

The Prefrontal Cortex—An Update: Time Is of the Essence

Review

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The physiology of the cerebral cortex is organized in hierarchical manner. At the bottom of the cortical organization, sensory and motor areas support specific sensory and motor functions. Progressively higher areas—of later phylogenetic and ontogenetic development—support functions that are progressively more integrative. The prefrontal cortex (PFC) constitutes the highest level of the cortical hierarchy dedicated to the representation and execution of actions.

The PFC can be subdivided in three major regions: orbital, medial, and lateral. The orbital and medial regions are involved in emotional behavior. The lateral region, which is maximally developed in the human, provides the cognitive support to the temporal organization of behavior, speech, and reasoning. This function of temporal organization is served by several subordinate functions that are closely intertwined (e.g., temporal integration, working memory, set). Whatever areal specialization can be discerned in the PFC is not so much attributable to the topographical distribution of those functions as to the nature of the cognitive information with which they operate. Much of the prevalent confusion in the PFC literature derives from two common errors. The first is to argue for one particular prefrontal function while opposing or neglecting others that complement it; the second is to localize any of them within a discrete portion of PFC.

The functions of the PFC rely closely on its connections with a vast array of other cerebral structures. None of its cognitive functions can be understood if taken out of a broad connectionist context. Any hypothetical modularity of the PFC is functionally meaningless if taken out of wide-ranging networks that extend far beyond the confines of any given prefrontal area. This is the reason why the discussion of the operations of the PFC is here preceded by the placement of the PFC in a cortical connectionist map of cognitive representations.

After reviewing the anatomy and connectivity of the PFC, I discuss its highest and most general functions, which are inferred mainly from neuropsychological studies. Then I proceed with a conceptual model of the cognitive organization of the neocortex, which derives from those studies as well as from our knowledge of cortical connectivity. Next, I deal with the dynamics of the PFC in cognitive operations and with current evidence on the functional specificity of its areas. The review concludes with recent insights from physiological research on monkeys into the prefrontal mechanisms of temporal integration. Although the focus here is on the PFC of the primate, it is reasonable to assume that

many of the principles discussed below apply also to the PFC of nonprimate species.

Anatomy and Connections

The PFC is the association cortex of the frontal lobe. In primates, it comprises areas 8–13, 24, 32, 46, and 47 according to the cytoarchitectonic map of Brodmann (1909), recently updated for the monkey by Petrides and Pandya (Figure 1). Phylogenetically, it is one of the latest cortices to develop, having attained maximum relative growth in the human brain (Brodmann, 1912; Jerison, 1994), where it constitutes nearly one-third of the neocortex. Furthermore, the PFC undergoes late development in the course of ontogeny. In the human, by myelogenic and synaptogenic criteria, the PFC is clearly late-maturing cortex (Flechsig, 1920; Conel, 1939; Huttenlocher, 1990; Huttenlocher and Dabholkar, 1997). In the monkey's PFC, myelogenesis also seems to develop late (Gibson, 1991). However, the assumption that the synaptic structure of the PFC lags behind that of other neocortical areas has been challenged with morphometric data (Bourgeois et al., 1994). In any case, imaging studies indicate that, in the human, prefrontal areas do not attain full maturity until adolescence (Chugani et al., 1987; Paus et al., 1999; Sowell et al., 1999). This conclusion is consistent with the behavioral evidence that these areas are critical for those higher cognitive functions that develop late, such as propositional speech and reasoning.

The profuse variety of connections of the PFC is obvi-

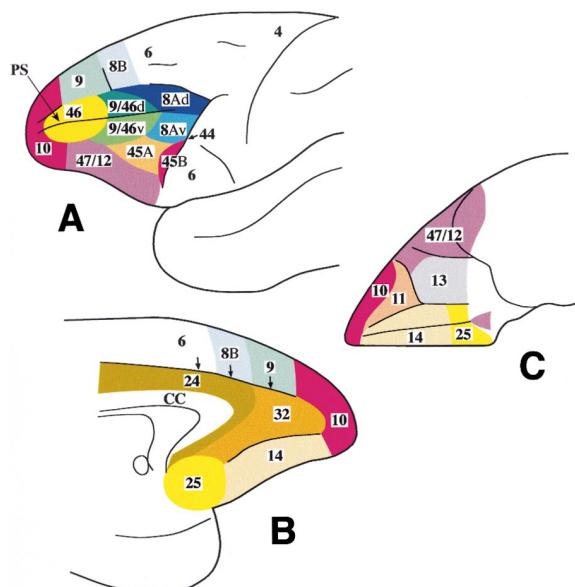


Figure 1. Cytoarchitectonic Map of the Monkey's Frontal Cortex

(A) Lateral view.

(B) Medial view.

(C) Inferior (orbital) view.

CC, corpus callosum; PS, principal sulcus. From Petrides and Pandya (1994), slightly modified, with permission.

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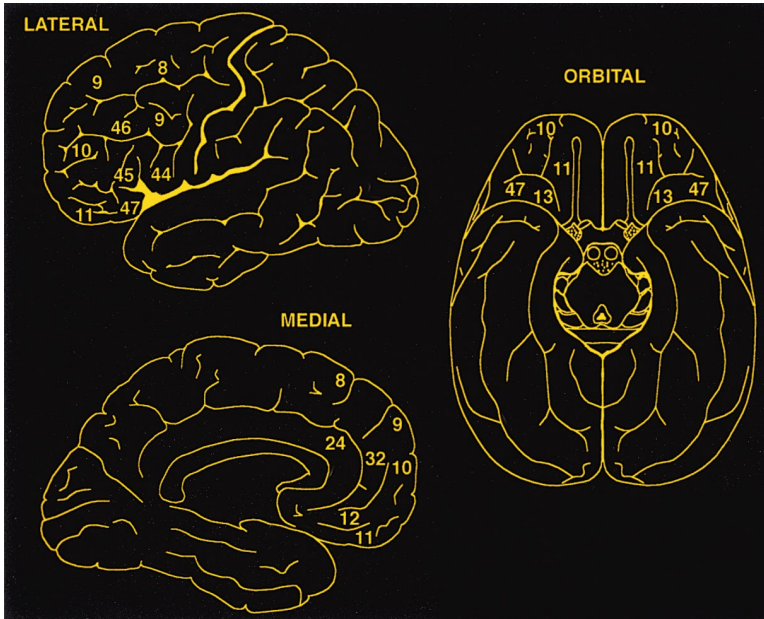


Figure 2. Cortex of the Human
Prefrontal areas are numbered according to Brodmann's cytoarchitectural map.

ously related to the variety of the information it integrates. For detailed accounts of PFC connections in the primate, the reader may wish to consult other reviews (Pandya and Yeterian, 1985; Fuster, 1997; Mesulam, 1998; Barbas, 2000). Here, I will only consider some of the extrinsic prefrontal connections.

The PFC is connected with the brainstem, the thalamus, the basal ganglia, and the limbic system. Much of that connectivity with subcortical structures is reciprocal. Especially well organized topologically are the connections between the PFC and the thalamus. The prefrontal connections with the mediodorsal thalamic nucleus have been used as a criterion for identifying the PFC in a wide variety of species (Fuster, 1997).

