present” (Edelman, 1989) until consequent action occurs. In working memory, conscious unity is assured by the persistence of cognitive content that the prefrontal cortex confers to the process of temporal integration.

Unity of consciousness is thereby reinforced in the temporal domain.

The temporal persistence of working memory and its neural substrate makes this attentive function the ideal grounds for the study of consciousness with current research methods, such as single-cell recording, coherence analysis, and neuroimaging. However, none of these methods can reveal anything other than neural cophenomena of consciousness. This must suffice, as there is no *causal* relationship between brain and mind, but rather a relationship of isomorphism (Fuster, 2003). For the structural and dynamic study of that isomorphism, correlation is sufficient. There is no mechanism of consciousness other than the mechanisms of attention or of any other mental function of whose cognitive or emotional content we are aware. It is through its role in any such function that the role of the prefrontal cortex in consciousness may be understood.

Free will is another neurophilosophical issue of concern to the student of the frontal lobe. There are several reasons for this. First, most of the cortex of the frontal convexity is known to be involved in one or another aspect of voluntary action. It is also involved in the representation of actions, as it harbors a profusion of interconnected and overlapping executive networks. The prefrontal cortex, at the top of the executive hierarchy, is critical in decision-making, the capacity to choose between alternatives of action (including inaction), which is the essence of freedom (Fuster, 2013). Although, for reasons repeatedly stated in these pages, that cortex cannot be called with impunity the “central executive,” much less the “center of will,” it is key to the temporal organization of willful behavior, reasoning, and speech. Yet, before we attribute free will in any form to the prefrontal cortex, some of the dynamic principles on which it operates should be considered again.

To organize its activities, the prefrontal cortex receives an immense quantity of afferent influences from the rest of the brain. These

influences come from both the internal and the external milieu. From the internal milieu, through the limbic system and the hypothalamus, the prefrontal cortex receives a wealth of information about the state of internal organs, hormonal levels, autonomic conditions, and more generally, about mood and emotion. From the external milieu, through the senses and posterior association cortex, the prefrontal cortex receives a constant barrage of sensory information, including feedback on the consequences of the actions of the organism on itself.

At the same time, from the rest of the cortex, which can be considered part of the internal milieu, the prefrontal cortex receives information about pre-existing knowledge, that is, information from the world of cognition, memory, and language. This fount of knowledge also brings to the prefrontal cortex influences from the world of culture, values, and ethics. These are the influences that Benjamin Constant called the “system of principles.” This system includes natural law, the so-called moral sense, and civic law. In the aggregate, it is what Anglo-Saxon liberalism calls “the rule of law,” without which freedom does not exist ([Locke, 1764](#)).

Consequently, at a given moment in our daily life, a host of internal and external influences enter in competition with one another, demanding attention from our executive cortex to shape decisions and actions. The majority of these influences are processed simultaneously, in parallel, and out of consciousness. Only a minority will lead to action, sometimes only one action (“winner takes all”). Presumably, in neuroeconomic terms, the action will be selected after a probabilistic estimate of maximum benefit and minimum risk. The other actions must wait for their chance.

The action can take many routes and many expressions. There is the movement processed by the basal ganglia and motor cortex. Then, there is the visceral and emotional action, processed by the same structures and by the limbic

brain. And then, there is the cognitive action that engages the prefrontal cortex together with other cortical regions and leads to myriad forms of language, spoken or written, and to artistic production or scientific discovery.

The following, therefore, seems a reasonable proposition. The prefrontal cortex is constantly subjected to a multitude of signals from the external and internal milieu. These signals engage in competition for action. The decision to act depends on the probability and strength of each of these signals, as well as the probability of benefits and risks from it. Therefore, freedom of action at a given time is defined literally and statistically by the degrees of freedom of the inputs and outputs of the prefrontal cortex. Thus, in neural terms, both determinism and freedom of action are relative and probabilistic. The old argument between the two becomes idle. All actions are the result of conscious or unconscious efforts to maintain, in a broad sense, the adaptation of the organism to its environment – homeostatic equilibrium as [Bernard \(1927\)](#) and [Cannon \(1932\)](#) understood it. (To the extent that these efforts are unconscious, we feel free to act, although in accord with Freudian dictum we may not be.) Neurobiologically, all actions are the result of the operation of a multidimensional cybernetic cycle of adaptation, that is, the perception-action cycle, with the prefrontal cortex on top of its cortical and subcortical inputs and outputs. The cycle has no true origin, and no action will be generated truly and only on top. Thus, the idea of a center of will becomes meaningless.

