

Frontal lobe and cognitive development

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Abstract

In phylogeny as in ontogeny, the association cortex of the frontal lobe, also known as the prefrontal cortex, is a late-developing region of the neocortex. It is also one of the cortical regions to undergo the greatest expansion in the course of both evolution and individual maturation. In the human adult, the prefrontal cortex constitutes as much as nearly one-third of the totality of the neocortex. The protracted, relatively large, development of the prefrontal cortex is manifest in gross morphology as well as fine structure. In the developing individual, its late maturation is made most apparent by the late myelination of its axonal connections. This and other indices of morphological development of the prefrontal cortex correlate with the development of cognitive functions that neuropsychological studies in animals and humans have ascribed to this cortex. In broad outline, the ventromedial areas of the prefrontal cortex, which with respect to other prefrontal areas develop relatively early, are involved in the expression and control of emotional and instinctual behaviors. On the other hand, the late maturing areas of the lateral prefrontal convexity are principally involved in higher executive functions. The most general executive function of the lateral prefrontal cortex is the temporal organization of goal-directed actions in the domains of behavior, cognition, and language. In all three domains, that global function is supported by a fundamental role of the lateral prefrontal cortex in temporal integration, that is, the integration of temporally discontinuous percepts and neural inputs into coherent structures of action. Temporal integration is in turn served by at least three cognitive functions of somewhat different prefrontal topography: working memory, preparatory set, and inhibitory control. These functions engage the prefrontal cortex in interactive cooperation with other neocortical regions. The development of language epitomizes the development of temporal integrative cognitive functions and their underlying neural substrate, notably the lateral prefrontal cortex and other late-developing cortical regions.

Introduction

The prefrontal cortex is the cortex of association of the frontal lobe. In the mammalian brain, this cortex is conventionally defined by two basic criteria: cytoarchitecture and connectivity. Both criteria serve us to delimit approximately the same cortical territory, which is characterized in all mammalian species by a prominent cellular layer IV, or granular layer, and a tight reciprocal connectivity with the mediodorsal nucleus of the thalamus. In the primate, human or nonhuman, the prefrontal cortex has three major anatomical aspects or regions: lateral, medial, and ventral or orbital (Fig. 1). Each prefrontal region is subdivided into areas of varying cytoarchitecture, providing the grounds for a number of cytoarchitectonic maps, such as that of Brodmann (1909). With few exceptions, such as that of area 8, which is largely devoted to the control of gaze and eye movements, it is not possible to ascribe a specific physiological function to any prefrontal area. However, it seems obvious that the prefrontal cortex is functionally heterogeneous. Whereas it cannot be functionally parceled out with regard to its cytoarchitecture, there is substantial evidence that, as a whole, the prefrontal cortex per-

forms a critical role in the organization of behavioral, linguistic, and cognitive actions. The psychological and physiological analysis of this role in the three action domains yields a topographic distribution of cognitive functions conforming to the following outline. All three prefrontal regions are involved in one or another aspect of attention. In addition, the medial and anterior cingulate region are involved in drive and motivation, the lateral region in working memory and set, and the orbital region (to some extent also the medial region) in the inhibitory control of impulses and interference.

This article deals with the developmental aspects of the prefrontal cortex and its cognitive functions. After a brief exposition of morphological development in both phylogenetic and ontogenetic terms, the article deals with the prefrontal cortex of the primate as the substrate for temporal integration, as well as the cognitive functions that support it. The cognitive functions of the adult human prefrontal cortex are viewed as the culmination of biological processes that lead to the highest expressions of temporal integration in language and intellectual performance.

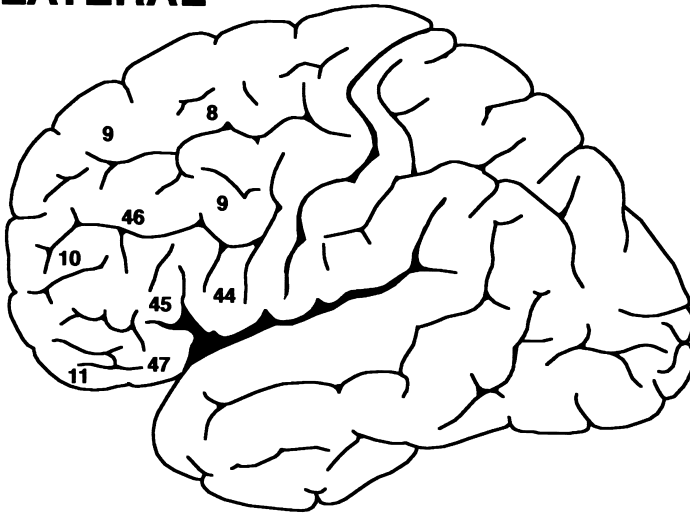
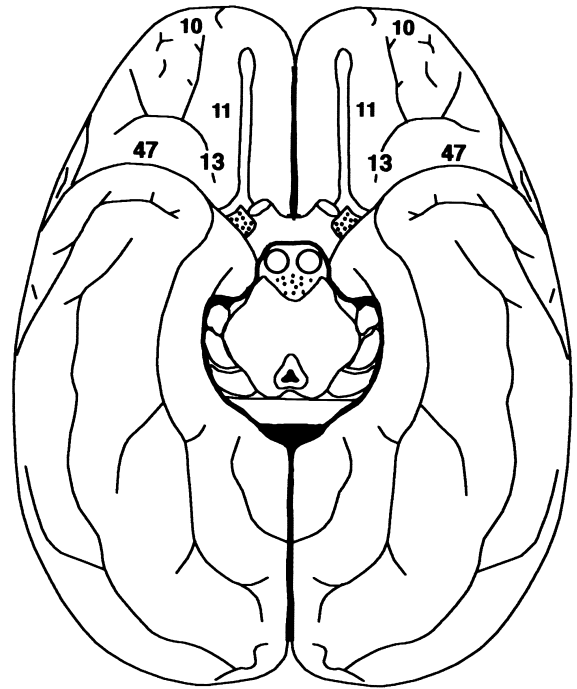
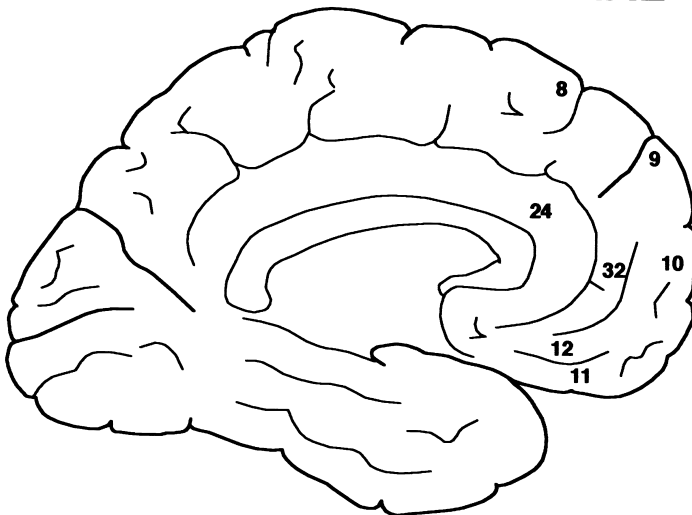
LATERAL**ORBITAL****MEDIAL**

Fig. 1. Three views of the cerebral hemispheres with the areas of the prefrontal cortex numbered in accord with Brodmann's cytoarchitectonic map.