The functional role of the afferent connections of the PFC can be broadly inferred from the functions of the contributing structures. In the aggregate, the afferent connections from the brainstem, the diencephalon and the limbic system convey to the PFC information about the internal environment, the level of arousal, the drives and motives of the animal, and the visceral concomitants of emotion. Especially relevant for the behavioral integrative functions of the PFC are its afferent connections from the amygdala and the hypothalamus. The amygdala projects to the ventral and medial aspects of the PFC (Porrino et al., 1981; Ray and Price, 1993), and so does the hypothalamus (Kievit and Kuypers, 1975; Jacobson et al., 1978). In all likelihood, these connections carry to the frontal lobe information not only about internal states but about the motivational significance of sensory stimuli. These connections probably play a major role in the representation and enactment of emotional behavior (Le Doux, 1993). The connections of the PFC with the hippocampus are also of major behavioral relevance. All prefrontal regions receive projections from the hippocampus, either directly or indirectly (Rosene and Van Hoesen, 1977; Amaral, 1987; Barbas and Blatt, 1995).

The PFC is connected with other cortices of association, but not with primary sensory or motor cortices. Each

of the major prefrontal regions—medial, orbital, and lateral—is connected with itself and with the other two (Jacobson and Trojanowski, 1977a, 1977b; Pandya and Yeterian, 1985). Some of the corticocortical connectivity of the PFC is interhemispheric, and almost all of it is reciprocal and topologically organized (Pandya and Yeterian, 1985; Cavada and Goldman-Rakic, 1989a, 1989b). In general, connections between association cortices both originate and terminate in upper cortical layers, especially II and III (Jones, 1981; Andersen et al., 1985). Those connections presumably constitute the structural frame of cognitive networks (Fuster, 1995). As the memory networks of posterior cortex acquire associations with action, they extend into PFC to shape the networks of executive memory.

Neuropsychology of the PFC

What we know about the higher integrative functions of the PFC is inferred mainly from neuropsychological studies in the human. Because of large variations in the location, extent, and clinical manifestations of prefrontal damage, that knowledge is the distillate of a vast literature. In essence, three distinct clusters of symptoms can be observed after lesions of the three major regions of the PFC: orbital or inferior, medial/cingulate, and lateral (Figure 2). Although many reported cases are mixed in terms of cortex affected and clinical picture, the three prefrontal “syndromes” provide insights into the major and most general functions of those regions.

Ever since Harlow (1848) described the famous case of Phineas Gage, it has been known that lesions of orbital PFC often induce dramatic changes of personality (Damasio et al., 1994; Fuster, 1997). Subjects with such lesions are impulsive and disinhibited in a host of instinctual behaviors. They are irritable and contentious, with a characteristic tendency to coarse humor and disregard for social and moral principles. Their impulsiveness frequently leads them to reckless high-risk behavior and conflicts with the law. In addition, orbitofrontal patients

almost uniformly exhibit a severe disorder of attention. This disorder is characterized by the failure to withstand interference from distraction. Monkeys with orbitofrontal damage show similar difficulties as do people with comparable damage in the control of instinctual impulses and internal or external distraction. The orbitofrontal cortex exerts its functions of inhibitory control via its efferents to the hypothalamus, the basal ganglia, and other neocortical areas, some in the PFC itself.

The medial region of the PFC, which includes the most anterior portion of the cingulate gyrus, also appears involved in general motility, attention, and emotion. Lesions of this region commonly lead to loss of spontaneity and difficulty in the initiation of movements and speech (Verfaellie and Heilman, 1987; Cummings, 1993). Large and bilateral lesions lead to akinetic mutism. Patients with medial/cingulate lesions are commonly apathetic, disinterested in the environment, and unable to concentrate their attention on behavioral or cognitive tasks. Conversely, the neuroimaging of normal subjects by positron emission tomography (PET) or functional magnetic resonance (fMRI) shows marked activations of the anterior cingulate in tasks that demand sustained effort and concentrated attention (Posner et al., 1988; Raichle, 1994). Such evidence led to the formulation of an “anterior attentional system” (Posner and Petersen, 1990), of which the anterior cingulate region would be an essential part (further discussion below).

Lesions of the lateral region induce the most characteristic cognitive deficits from frontal lobe injury. In humans with large lateral prefrontal damage, the most common disorder is the inability to formulate and to carry out plans and sequences of actions. Luria (1966) was the first to investigate and describe this disorder in a large number of patients. The deficit in planning, which extends to the representation and construction of sequences of spoken and written language (Luria 1970), is now widely recognized as a constant manifestation of large lateral PFC damage. It has two major aspects: one is the difficulty to consciously represent sequences of speech or behavior, especially if they are novel or complex; the other is the difficulty to initiate them and to execute them in orderly manner. These difficulties constitute what has been termed the dys-executive syndrome (Baddeley, 1986), which is usually accompanied by a severe attention disorder that Shallice (1988) characterizes as a loss of “supervisory attentional control.” In sum, from the neuropsychological evidence, it can be concluded that the lateral PFC plays a crucial role in the organization and execution of behavior, speech, and reasoning.

The PFC in the Cortical Cognitive Map

The cortex of the human appears divided by the Rolandic fissure into two major parts, each dedicated to a separate broad category of functions: the cortex of the occipital, temporal, and parietal lobes, dedicated to “sensory” functions; and the cortex of the frontal lobe, dedicated to “motor” functions. This dichotomy of cortices seems to represent the evolutionary expansion into the telencephalon of the dichotomy of structures that spans the entire length of the nerve axis from the spinal cord upwards: a posterior sensory moiety and an anterior motor one.

On the basis of a large body of anatomical, electrophysiological, and neuropsychological evidence reviewed elsewhere (Fuster, 1995), it is reasonable to treat the cortex behind the Rolandic fissure as the substrate for perceptual memory, and the frontal cortex for executive memory (Figure 3). According to this view, neuronal networks of perceptual memory are formed in postrolandic cortex and organized hierarchically over a base layer of primary sensory cortices (phyletic sensory memory). Progressively higher areas accommodate progressively more general categories of memory, including episodic and semantic memory—which together constitute declarative memory. That upward expansion of perceptual memory networks occurs along well-identified paths of corticocortical connection. Although the general categories of both memory and knowledge are hierarchically organized, individual items of memory or knowledge are to some degree heterarchical. Autobiographical memory contains both semantic and sensory components intermixed. Thus, the memory of an episode in one’s life is probably represented by a cortical network that spans several levels of the perceptual hierarchy.

The counterpart of the perceptual memory hierarchy in posterior cortex is an executive memory hierarchy in frontal cortex. Motor networks grow toward cortex of association (PFC) on a base of primary motor cortex (phyletic motor memory). At the lower level of that hierarchy, movements are defined mainly by the action of muscles or muscle groups. At higher levels, in premotor cortex, executive networks represent acts and programs of movement defined by goal and trajectory. Networks in some premotor areas represent elementary linguistic structures (notably “Broca’s area,” area 45). From the neuropsychological research briefly reviewed in the previous section, the lateral PFC appears to harbor networks representing schemas, plans, and concepts of action. In sum, the neuroanatomy and neuropsychology of the frontal lobe strongly suggest the upward hierarchical layering of executive memory, from the innate representation of elementary movement in motor cortex to the representation of sequential action in the PFC. That upward layering appears to take place in several interrelated domains of action (e.g., skeletal, linguistic), each containing executive representations of varying degrees of specificity and abstraction. As in posterior cortex, however, the organization of representations in frontal cortex does not appear strictly hierarchical, at least inasmuch as hierarchical representation implies serial processing from the top down. In the execution of complex actions, the activations of prefrontal, premotor, and motor networks do not always follow a strict temporal sequence (Kalaska et al., 1998). Even at the lowest cortical level (motor cortex), actions seem to be represented, to a degree, in terms of direction of movement (Georgopoulos et al., 1982). Thus, it is reasonable to suppose that executive networks, like perceptual networks, are to some degree heterarchical.