Under certain human conditions of coercion, accident, or illness, certain actions become limited or impossible, while others become compulsive and inevitable. Diseases of the cortex or subcortex may lead by themselves to a loss of the freedom to act. A person with excessive excitability of orbitofrontal cortex, in the Gilles de la Tourette syndrome or obsessive-compulsive disorder, will become a prisoner of his obsessions and compulsions. Conversely,

someone with defective function of that cortex will become a prisoner of his impulsivity and may deprive others of their own freedom.

Nevertheless, under normal conditions, the existential experience of freedom can be attributed to the simultaneous presence of several demands of approximately equivalent weight and priority on the executive cortex and, at the same time, the presence of several viable actions that are authorized, even guaranteed, by the rule of law. Some of the demands may come from obscure unconscious sources. Under the power of imagination, they can lead us to new, even revolutionary, actions in the social, scientific, artistic, or financial domains. It is for this reason, among others reviewed above (see *Imagination and Creative Intelligence*, above), that the prefrontal cortex has been called "the organ of creativity."

## IX. SUMMARY

The purpose of this chapter is to present the model of prefrontal function that by induction and deduction accommodates almost all of the empirical evidence in previous chapters. It is a connectionist model based on the assumption that the cortical representations of memories, percepts, and actions (i.e., the basic units of memory and knowledge) consist of widely distributed, overlapping, and profusely interactive neuronal networks called cognits. By virtue of associations formed by experience, one neuron or group of neurons in any cognit can be part of many other cognits, that is, memories or items of knowledge. Each cognit is surrounded by a penumbra of weak or unstable connections with others.

Perceptual cognits (acquired by sensory perception) are hierarchically organized in posterior cortex, whereas motor or executive cognits (acquired by action) are similarly organized in frontal cortex. Cognits representing discrete

sensations are distributed at low levels of the perceptual hierarchy, in or near sensory cortex. Hierarchically higher and more complex networks of temporal and parietal cortex represent higher and more complex perceptual cognits. Cognits representing discrete movements are distributed at low levels of the executive hierarchy, in or near motor cortex. The highest and most complex cognitive networks of premotor and prefrontal cortex represent complex plans or schemas of goal-directed action.

All cognitive functions (attention, perception, memory, language, and intelligence) consist of neural transactions within and between cognits. The dorsolateral prefrontal cortex is dedicated to the cognitive functions that control the execution of new sequences of goal-directed actions. This cortex performs its cognitive role in cooperation with orbitomedial and posterior association cortices, the striatum, and other subcortical structures. Distinct categories of motor-action cognits are represented in relatively segregated domains of frontal cortex. In the dorsolateral prefrontal cortex, there is an action domain for skeletal movement, another for eye movement, and yet another for speech. In orbitomedial frontal cortex, action domains can be identified for emotional behavior and its visceral manifestations.

The prefrontal cortex has six principal executive functions: planning, attentional set, working memory, decision-making, error monitoring and avoidance, and inhibitory control. All are preadaptive in that they have future effects on the adaptation of the organism to its environment.

*Planning* is the first major executive function, which is essential for the formulation and execution of novel plans of goal-directed behavior; these are represented in the form of abstract schemas of action in the polar frontal region. Their component cognits are represented at lower levels of the motor hierarchy. An orderly arrangement of executive cognits links the

various stages of the motor hierarchy to support the execution of plans. In plan execution, the dynamic processing flows downward from prefrontal to premotor to motor cortex. In the processing of sequential action, both parallel and serial processing take place within and between action domains and cognits.

*Attentional set* consists of the priming of sensory and motor systems for anticipated percepts and motor acts in the course of a sequence of goal-directed actions. This dual executive function is also future oriented by definition. The selection is made among items of an established repertoire of perceptual and executive cognits. Attentional set is based mainly in lateral prefrontal cortex and operates on posterior perceptual cortex and its cognits, as well as on its frontal executive cognits. Set extends to sensory structures and basal ganglia.

*Working memory* is attention focused on an internal representation or cognit for a purposive action in the proximate future. That representation consists of a recent sensory or motor event that must be provisionally retained for prospective action in solving a problem or pursuing a goal. Broadly and more accurately defined, working memory is the temporary retention of an updated long-term memory for prospective action. In neural terms, working memory consists in the sustained activation – by re-entry – of an executive cognitive network, which ordinarily involves the action domains of lateral prefrontal cortex and regions of posterior (perceptual) cortex.

*Decision-making* is the intentional choice of a course of action in the immediate or distant future. A deliberate decision is a multideterminate phenomenon, a “vector” of numerous and diverse neural influences that converge on frontal cortex from other brain regions. They need not be fully conscious. Foremost among these influences are the basic biological drives; their signals arrive through orbitomedial cortex. Other signals come from posterior cortical

cognits. Behind each decision is an estimation of the valence of the relevant stimuli and of the expected costs and benefits of the decided action. This estimation most likely involves probabilistic computations based on current inputs and past history (Bayesian).