Evolution

The prefrontal cortex, like the rest of the neocortex or *neopallium*, evolves in the dorsal telencephalon between two older structures, the laterally situated olfactory (piriform) pallium and the medially situated hippocampal pallium. The precise evolutionary process that gives rise to the neocortex is unresolved (Northcutt & Kaas, 1995). There are two major lines of thinking in this respect: One, that the neocortex develops as an expansion of those ancient structures (Pandya *et al.*, 1988); the other, that it develops from a ridge of cells along the dorsal wall of the ventricle (Butler, 1994). In any case, it is generally accepted that, with evolution, the neocortex as a whole increases in size and volume in proportion to body dimensions, (Stephan *et al.*, 1981; Jerison, 1990). The growth of the neocortex in evolution can be charac-

terized as a veritable phylogenetic "explosion" (Finlay & Darlington, 1995).

The most rostral aspect of the developing neopallium in primitive species constitutes what is to become the prefrontal cortex. Whereas the homology of the neocortex as a whole in the various mammalian species is undisputed, the homology of individual neocortical areas, prefrontal areas in particular, is a matter of some controversy. Nonetheless, the evidence from comparative studies of existing species and from the examination of the endocasts of specimens of extinct species—reviewed by Fuster, 1997b—leads to the conclusion that, in the course of evolution, the prefrontal cortex grows disproportionately more than other cortical regions (Fig. 2). According to Brodmann (1909), the prefrontal cortex constitutes 3.5% of the totality of the cortex in the cat, 12.5% in the dog, 11.5% in the macaque,

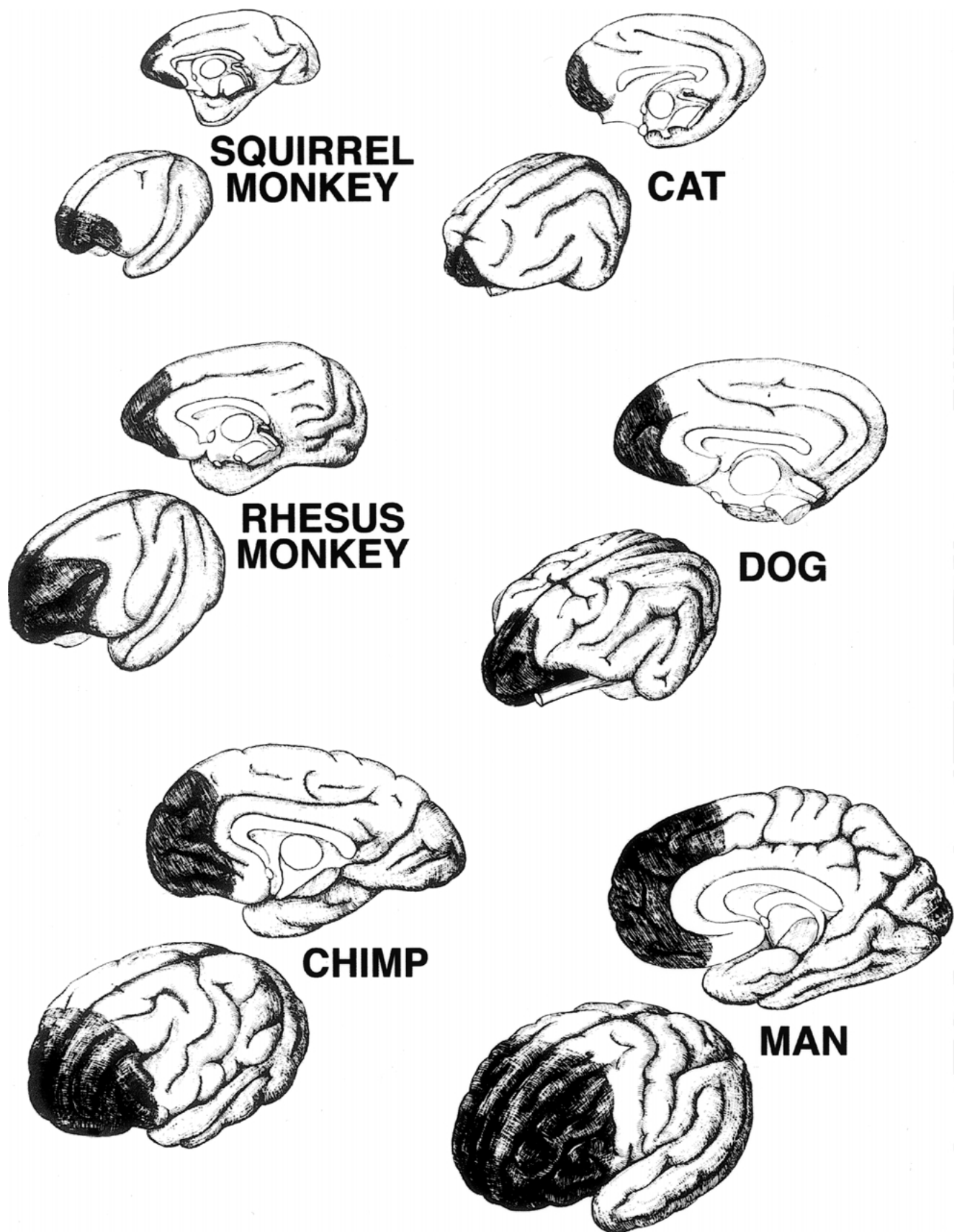


Fig. 2. Prefrontal cortex (*shaded*) in six animal species.

17% in the chimpanzee, and 29% in the human. Arguably, the disproportionate evolutionary growth of the prefrontal cortex parallels that of the associative cortex of temporal and parietal regions. It is a legitimate inference, in any event, that the evolutionary expansion of the cortex of association, both posterior and prefrontal, is closely related to the evolution of cognitive functions.

Judging from the evolutionary development of surface morphology (*i.e.*, sulci and gyri), as well as of the components of its thalamic nucleus (mediodorsal) and their cortical projections, the various portions of the prefrontal cortex do not appear to evolve equally at the same time. Rather, by those criteria, the lateral prefrontal region clearly evolves later and farther than the other prefrontal regions. This is in obvious agreement with the late and extraordinary development of higher integrative cognitive functions (*e.g.*, language) in higher species, especially the human. These functions, as we see below, are largely dependent on the lateral prefrontal cortex.

Ontogeny

In accord with the principle that ontogeny recapitulates phylogeny, the prefrontal cortex is one of the cortical areas to develop most and last in the course of individual development. Neuroimaging and morphometric studies substantiate this general assumption (Jernigan & Tallal, 1990; Pfefferbaum *et al.*, 1994; Reiss *et al.*, 1996; Giedd *et al.*, 1999). Some of these studies indicate that, in this cortical region as in others, the maturation of gray matter has a different time course than that of white matter. Prefrontal gray matter seems to increase volumetrically after birth, to reach a maximum at some time between 4 and 12 years of age and to decrease gradually thereafter (Pfefferbaum *et al.*, 1994; Giedd *et al.*, 1999). The increase in gray matter seems to occur concomitantly with a 40% reduction in synaptic density (Huttenlocher, 1979). Such reduction in synaptic density is consistent with the principle of selective specialization postulated at the basis of the formation of cognitive networks in the cerebral cortex (Edelman, 1987). In contrast to those developmental changes in gray matter, the volume of prefrontal white matter increases through childhood and early adolescence. According to some recent imaging studies (Sowell *et al.*, 1999, 2001), that increase continues beyond adolescence into young adulthood.