Imaging studies show that lateral prefrontal and premotor areas are activated at the beginning of the learning of a motor sequence; with practice and repetition, however, that activation subsides, while that of subcortical structures, notably the basal ganglia, increases (Grafton et al., 1992; Jenkins et al., 1994; Iacoboni et al., 1996; Petersen et al., 1998). Thus, as sequences become over-

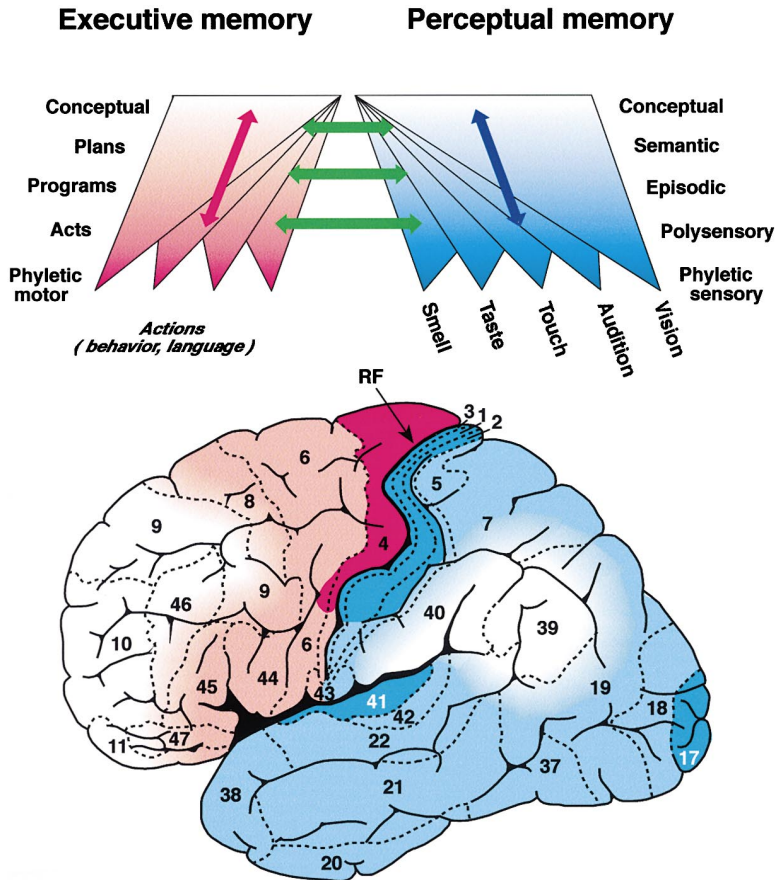


Figure 3. General Organization of Cognitive Representations in the Human Lateral Cortex (Top) Schema of the two major hierarchies of cortical memory. (Bottom) Distribution of memory networks indicated in broad outline by the same color code as in the upper figure. RF, Rolandic fissure.

learned and automatic, their representation seems to “migrate” to lower executive stages. The same imaging studies also show that, even after repetition and automation of their performance, sequences retain a degree of representation in lateral PFC. Whereas the automatic aspects of motor behavior may have been relegated to lower structures, the more abstract and schematic representations of sequential action, as well as the general rules and contingencies of motor tasks, appear to remain represented in prefrontal networks.

The theoretical scheme of memory representations just outlined may be considered a static cognitive map. It represents long-term memory after consolidation. Also, however, it is a changing and dynamic map, because the cortical networks of perceptual and executive memory constitute the anatomical substrate for all cognitive functions (e.g., perception, attention, reasoning, language). Cognitive functions activate those representational networks, which by their activation become operational. One of the cognitive operations is the acquisition of new memory, which cannot take place without the prior or concomitant retrieval of old memory. New memories consist invariably of the update and expansion of old ones, which new experience activates by associative recognition and recall. The same can be said for their hypothetical supporting networks.

The PFC in the Cortical Dynamics of Cognition

Many neuroimaging studies deal with the putative role of the PFC in the formation and recall of long-term memory

(Tulving et al., 1994; Kapur et al., 1995; Buckner et al., 1995; Fletcher et al., 1998a, 1998b). In these studies, the experimental subject is typically asked to remember sensory material for subsequent recall. There may be the additional requirement of mentally organizing or categorizing the material. Functional imaging methods are then utilized to determine levels of cortical activity—in terms of blood flow—during performance of those cognitive operations. A common procedure is to compare—by subtraction—the activity of a given area under one condition with the activity of the same area under another. Two relatively consistent observations have been made: (1) encoding new memory activates the left more than the right PFC; (2) conversely, retrieving stored memory activates the right more than the left PFC. These asymmetric encoding/retrieval activations of PFC cooccur with activations of other cortical areas.

The greater left PFC activation in encoding may reflect the greater demands of this operation on semantic (verbal) memory (Gabrieli et al., 1998)—which is represented mainly in the left hemisphere. Probably because of it, that activation is enhanced by semantically organizing the material encoded (Fletcher et al., 1998a). The right PFC activation in retrieval, on the other hand, seems attributable to the internal monitoring of retrieved material with respect to a preestablished semantic organization (Fletcher et al., 1998b). In summary, it is not altogether clear that the asymmetric activations of the two prefrontal cortices in encoding and retrieval are attributable to their differential involvement in these two cogni-

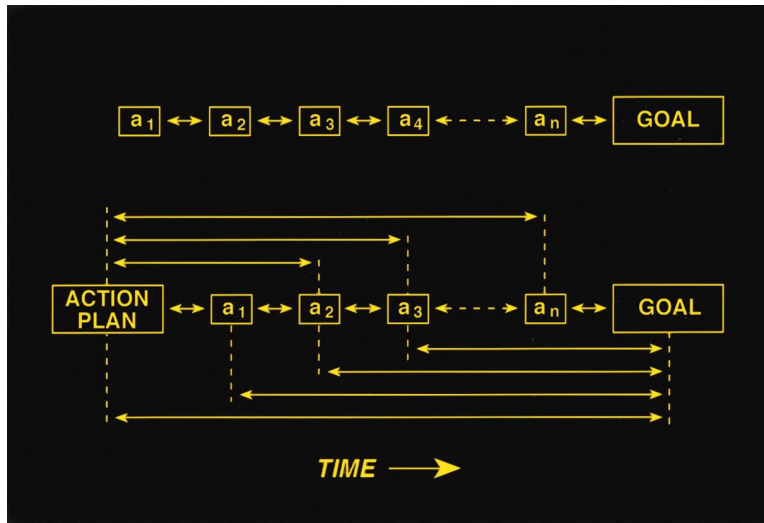


Figure 4. Two Forms of Temporal Sequencing of Actions

(Top) A routine and overlearned sequence of acts ($a_1 \dots a_n$) toward a goal. Each act leads to the next in chain-like fashion. Contingencies (two-way arrows) are present only between immediately successive acts.

