Role of the Lateral Prefrontal Cortex in Executive Behavioral Control

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Tanji J, Hoshi E. Role of the Lateral Prefrontal Cortex in Executive Behavioral Control. Physiol Rev 88: 37–57, 2008; doi:10.1152/physrev.00014.2007.—The lateral prefrontal cortex is critically involved in broad aspects of executive behavioral control. Early studies emphasized its role in the short-term retention of information retrieved from cortical association areas and in the inhibition of prepotent responses. Recent studies of subhuman primates and humans have revealed the role of this area in more general aspects of behavioral planning. Novel findings of neuronal activity have specified how neurons in this area take part in selective attention for action and in selecting an intended action. Furthermore, the involvement of the lateral prefrontal cortex in the implementation of behavioral rules and in setting multiple behavioral goals has been discovered. Recent studies have begun to reveal neuronal mechanisms for strategic behavioral planning and for the development of knowledge that enables the planning of macrostructures of event-action sequences at the conceptual level.

I. INTRODUCTION

The prefrontal cortex (PFC) of primates has traditionally been classified into at least three major subdivisions: lateral, medial, and ventral (orbitofrontal). Comprehensive reviews of the structures and functions of the PFC have appeared in various monographs (e.g., Refs. 75, 188, 259) and review articles (89, 147, 290).

In this review, we concentrate on recent developments in research on the lateral part of the PFC that includes area 12/47, 45, and 46 ventrally, as well as 8B and 9 dorsally, according to the cytoarchitectonic classification of Walker (274). Area 8A, which belongs to the oculomotor control region, is not considered here. The lateral prefrontal cortex (LPFC) is involved in many aspects of behavior in primates (Table 1). Here, we primarily deal with the issue of integrative action planning, which is viewed as constituting a core prefrontal function (140).

Toward the end of the 20th century, the primary research interests concerning the LPFC were the processing of information stored in short-term memory and at-
II. ANATOMICAL BACKGROUND

We first provide an anatomical framework with which to consider the role of the LPFC under various conditions that require subjects to exert adequate control over behavior. After a brief consideration of heterogeneity within the LPFC based on architectonic differentiation in the PFC and intrinsic anatomical connectivity, we examine the connections of the LPFC with cortical and subcortical areas that are relevant in its role in executive behavioral control. We deal with reports regarding the PFC of macaque monkeys, in which basic patterns in the architecture and anatomical connectivity of the PFC are basically similar to those in humans (200, 201).

TABLE 1. Behavioral factors in which the involvement of the lateral prefrontal cortex is viewed as essential

<table>
<thead>
<tr>
<th>Information processing</th>
<th>Selection and retrieval</th>
<th>Retention and monitoring</th>
<th>Transformation</th>
<th>Manipulation</th>
<th>Synthesis and generation</th>
<th>Attentional and cognitive-set regulation</th>
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A. General Trends in the Organization of the LPFC: Parcelation Into Dorsal and Ventral Tiers

When analyzing architectonic organization in the PFC, Barbas and Pandya (21) found two distinct trends in gradual changes in laminar characteristics that can be traced from the limbic periallocortex toward the isocortical areas. Based on cytoarchitectonic and myeloarchitectonic analysis, they observed that one of the architectonic trends takes a radial basoventral course from the periallocortex in the caudal orbitofrontal region to the adjacent preisocortex, and then to area 13. The next stage of advancement in architectonic differentiation begins from orbital areas 12, 11, and 14, followed by area 10, and the rostroventral area 46, and finally reaches the caudal part of ventral areas 46 and 8. The other trend takes a mediodorsal course from the periallocortex, around the rostral portion of the corpus callosum to the preisocortical areas 24, 25, and 32, and then to the medially situated isocortical areas 9, 10, and 14. The next stage includes lateral areas 10 and 9 and rostroventral area 46, progressing to the caudal part of dorsal areas 46 and 8. Thus the dorsal and ventral parts of the LPFC are viewed as having two distinct origins of architectonic differentiation. By examining corticocortical connections within the PFC using tracer techniques, Barbas and Pandya (21) further found that most interconnections were limited to areas within the same architectonic trend. Thus the dorsal part of the LPFC receives inputs largely from areas in the medial PFC, whereas the ventral LPFC receives afferents mostly from areas in the orbitofrontal cortex.