The augmentation of white-matter volume that takes place in the frontal lobe of the child and the adolescent is mostly, if not completely, attributable to the myelination of cortico-cortical axons, which constitute nearly 95% of the extrinsic connectivity throughout the neocortex. That process begins before birth and takes place gradually for many years until adult age. Since the early studies by Flechsig (1901, 1920), it has been known that the myelination of the various cortical areas follows a cer-

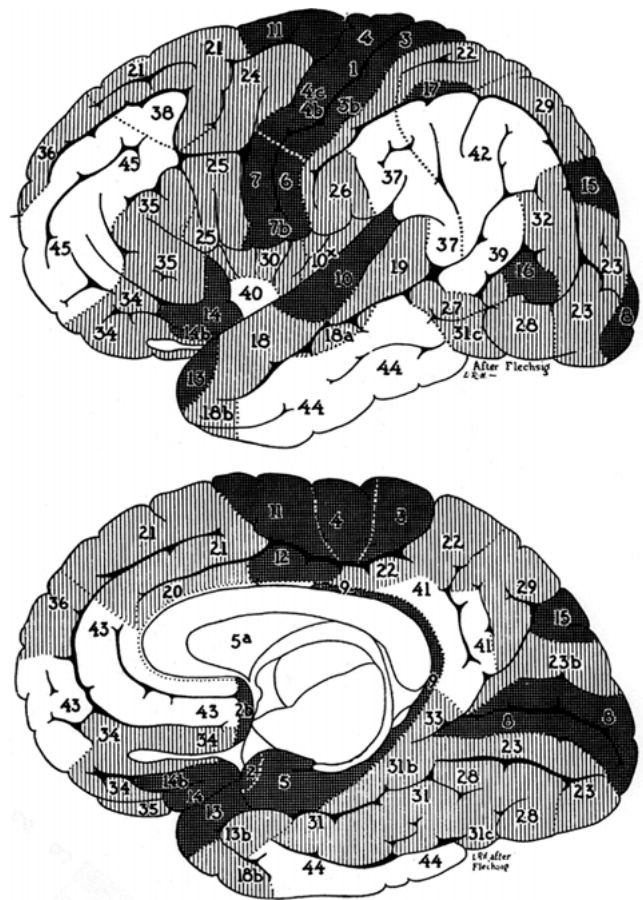


Fig. 3. Ontogenetic map of the prefrontal cortex according to Flechsig. The numeration of the areas indicates the order of their myelination.

tain order (Fig. 3). Although the precise order proposed by Flechsig has been disputed on technical grounds, it seems well established that the primary sensory and motor areas myelinate before the areas of association, the latter including the prefrontal cortex (Yakovlev & Lecours, 1967). Further, it appears that, in general, the cortical development of myelin follows approximately the same stepwise order of cortico-cortical connections, from area to area, that neuroanatomical studies indicate in the nonhuman primate (next section). It has reasonably been argued, on the basis of neuropsychological and linguistic data, that the cognitive development of the child is closely dependent on the development of cortical myelin (Gibson, 1991). Until the publication of recent neuroimaging studies mentioned above, however, it had not been surmised that in the human the myelination of higher areas of association, notably the prefrontal cortex, was not complete until the third decade of life.

Myelin enhances the speed of axonal conduction, and thus it can be assumed to facilitate the processing in cortical networks. Myelination, however, is only one of the indices of cortical maturation. Others, less readily measurable, include the prolongation of axons and the

arborization of dendrites. Perinatally, as in later life, the development of both the axons and dendrites of frontal areas seems to lag chronologically behind that of other cortical areas (Huttenlocher, 1990; Mrzljak *et al.*, 1990; Scheibel, 1990). Given the role of prefrontal networks in cognitive functions, it is reasonable to infer that the development of those networks underlies the development of highly integrative cognitive functions, such as language, that continue to develop well into adulthood.

Indeed, the cognitive development of the child and the adolescent appears to correlate with the development of the prefrontal cortex. This correlation is most obvious as we consider the evolution—with chronological age—of those cognitive functions of the prefrontal cortex that most contribute to intellectual maturation: attention, language, and creativity. All depend on the ability to organize behavior and cognition into goal-directed structures of action. According to Piaget (1952), the development of this ability follows certain trends through a series of well-defined stages and milestones. After a first stage of simple sensory-motor integration and primitive symbolization, the child—from 2 to 7—enters a representational stage of extended verbal symbolism. Language becomes progressively more elaborated and governed by external feedback, including language from other persons. The child learns to delay gratification. In the next period, from 7 to 11, language and behavior become more structured, more independent of external stimuli and more creative. Games, sports, erector sets and problem solving enter the picture. From 11 to 15 and beyond, the child begins to utilize logical reasoning for the construction of hypotheses and for the testing of alternative solutions. Both induction and deduction become the means to do it. Most critically, the subject becomes progressively better capable of integrating information in the time domain, and thus of constructing extended goal-directed gestalts of speech and behavior. These developments continue into late adolescence and into young adulthood, when, as we have seen, morphological indices point to the lingering maturation of the prefrontal cortex.

Connectivity

The cortex of the frontal lobe is exceptionally well connected with other brain structures, both cortical and subcortical. In particular the prefrontal cortex, as studies in the monkey demonstrate, is arguably the best connected of all cortical structures. The three prefrontal regions, medial, lateral, and orbital, are reciprocally connected with one another and with the nuclei of the anterior and dorsal thalamus. The medial and orbital regions, in addition, are connected with the hypothalamus and other limbic structures; some of these connections are indirect, through the thalamus. The lateral region sends connections to the basal

ganglia; in addition, it is profusely connected with the association cortex of occipital, temporal, and parietal regions (for detailed review of frontal connections, see Fuster, 1997b).

The precise functional role of the connections of the prefrontal cortex is not entirely known, but can be inferred from the functional role of the structures with which it is connected. In general terms, the prefrontal-limbic connections are involved in the control of emotional behavior, whereas the prefrontal-striatal connections are involved in the coordination of motor behavior. Of special importance for the cognitive aspects of all forms of behavior are the reciprocal connections of the lateral prefrontal cortex with the hippocampus and with the posterior association cortices. There are well-demonstrated reciprocal connections between the hippocampus and the prefrontal cortex, especially its lateral region, although their exact path has not been completely clarified. They seem to course through parahippocampal and entorhinal cortex (Van Hoesen, 1982). Given the proven, though still obscure, role of the hippocampus in the acquisition of memory, it appears very likely that those connections participate in the formation of networks of motor or executive memory in the prefrontal cortex.

In the monkey, the primary sensory areas of the cortex for vision, somesthesia, and audition—Brodmann's areas 17, 1 to 3, and 41—are the origin of three separate cortico-cortical pathways for the analysis and representation of stimuli of their respective modalities (Jones & Powell, 1970; Pandya & Veterian, 1985). Each pathway is made of a series of adjacent, cytoarchitectonically distinct, areas interconnected by axons that course through white matter, parallel to the cortical surface, in both directions—ascending and descending the pathway. Beyond the primary sensory areas, each pathway is made of progressively higher areas of posterior (post-central) cortex of sensory association for its respective modality. Each area projects not only to the next in the pathway but also, through long fibers, to a discrete area of frontal cortex. The primary areas for olfaction and taste reside in the frontal operculum. Cortical pathways for these two modalities are yet to be clarified.