(Bottom) A novel and complex sequence. Acts are contingent across time on the plan, on the goal, and on other acts. The lateral PFC is essential for the mediation of cross-temporal contingencies and thus for the organization of the sequence.

tive operations. The apparent functional dissociation of right and left PFC may be a product of the subtractive method if the material utilized to test the two operations carries a different semantic load. In any case, both the encoding and the retrieval of imaging studies are typically performed in the context of a task that requires the integration of sensory cues with cognitive actions across time. Thus, in both encoding and retrieval tasks, the executive memory networks of lateral PFC may be activated inasmuch as the tasks consist of temporally integrative acts based on internal or external contingencies.

Cortical networks also enter the dynamic state in the processing of novel and complex behavior. Such behavior requires the interaction of posterior and frontal memory networks. This interaction takes place in both hemispheres through the long reciprocal connections linking the two major sectors of cognition (green arrows in Figure 3). Routine, automatic, or overlearned behavioral sequences, however complex, do not engage the PFC and may be entirely organized in subcortical structures (basal ganglia, cerebellum, lateral thalamus, etc.), where imaging studies suggest they may be stored (Grafton et al., 1992; Petersen et al., 1998). Such sequences are performed in chain-like fashion, one act leading to the next. In them, no contingencies need be mediated across time. By contrast, sequences with cross-temporal contingencies, or with ambiguities and uncertainties in their controlling stimuli or in their motor acts, do engage the PFC. Such is the case with delay tasks (e.g., delayed-response and delayed matching), which are typically impaired by prefrontal lesions. Even after they have been thoroughly learned, the correct performance of such tasks requires the functional integrity of the PFC. This is because each of their trials contains at least one ambiguity that, to be resolved, demands the mediation of a contingency across time (“if now this, then later that; if earlier that, then now this”). These tasks integrate events in the temporal domain, which is a critical function, I argue, of the lateral PFC.

In novel and complex behavior and language, temporal integration is key to temporal order. The choice and

timing of an act in a novel and complex sequence are critically contingent on the schema or plan of the action, on its goal, and on other acts, however distant in time, that have preceded it or are expected to succeed it (Figure 4). Therefore, insofar as the lateral PFC is essential to the mediation of cross-temporal contingencies, it is essential to the temporal organization of behavioral and linguistic actions.

In conclusion, as has been deduced from human neuropsychology and corroborated in the monkey, the highest-ranking function of the lateral PFC is the temporal organization of behavior. Under it lies the subordinate function of temporal integration. The latter is in turn served by attention, working memory, and preparatory set, to be considered next. As we shall see, these three cognitive functions are widely distributed in PFC, and there is no empirical reason for attributing any one of them to a given prefrontal area; they appear to work together in all the lateral areas of the PFC.

The organization of behavioral sequences requires that *selective attention* be directed to the sensory inputs that guide them and the motor outputs that lead to their execution. This selective function operates at several levels of both sensory and motor systems. In the cerebral cortex, it appears essential for the rapid and efficient processing of information in a complex system of overlapping and intersecting networks. Attention has two complementary properties with corresponding neural mechanisms: focusing and filtering. Their underlying excitatory and inhibitory processes are still poorly understood. Both appear to be under prefrontal control inasmuch as they serve the integration of behavioral or cognitive actions.

Humans with lesions of anterior cingulate cortex (area 24), the frontal eye fields (area 8) or the superior and medial frontal gyri commonly exhibit some degree of spatial neglect and difficulties directing attention to discrete locations in visual space. They have trouble attending to novel stimuli in expected or unexpected locations, or shifting the focus of attention from one part of the visual field to another. Because the affected prefrontal areas, especially area 8, are connected with parietal areas that are also involved in spatial attention, a fronto-parietal

“network” for spatial attention has been postulated (Mesulam, 1981; Posner and Petersen, 1990). In support of this view, imaging studies show that tasks demanding high levels of spatial attention activate those same areas of prefrontal and parietal cortex (Pardo et al., 1990; Corbetta et al., 1993; Nobre et al., 1997; Kastner et al., 1999).

Some studies also show, however, prefrontal activations in tasks that demand attention to nonspatially defined stimuli (Vandenberghe et al., 1997; Duncan and Owen, 2000). The anterior cingulate region, in particular, is activated in a broad variety of attentional states and tasks that do not require spatial attention. Perhaps the close connections of this region with limbic structures account for its activation in situations that demand concentrated effort and close attention to detail (Pardo et al., 1990; Posner and Petersen, 1990; Taylor et al., 1994). Human and animal neuropsychology (Fuster, 1997) indicates that the orbital PFC plays a major role in the exclusionary aspect of attention, inhibiting or filtering out cognitive information that is extraneous to the task at hand.

In general, therefore, the involvement of the PFC in attention, and thus in selective information processing, is inseparable from its role in organizing goal-directed actions. The anterior cingulate seems involved in the motivation to perform them, the orbitofrontal cortex in the suppression of distractions that interfere with them, and the lateral cortex in the mediation of their cross-temporal contingencies. All three aspects of attention are supported by the PFC. This is most apparent in spatial tasks, where temporal integration depends on gaze control and thus on the frontal eye fields of areas 6 and 8. In any event, attention, goal-directedness, and temporal integration are common elements of most all the task paradigms utilized to explore the PFC by means of functional imaging. Not surprisingly, therefore, those paradigms activate several prefrontal areas in common (Figure 5). Temporal integration is present in practically all of those paradigms (though the subject’s need to mentally integrate the experimenter’s instructions with subsequent performance is neglected in most studies). Thus, the presumed tests of attention utilized in imaging studies are essentially tests of temporal integration, and it appears that for this reason they activate lateral prefrontal areas. After all, both working memory and preparatory set, the two basic cognitive supports of temporal integration in the lateral PFC, essentially consist of attention directed to internal representations. In any case, such related psychological functions as attentional selectivity, resolution of ambiguities, and suppression of distractions are essentially necessary for temporal integration and, therefore, can be considered essential parts of its process. They depend, most likely, on the selective activation of posterior cortical areas under prefrontal control (Desimone and Duncan, 1995; Fuster, 1995).

Memory and Set, for the Two Sides of Time

Working memory is the first temporal integrative function of the PFC to have been substantiated electrophysiologically. Cells in the PFC of the monkey were found to fire persistently at high rates while the animal retained an item of visual information in short term memory (Fuster and Alexander, 1971; Fuster, 1973); in delayed-response tasks, such “memory cells” fired more frequently during