Price and co-workers (44, 177) examined corticocortical connections of the orbital and medial PFC and defined two distinct networks: the orbital network and the medial network. The orbital network includes most of the areas on the posterior, central, and lateral orbital surfaces, whereas the medial prefrontal network includes all the areas on the medial wall and the related areas on the orbital surface. Areas within each network are mutually interconnected and have distinct connections with structures in other parts of the brain. The orbital network receives ample sensory inputs of multiple modalities, conveying visual, somatosensory, auditory, olfactory, and gustatory information (46). The medial network is characterized by outputs to the hypothalamus and the periaqueductal gray, which play major roles in autonomic and somatic (visceromotor) responses to emotional stimuli (170, 176).

Although the areas defined by the mediodorsal and basoventral trends (21) may not completely match the areas belonging to the medial and orbital networks (177), the existence of two large-scale networks in the PFC originating from the medial and ventral periallocortex has been established. The dorsal part of the LPFC (dorsal to the fundus of the principal sulcus) belongs to the me-
diodorsal network. In contrast, the ventral part of the LPFC (ventral to the fundus of the principal sulcus) belongs to the orbitoventral (basoventral) network.

B. Inputs to the PFC

1. Visual association cortex (areas TE and TEO)

Areas TE and TEO and the lower bank of the superior temporal sulcus (STS) in the inferior temporal cortex, which are essential for visual object recognition (264), project preferentially to areas in the orbitoventral network (lateral area 12, ventral area 8, and area 45) (46, 113, 242, 247, 283). The ventral part of the temporal pole, which receives visual information from the inferior temporal cortex, also projects to areas in the orbitoventral network (e.g., areas 11 and 13) (120). Areas in the mediodorsal network rarely receive inputs from areas TE and TEO or the ventral part of the temporal pole (16, 242, 283).

2. Polymodal area in the dorsal bank of the STS

The polymodal area in the dorsal bank of the STS (area TPO, temporal polymodal cortex) projects to both the mediodorsal and orbitoventral networks. In this projection, a rostrocaudal trend has been identified: more rostral areas (less differentiated areas) of the TPO preferentially project to the less differentiated areas in the PFC, and the more caudal areas of the TPO (more differentiated areas) project to the more differentiated areas in the PFC (247).

3. Auditory association cortex (superior temporal gyrus)

The LPPC across the two networks receives inputs from the auditory association cortex in the superior temporal gyrus. Topographical connections have been reported: the rostral part of area 46 and area 10 are preferentially interconnected with the rostral belt and parabelt auditory association cortex, whereas the caudal part of area 46 and the periaruncate cortex (area 8a) are preferentially linked with the caudal auditory association cortex (198, 219). The inferior part of the periaruncate cortex (area 45) is interconnected with both the rostral and caudal parts of the auditory association cortex (200). In addition to these connections with the LPPC, the auditory association cortex and the anterior superior temporal cortices are heavily interconnected with the medial prefrontal cortices (areas 10, 14, 25, and 32) (16) and orbital PFC (areas 12 and 13) (46). The dorsal part of the temporal pole, which receives auditory or polymodal inputs from the superior temporal cortex, projects preferentially to areas in the mediodorsal networks (e.g., areas 10, 14, 25, and 32) and lateral orbital cortex (area 12) (120).

4. Perisylvian somatosensory cortex

The ventral rim of the middle part of the principal sulcus and the medial part of area 12 (both in the orbitoventral network) are interconnected with the perisylvian somatosensory cortical areas: the second somatosensory area, area 2 of the primary somatosensory area, granular insular cortex, and PF in the rostral inferior parietal lobule (19, 48, 205).

5. Inferior parietal lobule

Several distinct areas have been identified in the inferior parietal lobule. Although the number of areas is still controversial, a recent report provided evidence that there are four distinct cytoarchitectonic areas in the convexity of the inferior parietal lobule: area Opt, PG, PFG, and PF in the caudal to rostral axis (183, 227). The LPFC, especially area 46, is interconnected with these parietal areas. There is a general trend in connections between area 46 and the inferior parietal lobule: dorsal area 46 is preferentially linked with more caudal areas such as the area Opt, whereas ventral area 46 is preferentially linked with more rostral areas such as areas PF and PFG (227). More specifically, the caudal part of the posterior parietal cortex is linked with the fundus and banks of the principal sulcus (4, 47, 199), whereas its rostral part is connected with the ventral lip of the principal sulcus and area 45 (4, 47, 198).