In cingulate prefrontal cortex there are mechanisms for monitoring the success or failure of each action in a series. Signals from that cortex serve the prefrontal and limbic systems to estimate predicted reward. Failure to attain it is called *prediction error*. Minimizing prediction errors complements the executive function of monitoring response outcome.

*Inhibitory control*, the sixth executive function of the prefrontal cortex, is the exclusionary aspect of attentional set, working memory, and decision-making. It protects behavioral structures from external or internal interference. By suppressing distraction, attention is safeguarded. The assisting inhibitory function is based primarily in orbitomedial prefrontal cortex and exerted on several cortical and subcortical regions, especially the basal ganglia.

The orbitomedial prefrontal cortex plays a crucial role in *emotional behavior*. There are several reasons for this: (1) this cortex sits at the crossroads of neurotransmitter systems involved in drive, motivation, and assessment of valence; (2) it receives, through the hypothalamus, a host of somatic – some of them autonomic – signals, including those related to basic drives (pain, hunger, sex, and aggression); (3) it receives from limbic structures, especially the amygdala, information about the motivational significance of external signals; (4) it is the source of descending inhibitory signals to hypothalamus and other subcortical structures that are essential for the control of instinctual impulses; and (5) it is the source of signals, again through the hypothalamus, to autonomic and endocrine systems involved in emotional behavior. Furthermore, the orbitomedial cortex, through its efferent fibers to lateral prefrontal

cortex, influences – or “colors emotionally” – cognitive executive functions. Conversely, afferent influences from lateral to orbitomedial cortex exert a degree of cognitive inhibitory control over emotional behavior.

The functions of the prefrontal cortex rarely work in isolation from one another. Characteristically in the human, they join together synergistically in the *temporal organization of action*, that is, the orderly sequencing of actions toward a goal. To understand the neural dynamics of temporal organization, the prefrontal cortex and its functions must be viewed within the biological framework of the *perception-action cycle*.

The perception-action cycle is the circular cybernetic flow of information processing between the organism and its environment in a sequence of goal-directed actions. It operates at all levels of the central nervous system. Simple, automatic, and well-rehearsed behaviors engage only the lower levels where, for sensory-motor integration, the cycle runs through the spinal cord and subcortical structures. Complex, novel, and temporally extended behaviors, however, engage the neocortex and the connections between prefrontal and posterior association cortex. The prefrontal cortex sits at the summit of the perception-action cycle integrating across time percepts and actions toward a goal.

*Temporal integration* is at the foundation of temporal organization. To that end, the prefrontal cortex performs the crucial role of integrating cross-temporal contingencies. Working memory is the most important of the executive functions that the prefrontal cortex utilizes to mediate cross-temporal contingencies.

Because of its crucial role in temporal integration and organization, the prefrontal cortex, especially in the left hemisphere, is essential for the construction and understanding of *language*. It is thus important for the syntax of language, a special case of the “syntax of action.”

Language engages the perception-action cycle at its highest levels in the interaction of the organism with the environment, which now includes the interlocutor and the written page. At these levels, cross-temporal contingencies are mediated by reciprocal interactions between frontal cortex, including Broca’s area, and posterior association cortex, including Wernicke’s area. Again, working memory plays a key role in language, in the underlying operations of temporal integration of words and sentences.

*Creative intelligence*, the ability to construct new forms of action and expression, undergoes enormous expansion in the human with the expansion of the prefrontal cortex and its connectivity. This kind of intelligence, like all prefrontal functions, is open to the future. With maturation, all executive and emotional functions of the prefrontal cortex become available to *imagination*. The creative act is essentially a re-creation of the past with the assistance of imagination. Thus, out of the past, the prefrontal cortex helps to imagine and create new forms of social, esthetic, scientific, ethical, or economic value.

The chapter ends with a brief discussion of two philosophical issues related to the functions of the prefrontal cortex: consciousness and free will. Neither entity has a specific neural substrate, either in the prefrontal cortex or elsewhere. Yet the prefrontal cortex is relevant to both. Consciousness is a phenomenon of cortical activation. Its subjective content – the “flow of consciousness” – varies with the areas and cognitive or emotional networks activated at any given time. The selection of actions and decision-making (the essence of “free will”) depend on a multitude of inputs to the frontal cortex from many sectors of the organism and its environment (some unconscious). The decision to act in a certain way emerges from the competition between those inputs calling for action, as well as from the prospective probabilities of cost and benefit attached to each action.

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