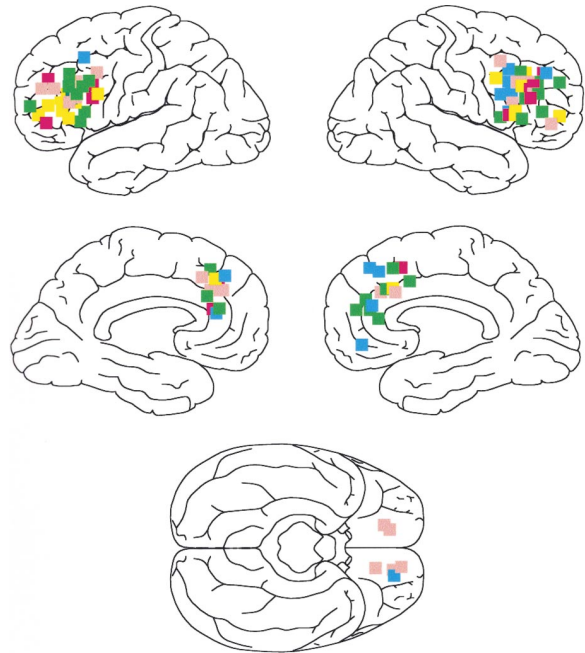


Figure 5. Frontal Activations under Five Cognitive Demands

Colored squares mark the estimated loci of peak activation of frontal cortex during performance of cognitive tasks that test the effect of response conflict (green), novelty (pink), working-memory load (yellow), working-memory delay (red), and perceptual difficulty (blue). The estimates of peak location result from metaanalysis of several neuroimaging studies. Note that assorted tasks and demands activate three prefrontal regions bilaterally. From Duncan and Owen (2000), slightly modified, with permission.

delay periods, that is, periods when short-term memory was required, than during intertrial (baseline) periods. That kind of firing activity related to spatial memory, which persisted through delays of tens of seconds (up to 2 or 3 min), had four important properties: (1) it was absent after stimuli that did not call for prospective action; (2) it was absent in the mere expectation of reward; (3) it was correlated with the accuracy of the animal’s performance (i.e., efficiency of short-term memory); and (4) it could be diminished or aborted by distracting stimuli occurring in the delay period (e.g., taped playback of monkey voices). These properties of their firing, especially during long delays (>10 s), strongly implicated those cells in the retention of the memorandum. Arguably, memory cells opened systems neuroscience to the study of mental representation.

Spatial memory cells such as those just described were subsequently observed in the PFC by many investigators (e.g., Niki, 1974; Niki and Watanabe, 1976; Joseph and Barone, 1987; Quintana et al., 1988). Goldman-Rakic and her colleagues (Funahashi et al., 1989), in a delayed-response task with brief delays and eye movement as the behavioral indicator, demonstrated memory cells for discrete light-spot positions in the four quadrants of the two-dimensional visual field.

In delayed-response tests, memory cells of the kind just described ostensibly retain the position of the visual cue or memorandum that the animal must retain for subsequent motor response. By using various other

types of delay tasks, especially delayed matching to sample, memory cells have also been found—in lateral PFC—that are attuned to visual-nonspatial (Fuster et al., 1982; Miller et al., 1996), auditory (Bodner et al., 1996), or tactile (Romo et al., 1999) memoranda. In any case, the involvement of prefrontal cells in working memory appears strictly related to the need to retain information for an impending action that is in some way dependent on that information. Prefrontal cells “remember for action.”

Functional neuroimaging reveals PFC activations in a variety of working memory tasks. Such activations presumably reflect the excitation of large assemblies of memory cells. Thus, lateral activation has been demonstrated when the memorandum is visuospatial (Jonides et al., 1993; McCarthy et al., 1994), visual-nonspatial (Cohen et al., 1994; Swartz et al., 1995), or verbal (Grasby et al., 1993; Petrides et al., 1993b; Smith et al., 1996). Nonetheless, current imaging methods lack the sufficient spatial and temporal resolution to detect topographic differences related to specific memoranda or the time course of cellular excitability in memory periods.

It has long been known that the PFC, especially its lateral region, is involved in the expectation of, and preparation for, anticipated events. This prospective involvement of the PFC is most probably related to the proven deficit of frontal patients in planning. Electrophysiologically, the anticipatory aspects of prefrontal integration are at the root of the surface-negative field potentials—notably the “expectancy wave”—recorded over frontal regions in the time between a stimulus and a response contingent on it (Kutas and Donchin, 1980; Brunia et al., 1985; Singh and Knight, 1990). Another electrical manifestation of anticipation in the PFC is the presence of cells that, during the delay of a delay task, fire at high levels in the apparent expectation of the motor response or another stimulus related to it (Niki and Watanabe, 1979; Fuster et al., 1982; Boch and Goldberg, 1989; Sawaguchi et al., 1989; Rainer et al., 1999). That kind of preparatory activity has also been inferred from the results of neuroimaging during planning (Partiot et al., 1995; Baker et al., 1996). In sum, considerable evidence from several methodologies supports a prospective role of the PFC, in addition to its retrospective role of working memory. Ingvar (1985) dubbed that prospective role the “memory of the future.”

Quintana and Fuster (1999) found two types of units, working-memory cells and preparatory-set cells, topographically intermingled in the dorsolateral PFC of monkeys performing a delay task with variable probabilities of contingency between color and direction of manual choice. A trial began with the brief presentation of a color, which the animal had to retain for pairing it with a second stimulus some 12 s later. Depending on the combination of those two stimuli, the animal had to choose a right or a left location. After the animal had been extensively trained to perform the task, each color carried a given probability that the second stimulus would demand a response to one side or to the other. Thus, some colors predicted response location with 100% probability and others with 75%. In the cortex above the principal sulcus (areas 9 and 46), some cells discriminated the colors (by differences in firing frequency), and their activity during the delay descended

gradually toward baseline level (Figure 6); these sensory-coupled units behaved like conventional working-memory cells for color. Intermixed with them in the same area, direction-coupled cells were found, which showed a temporally reciprocal behavior. Their discharge increased in the course of the delay, and they fired at different rates at the time of the motor choice, depending on whether it was the right or the left. Further, the slope of accelerating discharge in the delay period was greater when the monkey could predict side with certainty (100%) than when he could not.

Thus, neuropsychological, electrical, and imaging data point to the coexistence in lateral PFC of two neural substrates of active representation, one for the recent past and the other for the anticipated future. There is no evidence of anatomical segregation of those two substrates. Quite the contrary, there is microelectrode evidence that the two overlap to a considerable extent. Some prefrontal cells seem to “look” to the past and others, nearby, to the future. It is reasonable to assume that the two populations of cells are part of the same cortical network of long-term memory that represents the associated sensory and motor components of a given task or behavioral sequence. That network is presumably activated for the task, its neurons to bridge temporal contingencies and to guide-through motor systems—the behavior to its goal. Thus, the two temporal perspectives of a behavioral sequence would be integrated by the sustained activation of the network’s components. Working memory would consist of the activation of the perceptual components. A temporally symmetric and complementary function of preparatory set, or “motor attention,” would activate the network’s motor components and thus prime executive systems for the anticipated action.

Areal Specificity in PFC: The “What,” the “Where,” and the “When”

Beginning in the 1930’s (Jacobsen, 1931), a long series of lesion studies on the monkey showed that the lateral PFC was essential for delay tasks. In these tasks, the animal must memorize items of information through periods of forced delay. From deficits induced in those tasks by ablating lateral PFC, its role was deduced in the kind of short-term memory which is now conventionally called working memory—applying to the monkey a term with somewhat different meaning in human cognition (Baddeley 1986). Since the tasks (e.g., delayed-response) commonly required memorization of a spatially defined visual stimulus, some researchers further assumed that the lateral PFC cortex was the storage site for memory of spatial location. However, the reversible lesion of this cortex—by local cooling—induced a temporary deficit in delayed color matching (a nonspatial memory task) that was of the same magnitude as the deficit in delayed response (Bauer and Fuster, 1976). Furthermore, microelectrode recording in monkeys performing both tasks revealed spatial and nonspatial memory cells throughout the lateral PFC (Fuster et al., 1982).