6. Superior parietal lobule and medial parietal cortex

Only weak outputs from the superior parietal lobule, if any, reach dorsal area 46 of the PFC (113). Rather, they primarily reach the dorsal premotor cortex in Brodmann’s area 6 (199, 201). In contrast, the medial posterior parietal cortex and the caudal cingulate areas (areas PGm, 29, 30, 23, and 31) are preferentially interconnected with areas in the mediodorsal network, including the dorsal part of the LPFC (47, 160, 201).

7. Amygdala, perirhinal cortex, and hypothalamus

The amygdala projects to the less differentiated areas in both the mediodorsal and orbitoventral networks (2, 15, 45, 202). However, the caudal part of the LPFC, which is a highly differentiated area, receives few direct inputs from the amygdala (2, 15, 202). The perirhinal cortex (areas 35 and 36) is preferentially interconnected with areas in the orbitoventral network (areas 11, 12, and 13) (121, 128). The hypothalamus projects to wide areas in the PFC, including the LPFC (214), although areas in the medial PFC constitute most of the outputs to the hypothalamus (176).
8. Parahippocampal cortex, entorhinal cortex, subiculum, and hippocampal formation

The parahippocampal cortex (areas TF/TH) projects to wide areas across the two networks, with some preference for the mediodorsal network, including the LPFC (121, 128). The hippocampal formation, subiculum, and entorhinal cortex preferentially send outputs to the mediodorsal frontal cortex (areas 24, 32, 25, and 14) (14, 161). The LPFC is innervated predominantly by the presubiculum, but it receives sparser inputs from the hippocampal formation (14, 92).

9. Thalamus

The PFC is interconnected with multiple nuclei in the thalamus, including the ventral nuclei, mediodorsal nucleus, and medial pulvinar nucleus (17, 91, 112, 115). The ventral anterior nucleus, linked with the PFC, is innervated by the output stage of the basal ganglia (substantia nigra pars reticulata and the internal segment of the globus pallidus) (107, 292). The ventral lateral nucleus mediates the projection from the cerebellar nuclei to the PFC (144). The mediodorsal nucleus, linked with the thalamic and orbital PFC, receives inputs from a variety of structures, including the ventral pallidum, substantia innominata, amygdala, entorhinal and perirhinal cortices, subiculum, olfactory cortex, hypothalamus, and temporal pole (91, 231). In contrast, the lateral part of the mediodorsal nucleus, which is preferentially interconnected with the LPFC, is innervated by the superior colliculus, substantia nigra pars reticulata, and claustrum (62, 91, 107). Topographical connections have been shown between the thalamus and the mediodorsal nucleus: the dorsal and ventral LPFCs tend to be interconnected with the dorsal and ventral mediodorsal nuclei, respectively (91, 255). The medial pulvinar receives inputs from the superior colliculus, parahippocampal cortex, posterior cingulate, and retrosplenial cortex (13, 25). Taken together, the thalamus mediates pathways to the PFC from the basal ganglia, cerebellum, and a variety of limbic structures, including the hippocampus and amygdala.

10. Monoaminergic inputs

The PFC receives ample monoaminergic inputs (34): dopamine, norepinephrine, and serotonin (203, 286). Innervations of dopamine fibers are more prominent in mediodorsal areas such as areas 9, 8B, and 24. The density of dopamine terminals decreases in the lateral and orbital areas (26, 132, 287). Similarly, innervation with norepinephrine is more intense in areas 9, 8B, and 24 (133). In contrast, overall serotonergic innervation is more uniform across areas in the PFC (134). The densities of monoaminergic axon terminals and distributions of receptor subtypes differ markedly across cortical layers (26, 90, 134) and across subclasses of neurons (256, 257), suggesting that monoamines play important roles in information processing by the PFC (5, 49, 216, 240, 285).