The successive interlocking areas that constitute a cortical pathway are connected with each other in accord with the principles of connectivity that prevail throughout the central nervous system. These principles include feed-forward, feedback, convergence, divergence, and lateral connection. In both anatomical and physiological terms, the areas of each pathway are hierarchically organized. This has been best demonstrated in the visual system of the primate (Felleman & Van Essen, 1991). The hierarchical organization of a pathway implies that each area in it represents and analyzes sensory stimuli that are more complex and/or more abstract than those represented and analyzed in lower areas.

All areas of sensory association in posterior cortex send fiber projections to the lateral prefrontal cortex (Jones & Powell, 1970; Pandya & Yeterian, 1985). As a result, this cortex constitutes a major target of sensory convergence. Cross-modal association is a characteristic of neurons in certain sectors of this cortex (see below). Presumably, sensory convergence is an essential contribution to the formation of executive memory networks and to the role of lateral prefrontal cortex in cognitive integrative functions.

Cognitive functions of the prefrontal cortex

TEMPORAL INTEGRATION

The principal and also most general function of the prefrontal cortex is the temporal organization of actions toward biological or cognitive goals (Luria, 1966; Fuster, 1997b). This is the essence of the role of the prefrontal cortex within the more general role of the frontal cortex at large in the execution of all forms of action (somatic movement, eye movement, emotional behavior, intellectual performance, speech, etc.). The prefrontal cortex—its lateral region in particular—specializes in the temporal structuring of new and complex goal-directed series of actions, whether in the form of behavior, speech, or reasoning. It is the novelty and complexity of those actions that qualify the prefrontal cortex as the so-called “organ of creativity.” Further, the participation of the prefrontal cortex in the choice between alternatives, in decision making, and in executing temporally structured action are the reasons that this cortex has also been considered the “central executive.”

At the root of the temporal ordering and timing of actions, is the neural process of integrating information

along the time axis. The temporal organization of novel and complex behavioral sequences is not possible without temporal integration, that is, without the integration of temporally separate stimuli, actions, and action plans into goal-directed sequences of behavior. This process of integration, which requires the continuous mediation of cross-temporal contingencies (Fig. 4), is the essential physiological role of the prefrontal cortex. All the cognitive functions of this cortex, especially of its lateral region, serve the mediation of cross-temporal contingencies, and thereby temporal integration, in one way or another.

In order to perform its integrative role, the prefrontal cortex must be accessible, or have access, to all the items of sensory, motor, and mnemonic information that form the structure of behavior at hand. One way to understand that accessibility in physiological terms is to construe the neuronal populations of the prefrontal cortex as cellular constituents of widely distributed cortical networks representing the structure of behavior and the associations between its constituent items. This would imply that the execution of temporally structured behavior is the result of the activation of that executive network and the timely activation of its constituent neuronal components. Because the network has been formed by experience in exposure to the environment, it is reasonable to expect that prefrontal neurons will respond in similar (correlated) manner to stimuli that are associated and contingent from with each other in the guidance of a temporally structured task.

That expectation was verified in monkeys trained to perform a task that required the temporal integration of associated stimuli of different modality (Fuster *et al.*, 2000). Our use of stimuli of different modality was to insure that any prospective neuronal correlation between

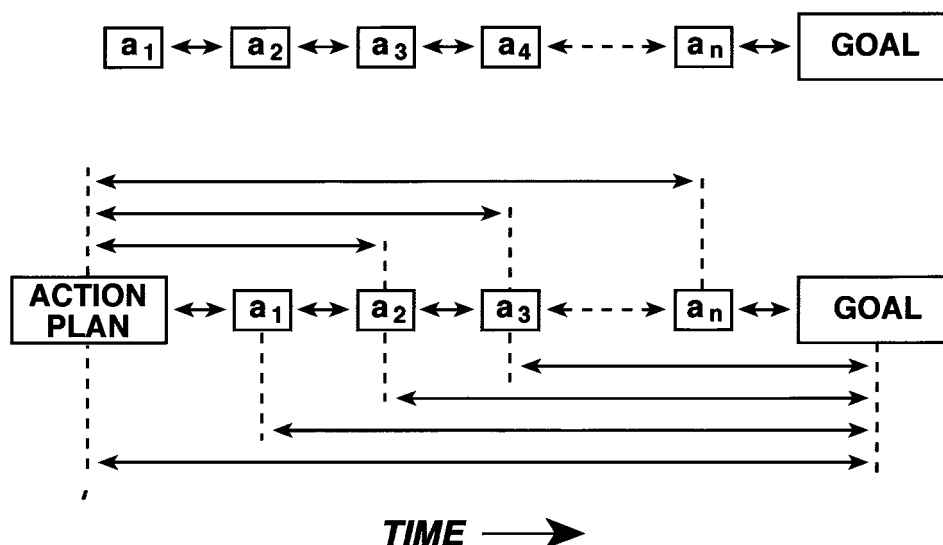


Fig. 4. A: Routine or well-rehearsed series of acts, one act leading to the next, in chain-like fashion, toward a goal. The sequence can be integrated without prefrontal intervention. B: Novel and complex sequence with cross-temporal contingencies (*long arrows*). The mediation of those contingencies necessitates the temporal integrative role of the prefrontal cortex.

stimuli could be attributed to cognitive association and not to differences in physical parameters of sensory stimulation. The task (Fig. 5A) consisted of the following serial events: (1) a brief tone of high or low pitch; (2) a delay of 10 sec.; (3) two colors, red and green, presented simultaneously; (4) choice of a color depending on the tone—red for high tone, green for low tone. (Tones and color positions change at random from trial to trial.) In sum, the task was based on the association of stimuli across time and across modalities.

In the lateral prefrontal cortex of monkeys performing the task (Fig. 5B), a large category of neurons was found that, to judge from their firing frequency at the time of stimulus presentation, discriminated the sensory stimuli with different levels of discharge. Some neurons differentiated high tone from low tone, others red from green, and still others did both. The analysis of firing discharge at the time of the stimuli revealed a correlation in accord with the task rule: neurons that preferred the high tone also preferred the red color, whereas neurons that preferred the low tone also preferred the green color (Fig. 5C). Not only the direction but also the degree of preference were correlated. Further, those correlations disappeared or were reversed in trials terminating in error: when the monkey erred, the cells also “erred.” These results indicate that, during the performance of a temporal integrative task, neurons in the prefrontal cortex associate stimuli across time and across sensory modalities, in accord with the rules of a sequential task. A reasonable implication of our results is that those neurons are part of networks of long-term executive memory that were formed by the learning of the task, and that those networks are activated during the task in order to mediate cross-temporal contingencies between associated sensory stimuli.