Nonetheless, some investigators used an anatomical rationale in support of a functional dissociation between dorsal and ventral areas of the lateral PFC in visual

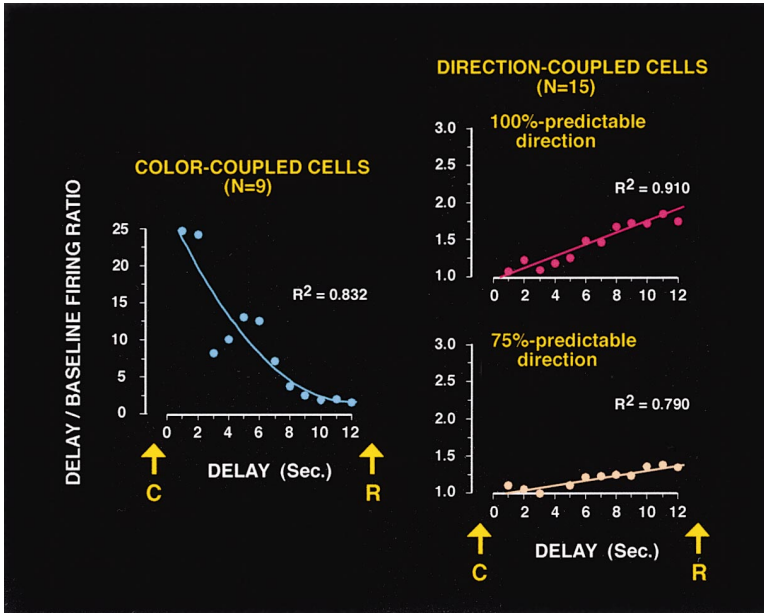


Figure 6. Working-Memory and Preparatory-Set Cells in PFC

The monkey's task requires integration of two sequential stimuli—12 s apart—for hand response to left or right. The first stimulus, a brief color display, predicts the probability of response direction (after the second stimulus): 100% if yellow or blue, 75% if red or green. Some cells (left graph) react selectively to the color, and their discharge descends thereafter in the course of the delay. During that same period, other cells in the vicinity (right graph) accelerate their discharge and react selectively to the side of manual response. C, color cue; R, manual response.

memory. The former areas receive the dorsal visual pathway, the “where” pathway from parietal cortex; the ventral areas, on the other hand, receive the ventral visual pathway, the “what” pathway from inferotemporal cortex (Ungerleider and Mishkin, 1982). Accordingly, two visual working memory functions were hypothesized for dorsal and ventral prefrontal areas, the former specializing in “location memory” and the latter in “object memory.” Wilson et al. (1993) provided some empirical support to this hypothesis with the observation, in ventral cortex, of more cells attuned to nonspatial memory than to spatial memory. Prior studies—mentioned in the previous section—had shown spatial memory cells in dorsolateral cortex. Based on these observations, the “domain specificity” of spatial and nonspatial memory in PFC was postulated (Goldman-Rakic et al., 2000). This notion, however, has now been contradicted by a substantial number of studies, in the human as well as the monkey.

Neuroimaging in the human has failed to demonstrate a clear specialization of separate prefrontal areas in spatial and nonspatial working memory (Courtney et al., 1996; Owen et al., 1998; Ungerleider et al., 1998; Postle and D'Esposito, 1999; Prabhakaran et al., 2000). It has, however, substantiated the involvement of certain lateral and inferior areas of the frontal lobe, including Broca's, in the memorization of semantic material (Paulesu et al., 1993; Andreasen et al., 1995; Fiez et al., 1996; Smith and Jonides, 1999). Neuroimaging also substantiates the activation of large areas of lateral PFC in temporal integration, which is a uniform requirement of all working-memory tasks, as well as of many others (Duncan and Owen, 2000).

The fundamental integrative role of lateral prefrontal areas, in contrast to their hypothetical “where-versus-what” specialization, has received considerable support from microelectrode studies in the monkey. Many neurons in lateral PFC respond selectively to both the identity and the location (Rao et al., 1997; Rainer et al., 1998),

or the color and the movement (Sakagami and Tsutsui, 1999), of visual stimuli in memory tasks. Other neurons integrate the associated features of visual objects that define the perceptual category to which the objects belong (Freedman et al., 2001). Visuo-motor integration is exemplified by cells that associate visual stimuli with behavioral responses (Watanabe, 1992; Bichot and Schall, 1999; Scialidhe et al., 1999; Asaad et al., 2000). Such associations have been seen to develop in the course of learning (Asaad et al., 1998; Rainer and Miller, 2000). The reward that motivates monkeys to perform their tasks is yet another associated component of those tasks and thus of integrative PFC networks. It has been known for some time that prefrontal units increase their firing in temporal correlation with the delivery of that reward (Rosenkilde et al., 1981; Watanabe, 1996; Hikosaka and Watanabe, 2000). Such units are most common in orbital PFC. Some differentiate rewards with remarkable specificity (Tremblay and Schultz, 1999).

A compelling example of temporal integration in the PFC is given by cells that respond specifically, and in correlated manner, to two temporally separate stimuli of different sensory modality that have been associated by experience (Fuster et al., 2000). Monkeys were trained for several months to perform the task in Figure 7. A trial began with a brief tone, high or low pitch, which the animal had to remember for 10 s in order to choose one of two colors. The high tone required choice of red; the low tone, green. In dorsolateral prefrontal cortex (areas 8, 9, and 46), a large contingent of cells discriminated the tones and the colors in behaviorally coherent fashion. Thus, some cells preferred the high-tone over the low-tone and, after the delay, the red over the green. Others preferred the low tone and, later, its associated color, green. The tone/color correlation disappeared or became much diminished in trials ending with monkey error. Thus, the two types of cells seemed to belong to executive networks that, for a behavioral goal, integrated sounds with colors across time.

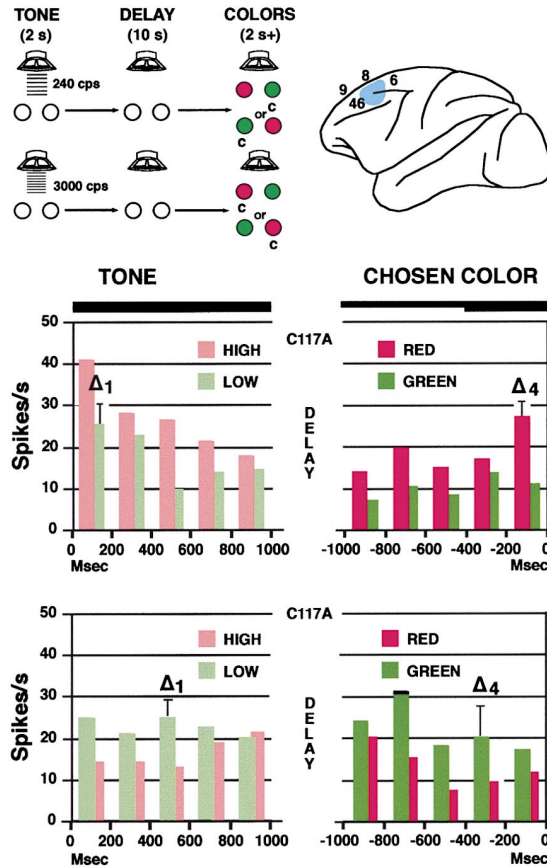


Figure 7. Cross-Temporal Integration of Sound and Color in Frontal Cortex
 (Top, left) Sequence of events in the behavioral task: (1) brief tone from overhead loudspeaker, (2) 10 s delay, (3) two colors simultaneously in two buttons, (4) animal rewarded for choosing the color (c) that matches the tone—see text. (Tone and color position change at random between trials.)
 (Top, right) Diagram of monkey's brain. Numbers indicate cytoarchitectonic areas; in blue, frontal region from which tone- and color-reactive cells were recorded.
 (Below) Firing frequency histograms of two cells, one selective for high-tone and red (top), and the other for low-tone and green (bottom). Histograms are from 1 s period beginning with tone onset (left), and from 1 s period immediately preceding choice of color (right). Δ_1 marks 200 ms bin of maximal cell discrimination of tones, and Δ_2 of colors. Note the correlation of preferential cell reactions to tones and colors according to the task rule. From Fuster et al. (2000), modified.

Neurons such as those just described uphold an emerging principle of prefrontal function already advanced in the previous section. The networks that in the course of behavior integrate information in a timely manner are essentially the same networks that represent that information in long-term executive memory. Consequently, executive working memory seems to be essentially based on the ad hoc activation of executive networks of long-term memory (Fuster, 1995). Accordingly, those networks associate, and thus encode, all the sensory and motor components of a task. Higher prefrontal networks represent the temporal contingencies between those components, the “rules” of performance of the task (Passingham, 1993; White and Wise, 1999).

These views do not exclude new information from working memory. Indeed, new stimuli can be readily incorporated into an activated network of long-term memory by processes of categorization, perceptual constancy, and contextual association.

Cortical Mechanisms of Temporal Integration

The mechanisms of temporal integration and the role of the PFC in them are still poorly understood, although we know enough about them for some reasonable conjectures. Here are two critical questions to be resolved: (1) How are the components of an executive cortical network timely and selectively activated in the execution of a goal-directed sequence of behavior? (2) How is a cortical network maintained active in the process of bridging temporally separate components of the sequence?

Humans with prefrontal damage, as already mentioned, have difficulties focusing and maintaining attention; these difficulties are accompanied by a diminution of the potentials evoked by sensory stimuli in posterior cortical areas (Knight 1984; Daffner et al., 2000). Thus, to process perceptual information in the focus of attention, those areas seem to require excitatory modulation from the PFC. That kind of modulation would be essential for the retrieval of context-dependent perceptual information in posterior cortex. In turn, feedback from this cortex would activate frontal executive networks. These assumptions are supported by evidence that, in heightened visual search and attentive set-shifting, visual as well as prefrontal cortical areas are activated (Kastner et al., 1999; Konishi et al., 1999). Recent microelectrode studies in monkeys with callosal severance point to the importance of the prefrontal modulation of inferotemporal cells for visual memory retrieval (Hasegawa et al., 1998; Tomita et al., 1999).

For the retrieval of an executive memory, inputs from posterior cortex and the internal environment activate a network of neurons in the PFC. That network represents in its connectational architecture a schema of sequential action—e.g., a trial in a delay task. With the retrieval of the memory of that schema, the network becomes operational. From then on, the focus and timing of sensory and motor processing are presumably controlled by selective serial activations of the components of that prefrontal network in cooperation with subcortical structures (e.g., thalamus, basal ganglia) and with posterior associative cortices. Each prefrontal activation is subject to feedback from internal and external environment. Hence, the so-called monitoring function of the PFC, which has been postulated on the basis of lesion experiments (Petrides, 1991) and supported by neuroimaging (Petrides et al., 1993a; Fletcher et al., 1998b).

When there is a temporal discontinuity in the execution of a behavioral sequence, prefrontal mechanisms are necessary and come into play for integrating information across the discontinuity. That some of that integration takes place locally in discrete PFC areas—by joint operation of working memory and preparatory set—is suggested by the evidence of neighboring PFC cells that are attuned either to the memory of a sensory stimulus or to the prospective response to it (Figure 6).

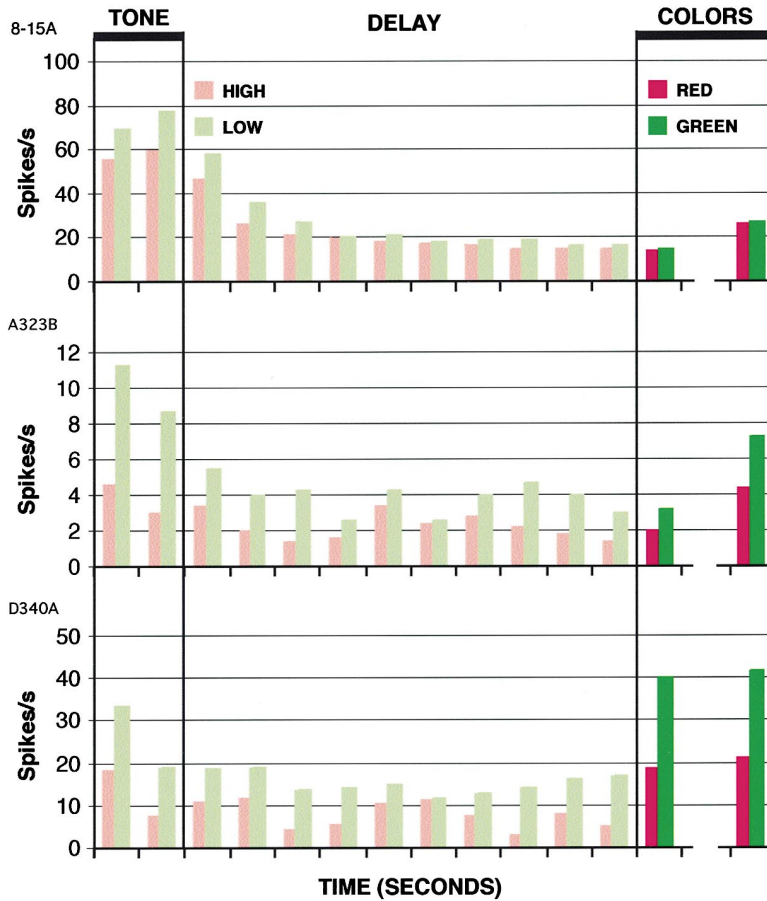


Figure 8. Working Memory Discharge Attuned to Sound/Color Association in Long-Term Memory

Average frequency histograms of three cells that, in the task of Figure 7, prefer the low tone. Their discharge during the delay is higher in the time between low-tone and green choice than between high-tone and red choice. At color presentation, the second and third cells from top show clear preference for the color matching the low tone, green. From Fuster et al. (2000), modified.

Even more suggestive of local temporal integration is the stimulus-selective discharge of some PFC cells in the time between two associated stimuli of different modality, a sound and a color, that the monkey must integrate across that time (Fuster et al., 2000). Not only do those cells respond similarly to the two stimuli, but their discharge during the interposed delay is also attuned to both (Figure 8). This implies that the first stimulus (sound) activates the network that associates it with the second (color), and the network stays activated through the time between the two. Thus, the cellular activation in short-term memory is not so much related to one stimulus or to the other as to the association between the two, which is in long-term memory.