WORKING MEMORY

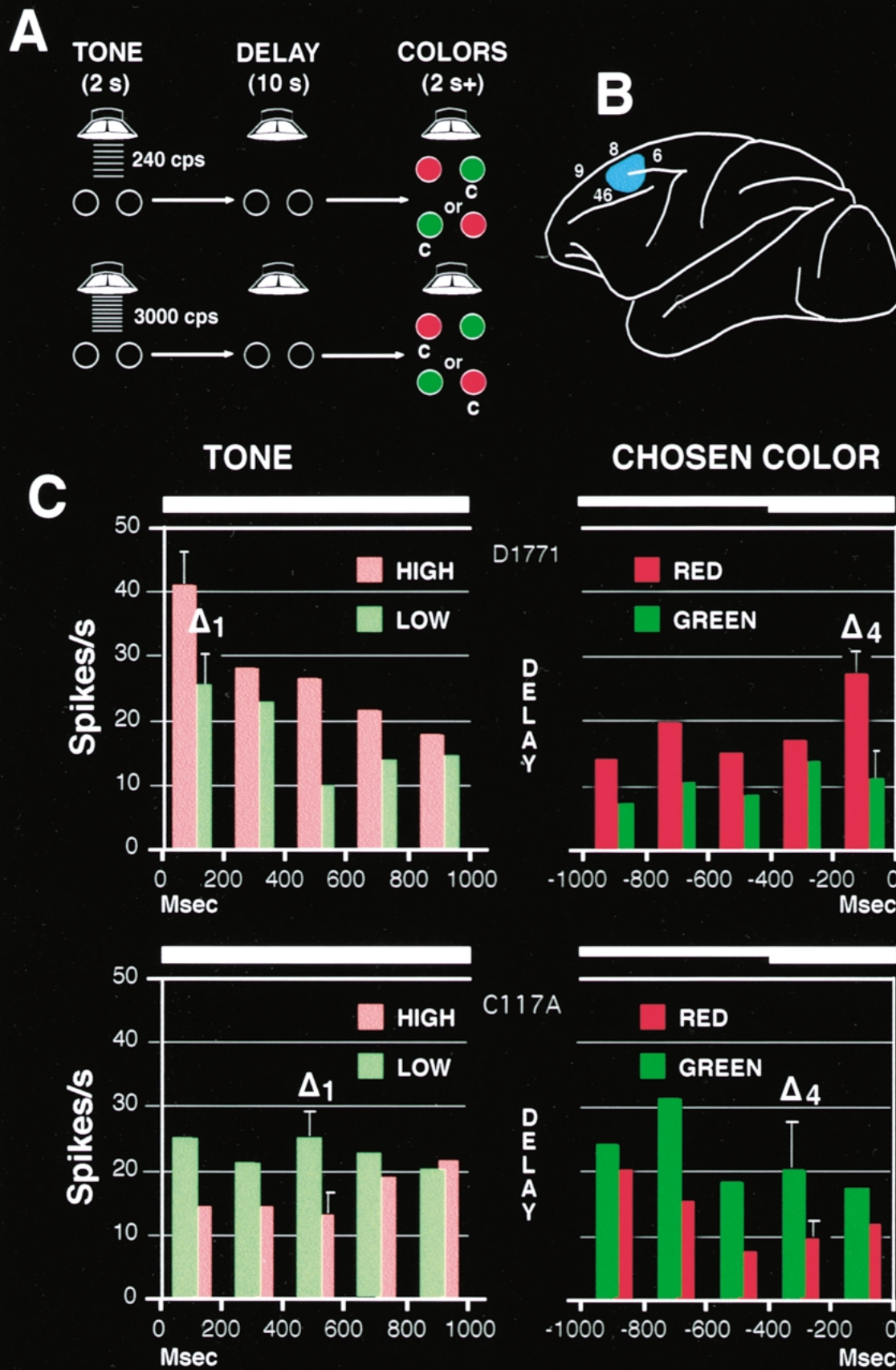
From the published results in a vast neuropsychological, physiological, and imaging literature (reviewed in Fuster, 2001), we now know that the mediation of cross-temporal contingencies, and therefore temporal integration, rely on two time-bridging functions of the lateral prefrontal cortex: working memory and set.

Working memory (Baddeley, 1986) is the temporary retention of an item of information—*e.g.*, a sensory cue—for the solution of a problem or for a mental operation. Working memory is memory *for* the short term, rather than short-term memory. It is attention focused on an internal representation. Elsewhere (1997a), I have argued that working memory essentially consists of the temporary activation of a widely distributed cortical network of long-term memory. My argument is based on the evidence that, during the short-term retention of sensory information for a prospective act, neurons in widespread areas of the cortex exhibit sustained activation. Further, the working memory of a given stimulus

can elicit sustained neuronal activation in several areas of the cortex at the same time. The neuronal correlates of working memory were first discovered, and have been repeatedly confirmed, in the prefrontal cortex of monkeys performing delay tasks (Fuster & Alexander, 1971; Fuster *et al.*, 1982; Funahashi *et al.*, 1989; Miller *et al.*, 1996).

The sustained activation of prefrontal “memory neurons” during working memory has the following characteristics (Fuster, 1973): (1) it is related in magnitude to the accuracy of performance of the task; (2) it is dependent on the need to perform a prospective motor act; (3) it is not dependent on the expectation of reward; and (4) it can be suppressed or diminished by distraction. In the context of a behavioral task, such as a delay task, the content of working memory is not limited to the specific sensory parameters of the cue that the animal must remember for a few seconds to perform the task with maximum accuracy. Also included in that content are other associated features of the cue that are part of the long-term executive memory of the task (*e.g.*, position of cue in the apparatus, manipulanda, response, etc.). Consequently, during the memory period (delay), some cells show uniform activation in all trials of the task, without relation to any particular cue. Others also show sustained activation in all trials, but the magnitude of that activation differs with the particular cue for the trial. For example, the three cells in Figure 6 (task in Fig. 5B) show sustained delay activation that is higher in the retention of the low tone than in that of the high tone. In addition, the cells show the tone-color correlation described in the previous section. Presumably therefore, prefrontal cells of this kind belong to executive networks that encode a number of associated characteristics of the cue in the task environment, including the pitch of the auditory memorandum.

The neural mechanisms of working memory have been the subject of many studies. The inactivation, by cooling, of the lateral prefrontal cortex induces a reversible deficit in the performance of a visual memory task (delayed matching to sample with colors). At the same time, it induces a diminution of differences in the sustained memory activity of cells in the inferotemporal cortex—visual memory cortex (Fuster *et al.*, 1985). A reasonable interpretation of these findings is that prefrontal cooling deprives inferotemporal cells of the capacity to retain visual stimuli in working memory. This interpretation implies that, in visual working memory, inferotemporal networks are normally under a degree of executive control from the prefrontal cortex (Desimone & Duncan, 1995) and are released from that control by prefrontal cooling. The results are also compatible with the notion that working memory is based on the reverberation of activity between the executive networks of the prefrontal cortex and the sensory networks of posterior cortex. Cooling of either cortex would interrupt the reentrant circuits that sustain



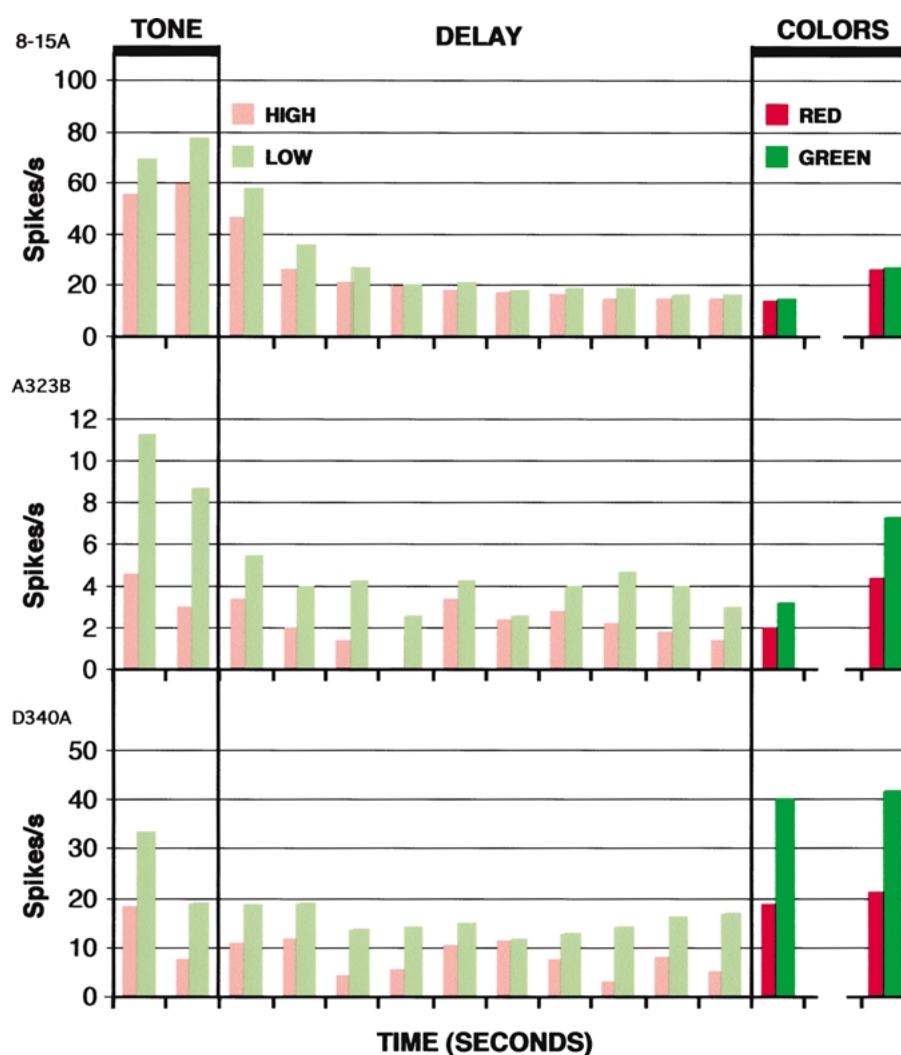


Fig. 6. Frequency histograms of three prefrontal cells selective for low tone and green—according to the task rule. Note the sustained, low-tone preferential firing during the working-memory period (delay). (From Fuster *et al.*, 2000, with permission).

that reverberation. Reentrant circuitry is an essential feature of some of the most plausible computational models of working memory (Zipser *et al.*, 1993; Compte *et al.*, 2000).

PREPARATORY SET

Whereas working memory is a temporally retrospective function to retain items of recent sensory information, prospective set is a temporally prospective function, also based in the lateral prefrontal cortex, to prepare the organism for actions contingent on that information. Preparatory set can be appropriately considered the

inclusive component of *motor attention* (Fuster, 1997b). (The exclusionary component is dealt with below, under *Inhibitory Control*.) This set function of the lateral prefrontal cortex has been substantiated by electrophysiological evidence. Between a sensory cue and a motor response contingent on it, slow potentials can be recorded from the surface of the frontal lobe in the human (Fig. 7) that are related in amplitude to the reaction time and the accuracy of the response (Brunia *et al.*, 1985). Two such potentials have been identified, though both seem to be part of a continuum along temporal and frontal-surface gradients. The first is the contingent negative variation (CNV), also called the “expectancy

Fig. 5. A: Diagram of the cross-modal, audio-visual task, as described in the text. B: Lateral view of the monkey’s brain with the area indicated (blue) where cells were found that discriminated sounds and colors in accord with the rule of the task (numbers refer to areas in Brodmann’s map). C: Average firing-frequency histograms of two prefrontal cells during the tone and color-choice periods of the task. Both cells are activated in accord with the task rule. The cell on top (D1771) fires preferentially to high-pitch tone and red; that on the bottom (C117A) prefers low-pitch tone and green. (From Fuster *et al.*, 2000, with permission).

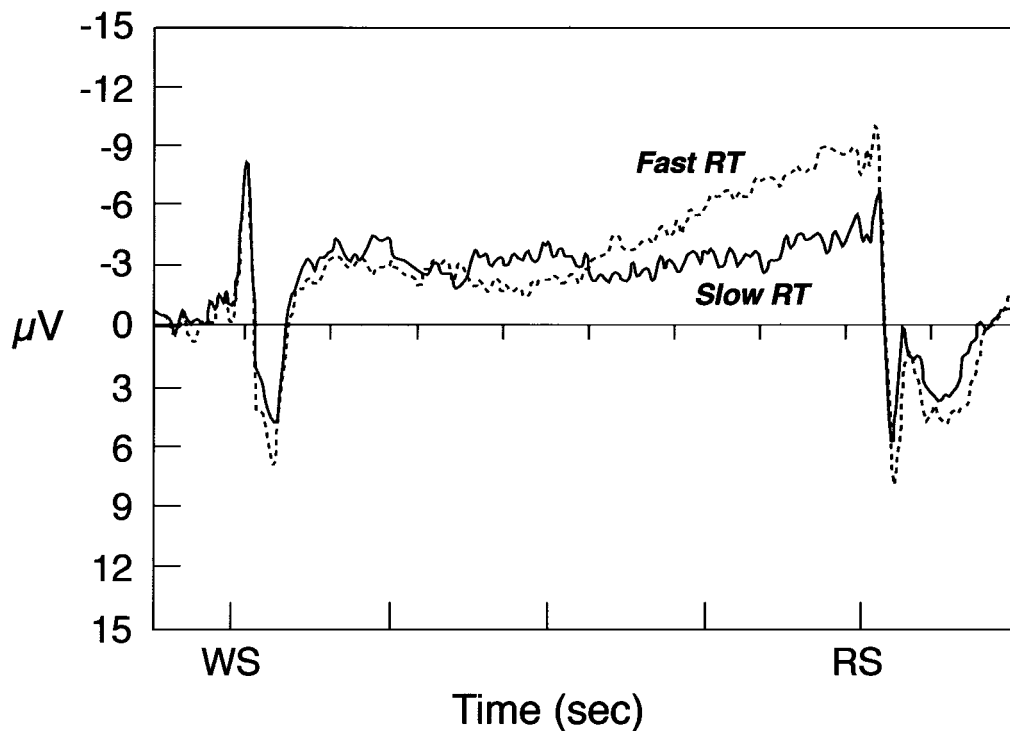


Fig. 7. Increasing surface potential from the frontal cortex of the human in the interval between a sensory cue (WS) and a motor response (RS). The amplitude of the potential is greater when the reaction time (RT) of the subject is fast than when it is slow. (From Brunia *et al.*, 1985, with permission).

wave," which is dependent on the necessity to mediate the cross-temporal contingency between cue and response. The second is the so-called readiness potential (RP), dependent on the necessity to prepare a motor action. The CNV has a somewhat more anterior, prefrontal, source than the RP, which appears to originate in premotor and motor cortex. Both potentials increase in magnitude with time as the response approaches and appear to reflect the increasing activity of underlying neurons in preparation for the response.

In the monkey, during the delay period of delayed-matching and delayed-response tasks, the discharge of some prefrontal cells increases as the choice or matching response approaches (Niki & Watanabe, 1979; Fuster *et al.*, 1982). In a double-contingency color-matching task, the magnitude of that increase (Fig. 8) was found to depend on the degree of certainty with which the animal could predict the direction of the prospective motor response, to the right or to the left side of a panel (Quintana & Fuster, 1999). These cells appear to represent the neuronal source of the CNV-RP potentials, and thus the neuronal substrate for the preparation of executive action.