Temporal integration also seems to result, however, from the cooperation of the PFC with other cortical areas. Working memory is as widely distributed as the long-term memory that supports it. Cells in posterior cortex of sensory association show working-memory properties for stimuli of the specific modality they process. Thus, there are memory cells for vision in inferotemporal cortex (Fuster and Jervey, 1982; Miller et al., 1993), for touch in somatosensory cortex (Koch and Fuster, 1989; Zhou and Fuster, 1996), and for location in posterior parietal cortex (Andersen et al., 1990). There is also mounting evidence that, in the maintenance of working memory, the PFC interacts with those cortices. By the cooling of lateral PFC in monkeys performing a color delayed matching task (Fuster et al., 1985), two correlated effects were obtained: (1) a behavioral deficit

of working memory for color, and (2) a decrease in the ability of some inferotemporal cells to discriminate colors in the memory period (delay). Both effects occurred in the absence of perceptual or motor deficit. Similar effects were observed by inferotemporal cooling on behavior and on PFC cells. These findings suggest that the cooling of either cortex, prefrontal or inferotemporal, interrupts loops of reverberating activity between them that are necessary for visual working memory. Also by cooling, cellular interactions have been exposed between PFC and parietal cortex (Quintana et al., 1989; Chafee and Goldman-Rakic, 2000).

The reverberation through recurrent neuronal circuits suggested by cooling experiments is a likely mechanism of working memory, and thus of temporal integration. Such a mechanism was postulated by Hebb (1949) for short-term memory in local cortical circuitry. In a fully recurrent computer network model trained to perform sample-and-hold operations as delay tasks require, Zipser et al. (1993) observed "cells" (hidden units) that behaved much like real working-memory cells of PFC or inferotemporal cortex during delay tasks. Therefore, working memory is emerging as a mechanism of temporal integration essentially based on the concurrent and recurrent activation of cell assemblies in long-term memory networks of frontal and posterior cortex. During the delay period of delay tasks, a different recurrent loop of cortical connectivity would be active depending on the modality of the memorandum (Figure 9).

Finally, temporal integration and its ancillary prefrontal

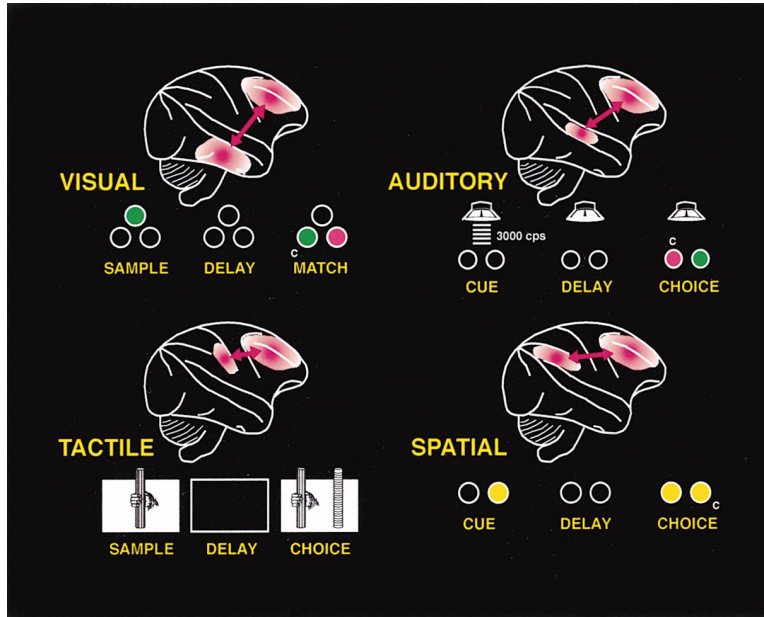


Figure 9. Cortical Interactions in Working Memory

Depending on the modality of the memorandum, the PFC interacts through reciprocal and reentrant connections with different areas of posterior association cortex: inferior temporal if visual, superior temporal if auditory, anterior parietal if tactile, and posterior parietal if spatial.

tal functions (attention, working memory, set, monitoring) operate within the broader dynamics of the perception-action cycle, which is founded on basic biological principles (Fuster, 1997). All adaptive behavior rests on the circular processing of information between the organism and its environment. Sensory information leads to motor actions, which produce changes in the environment, which lead to new sensory inputs, which lead to new actions, and so on. Figure 10 illustrates schematically the dynamics of cortical connectivity in the perception-action cycle. Automatic, reflex and overlearned se-

quences are integrated in lower levels of the nervous system and of the perception-action cycle. New and complex sequences, however, are integrated at the apex of the perception-action cycle under prefrontal control.

Conclusions

The PFC is one of the last territories of the neocortex to develop, in evolution as well as ontogeny. In general terms, the entire PFC is dedicated to the memory, planning, or execution of actions. The orbital and medial PFC, which is well connected with the brainstem and limbic formations, plays a major role in emotional behavior and the control of basic drives. The lateral PFC is the neural substrate for the cognitive functions that support the temporal organization of behavior. That substrate appears to consist of neuronal networks representing by associative connections the long-term memory of behavioral sequences and the plans or schemas of action (executive memory). To conduct its executive functions, the lateral PFC interacts with subcortical structures and with other parts of association cortex. A cardinal function of the lateral PFC is the temporal integration of information for the attainment of prospective behavioral goals. It is served by two complementary and temporally symmetric functions: working memory and preparatory set. Both work together toward those goals in every sphere of action, including speech. Their role is to mediate contingencies across time between events represented in a network of executive memory. Evidence from several methodologies indicates that working memory essentially consists of the sustained activation of one such network. Further, there is evidence indicating that the activation is maintained through recurrent circuits between cells of PFC and cells of posterior cortex. All the integrative functions of the PFC operate within the broad biological context of the sensory-motor cycle of interactions that links the organism with its environment at all levels of the nervous system. The PFC closes that cycle at the summit, integrating in the time domain cognitive representations of

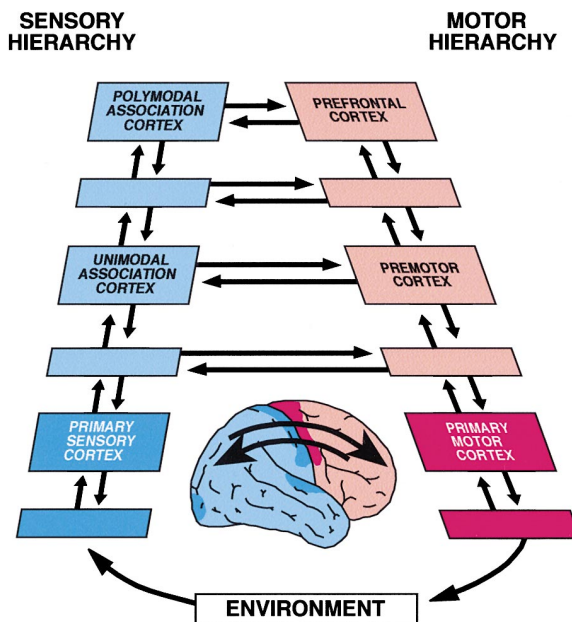


Figure 10. Cortical Dynamics in the Perception-Action Cycle

Unlabeled rectangles stand for intermediate areas or subareas of labeled cortex. All arrows represent connective pathways identified in the monkey. The picture of the human brain emphasizes reciprocal connectivity between posterior and frontal cortex.

perception and of action as required in goal-directed behavior.

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