The involvement of the lateral prefrontal cortex of the monkey in the preparation for executive action is in all likelihood related to the role of the cortex of the convexity of the frontal lobe of the human in planning. One of the most consistent clinical symptoms of patients with large injuries of this cortex is the inability to formulate

and to carry out plans of action. The deficit in the ability to plan for future action seems to reflect, on a broader temporal scale, the failure of the function of short-term set for action that, as described above, the electrophysiology of the lateral prefrontal cortex suggests in both man and monkey.

INHIBITORY CONTROL

The neuropsychology of the frontal lobe in humans and monkeys points to another temporal integrative function of the frontal lobe: inhibitory control. Lesion experiments and clinical evidence (reviewed in Fuster, 1997b) indicate that the neural substrate for this inhibitory function resides mainly in the medial and orbital aspects of the prefrontal cortex. The apparent physiological objective of inhibitory influences from orbitomedial cortex is the suppression of internal and external inputs that can interfere with whatever structure of behavior, speech, or cognition is about to be undertaken or currently underway. However, the neurophysiological mechanisms of prefrontal inhibitory control are still unknown.

One source of interference with current structured actions consists of internal biological drives and impulses. Patients with orbitomedial prefrontal lesions exhibit inordinate impulsiveness, irritability, hyperactivity, and poor control of instincts. The disinhibited drives and impulses have their origin in the diencephalon and the brain stem. They are normally

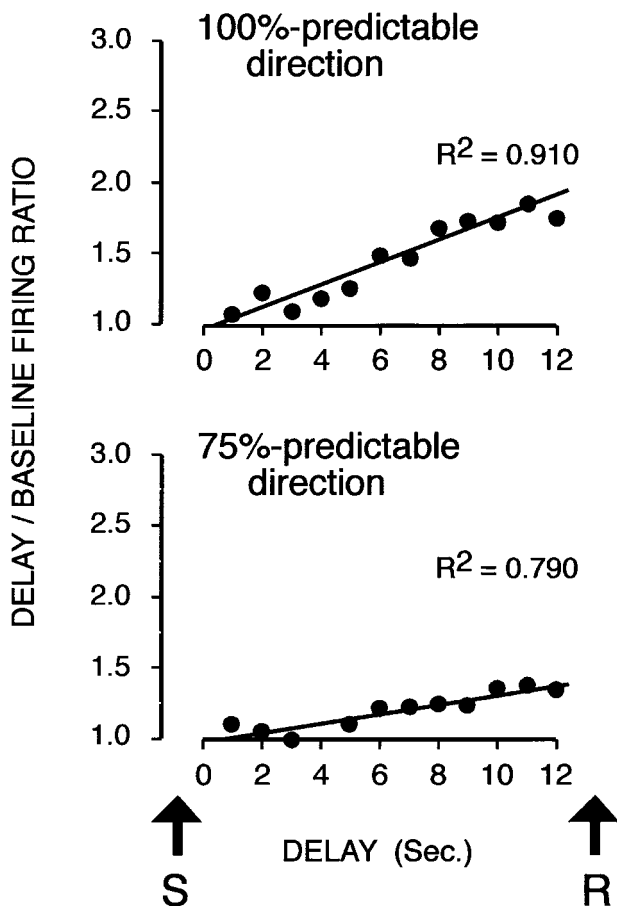


Fig. 8. Average firing of 15 direction-coupled prefrontal cells during the period of delay between the sample (S) and the choice response (R) in a delayed-matching task with colors. The task contains a double contingency: the choice of directional response (right or left) is contingent on the sample color and, in addition, on a second visual cue at the end of the delay. Some sample colors predict the direction with 100% and others with 75% probability. Note that cell firing increases gradually in anticipation of the response, and that the increase is greater with 100- than 75-percent predictability.

under control from the orbitomedial prefrontal cortex via anatomically identified efferent outputs to those subcortical structures, notably the hypothalamus.

Another source of possible interference is a host of influences from sensory systems that are unrelated to current action and can obstruct it or lead it astray. These interfering influences may arrive to the prefrontal cortex from sensory areas of posterior cortex; in the course of goal-directed action, they are probably suppressed by inhibitory feedback from the orbitomedial prefrontal cortex upon those areas. This kind of inhibitory control from the prefrontal cortex is a major component (exclusionary component) of sensory attention. In the absence of it, humans and monkeys with lesions of orbitofrontal cortex exhibit abnormal distractibility in addition to hyperactivity and hyperreactivity to sensory stimuli. The exclusionary component of sensory attention is a cog-

nitive function of wide cortical distribution dedicated to the suppression of sensory distraction. The inhibition of distraction complements the intensive, focusing component of selective sensory attention. Both components are supported by prefrontal outputs, which exert control over the cognitive functions of other cortical regions (Desimone & Duncan, 1995). The attentive control from prefrontal cortex, with its effects of both selective focusing and exclusionary inhibition, is essential for the integrity of any complex structure of goal-directed action.

A third source of interference is constituted by motor representations of action that are unrelated to, or in some manner incompatible with, actions currently in the process of temporal structuring. Included among them is a large array of motor habits, tendencies and impulses established in long-term memory and thus in the cortical and subcortical circuitry of motor systems. The suppression of those untoward influences from the motor sector is the essence of the exclusionary aspect of motor attention.

One of the hallmarks of the psychosocial development of the child is the progressive establishment of inhibitory control over internal impulses, over sensorium, and over motility. As the child grows, the two principal components of attention, inclusive and exclusionary, mature gradually. The child becomes more capable of focusing and concentrating attention on ongoing tasks. At the same time, the child becomes less distractible, less impulsive, and more capable of self-control. The most striking characteristics of the attention deficit disorders of childhood are the difficulties to focus and concentrate, the distractibility, the impulsiveness, and the hyperactivity. All these are manifestations of the absence of effective inhibitory control. Because of the evidence of a critical role of the orbitomedial prefrontal cortex in this function, it has been reasonably postulated that the attention deficit disorders of the developing child are attributable to the laggard maturation of that portion of the prefrontal cortex (Barkley, 1997).

References

- BADDELEY, A. (1986) *Working Memory*. Oxford: Clarendon Press.
- BARKLEY, R. A. (1997) Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin* **121**, 65–94.
- BRODMANN, K. (1909) *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Leipzig: Barth.
- BRUNIA, C. H. M., HAAGH, S. A. V. M. & SCHEIRS, J. G. M. (1985) Waiting to respond: Electrophysiological measurements in man during preparation for a voluntary movement. In *Motor Behavior* (edited by HEUER, H., KLEINBECK, U. & SCHMIDT, K.-H.) pp. 35–78. New York: Springer.

- BUTLER, A. B. (1994) The evolution of the dorsal pallium in the telencephalon of amniotes: Cladistic analysis and a new hypothesis. *Brain Research Reviews* **19**, 66–101.
- COMPTE, A., BRUNEL, N., GOLDMAN-RAKIC, P. S. & WANG, X.-J. (2000) Synaptic mechanisms and network dynamics underlying spatial working memory in a cortical network model. *Cerebral Cortex* **10**, 910–923.
- DESIMONE, R. & DUNCAN, J. (1995) Neural mechanisms of selective visual attention. *Annual Review of Neuroscience* **18**, 193–222.
- EDELMAN, G. M. (1987) *Neural Darwinism*. New York: Basic Books.
- FELLEMAN, D. J. & VAN ESSEN, D. C. (1991) Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex* **47**, 1047–3211.
- FINLAY, B. L. & DARLINGTON, R. B. (1995) Linked regularities in the development and evolution of mammalian brains. *Science* **268**, 1578–1584.
- FLECHSIG, P. (1901) Developmental (myelogenetic) localization of the cerebral cortex in the human subject. *Lancet* **2**, 1027–1029.
- FLECHSIG, P. (1920) *Anatomie des Menschlichen Gehirns und Rückenmarks auf Myelogenetischer Grundlage*. Leipzig: Thieme.
- FUNAHASHI, S., BRUCE, C. J. & GOLDMAN-RAKIC, P. S. (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *Journal of Neurophysiology* **61**, 331–349.
- FUSTER, J. M. (1973) Unit activity in prefrontal cortex during delayed-response performance: Neuronal correlates of transient memory. *Journal of Neurophysiology* **36**, 61–78.
- FUSTER, J. M. (1997a) Network memory. *Trends in Neurosciences* **20**, 451–459.
- FUSTER, J. M. (1997b) *The Prefrontal Cortex—Anatomy, Physiology, and Neuropsychology of the Frontal Lobe*. Philadelphia: Lippincott-Raven.
- FUSTER, J. M. (2001) The prefrontal cortex—An update: Time is of the essence. *Neuron* **30**, 319–333.
- FUSTER, J. M. & ALEXANDER, G. E. (1971) Neuron activity related to short-term memory. *Science* **173**, 652–654.
- FUSTER, J. M., BAUER, R. H. & JERVEY, J. P. (1982) Cellular discharge in the dorsolateral prefrontal cortex of the monkey in cognitive tasks. *Experimental Neurology* **77**, 679–694.
- FUSTER, J. M., BAUER, R. H. & JERVEY, J. P. (1985) Functional interactions between inferotemporal and prefrontal cortex in a cognitive task. *Brain Research* **330**, 299–307.
- FUSTER, J. M., BODNER, M. & KROGER, J. K. (2000) Cross-modal and cross-temporal association in neurons of frontal cortex. *Nature* **405**, 347–351.
- GIBSON, K. R. (1991) Myelination and behavioral development: A comparative perspective on questions of neoteny, altriciality and intelligence. In *Brain Maturation and Cognitive Development* (edited by GIBSON, K. R. & PETERSEN, A. C.) pp. 29–63. New York: Aldine de Gruyter.
- GIEDD, J. N., BLUMENTHAL, J., JEFFRIES, N. O., CASTELLANOS, F. X., LIU, H., ZIJDENBOS, A., PAUS, T., EVANS, A. C. & RAPAPORT, J. L. (1999) Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience* **2**, 861–863.
- HUTTENLOCHER, P. R. (1979) Synaptic density in human frontal cortex—Developmental changes and effects of aging. *Brain Research* **163**, 195–205.
- HUTTENLOCHER, P. R. (1990) Morphometric study of human cerebral cortex development. *Neuropsychologia* **28**, 517–527.
- JERISON, H. J. (1990) Fossil brains and the evolution of the neocortex. In *The Neocortex: Ontogeny and Phylogeny* (edited by FINLAY, B. L., INNOCENTI, G. & SCHEICH, H.) pp. 5–19. New York: Plenum Press.
- JERNIGAN, T. L. & TALLAL, P. (1990) Late childhood changes in brain morphology observable with MRI. *Developmental Medicine and Child Neurology* **32**, 379–385.
- JONES, E. G. & POWELL, T. P. S. (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain* **93**, 793–820.
- LURIA, A. R. (1966) *Higher Cortical Functions in Man*. New York: Basic Books.
- MILLER, E. K., ERICKSON, C. A. & DESIMONE, R. (1996) Neural mechanisms of visual working memory in the prefrontal cortex of the macaque. *Journal of Neuroscience* **16**, 5154–5167.
- MRZLJAK, L., UYLINGS, H. B. M., VAN EDEN, C. G. & JUDÁS, M. (1990) Neuronal development in human prefrontal cortex in prenatal and postnatal stages. In *The Prefrontal Cortex: Its Structure, Function and Pathology* (edited by UYLINGS, H. B. M., VAN EDEN, C. G., DE BRUIN, J. P. C., CORNER, M. A. & FEENSTRA, M. G. P.) pp. 185–222. Amsterdam: Elsevier.
- NIKI, H. & WATANABE, M. (1979) Prefrontal and cingulate unit activity during timing behavior in the monkey. *Brain Research* **171**, 213–224.
- NORTHCUTT, G. & KAAS, J. H. (1995) The emergence and evolution of mammalian neocortex. *Trends in Neurosciences* **18**, 373–379.
- PANDYA, D. N. & YETERIAN, E. H. (1985) Architecture and connections of cortical association areas. In *Cerebral Cortex, Vol. 4* (edited by PETERS, A. & JONES, E. G.) pp. 3–61. New York: Plenum Press.
- PFEFFERBAUM, A., MATHALON, D. H., SULLIVAN, E. V., RAWLES, J. M., ZIPURSKY, R. B. & LIM, K. O. (1994) A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Archives of Neurology* **51**, 874–887.
- PIAGET, J. (1952) *The Origins of Intelligence in Children*. New York: International Universities Press.
- QUINTANA, J. & FUSTER, J. M. (1999) From perception to action: Temporal integrative functions of prefrontal and parietal neurons. *Cerebral Cortex* **9**, 213–221.
- REISS, A. L., ABRAMS, M. T., SINGER, H. S., ROSS, J. L. & DENCKLA, M. B. (1996) Brain development, gender and IQ in children: A volumetric imaging study. *Brain* **119**, 1763–1774.
- SCHEIBEL, A. B. (1990) Dendritic correlates of higher cognitive function. In *Neurobiology of Higher Cognitive Function* (edited by SCHEIBEL, A. B. & WECHSLER, A.) pp. 239–270. New York: The Guilford Press.
- SOWELL, E. R., THOMPSON, P. M., HOLMES, C. J., JERNIGAN, T. L. & TOGA, A. W. (1999) *In vivo* evidence for post-adolescent brain maturation in frontal and striatal regions. *Nature Neuroscience* **2**, 859–861.

- SOWELL, E. R., THOMPSON, P. M., TESSNER, K. D. & TOGA, A. W. (2001) Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during post adolescent brain maturation. *Journal of Neuroscience* **21**, 8819–8829.
- STEPHAN, H., FRAHM, H. & BARON, G. (1981) New and revised data on volumes of brain structures in insectivores and primates. *Folia Primatologia* **35**, 1–29.
- VAN HOESSEN, G. W. (1982) The parahippocampal gyrus. *Trends in Neurosciences* **5**, 345–350.
- YAKOVLEV, P. I. & LECOURS, A. R. (1967). The myelogenetic cycles of regional maturation of the brain. In *Regional Development of the Brain in Early Life* (edited by MINKOWSKI, A.) pp. 3–70. Oxford: Blackwell.
- ZIPSER, D., KEHOE, B., LITTLEWORT, G. & FUSTER, J. M. (1993) A spiking network model of short-term active memory. *Journal of Neuroscience* **13**, 3406–3420.