C. Connections With Cortical Motor Areas, Basal Ganglia, and the Cerebellum

1. Motor areas in the frontal cortex

The PFC is interconnected with multiple motor areas in the frontal cortex (24, 99, 135, 157, 261), which is believed to play important roles in the cognitive control of motor behavior. Connections with the lateral premotor cortex (area 6) differ between the dorsal and ventral parts of the LPFC. The dorsal part is linked with the dorsal premotor cortex, medial to the spur of the arcuate sulcus, whereas the ventral part is linked with the ventral premotor cortex, lateral to the spur (20, 46, 139, 200, 201, 205, 279). In contrast, both dorsal and ventral parts of the LPFC are linked with the rostral cingulate motor area (area 24c), presupplementary motor area (area 6), and supplementary eye field (area 6) (46, 103, 138, 139, 278). Area 8A, which is involved in eye and head movements, is also interconnected with both the dorsal and ventral parts of the LPFC (18, 104, 200, 201).

2. Basal ganglia

Wide areas of the LPFC project to the input stage of the basal ganglia (caudate and putamen) in a topographical manner (114, 246). The dorsal part of the LPFC projects preferentially to the dorsal and central part of the caudate nucleus, and the ventral part projects to the ventral and central caudate nucleus (293). A topographical connection has been reported in projections from the orbital and medial PFC. The medial PFC preferentially projects to the ventral striatum (medial caudate nucleus, nucleus accumbens, ventral putamen). In contrast, the orbital PFC projects to central and lateral parts of the caudate nucleus and to the ventromedial putamen (64). Because parallel and looped architectures are suggested to be basic principles of the corticobasal ganglia system (1), it is likely that there are multiple parallel circuits running through the PFC and the basal ganglia, with each circuit involved in distinct aspects of behavioral control. The subthalamic nucleus, which is another input stage of the basal ganglia (153, 168), receives inputs only from restricted areas of the PFC; it was reported that the area 9, but not the area 46, sends its outputs to it (159). Further studies are necessary to reveal more precise profiles of the projection patterns from the PFC to the subthalamic nucleus.

3. Cerebellum

Areas medial to the principal sulcus and medial PFC (areas in the mediodorsal network) send outputs to the
basilar pons (83, 243), the neurons of which send outputs that connect to neurons in the deep cerebellar nuclei and granule cells in the cerebellar cortex (108). In contrast, only a small number of areas (caudal ventral area 46 and area 45) in the orbitoventral network send less intense outputs to the pontine nuclei. The ventral and orbital prefrontal cortices do not send outputs to the pontine nuclei (83, 243). Using a strain of herpes virus, which is transported in the retrograde direction across neuronal synapses, Middleton and Strick (144) identified that dorsal area 46 and area 9, but not ventral area 46 or area 12, receive substantial inputs from deep cerebellar nuclei. Thus it appears that areas in the mediodorsal network are linked with the cerebellum, whereas the cerebellar link is much weaker in the orbitoventral network.

D. Summary of Connections of the LPFC

We summarized the basic anatomical connectivity of the LPFC in dealing with multiple inputs and outputs (Fig. 1). The dorsal and ventral parts of the LPFC can be viewed as part of two distinct, large-scale networks within the PFC: the dorsal part is part of a mediodorsal network originating from the periallocortex in the medial PFC, and the lateral part is part of an orbitoventral network originating from the periallocortex in the orbital PFC. The orbitoventral network is characterized by multiple sensory inputs, including visual, auditory, somatosensory, gustatory, and olfactory. This pattern of connections suggests that this network plays a major role in receiving multiple sensory signals to retrieve and integrate necessary information. In contrast, the mediodorsal network receives inputs from multimodal areas in the temporal cortex or auditory areas in the superior temporal gyrus. This suggests that the dorsal network receives signals that are already processed and are multimodal in nature. Intensive interconnections within each network allow the integration of multiple sets of information that each network receives. Thus the dorsal and ventral parts of the LPFC seem to process information based on dis-
distinct inputs. Additionally, there are extensive interconnections between the two networks (21, 184, 200), allowing the PFC to integrate multiple sets of information on a large scale.

The LPFC is directly or indirectly connected with widespread structures in the brain through the orbital and medial prefrontal cortices: the association cortex, limbic cortex, and subcortical structures. This organization places the PFC in a unique position and highlights its critical role in collecting and integrating diverse sets of information. On the other hand, the LPFC is interconnected with premotor areas, the basal ganglia, and the cerebellum. Through these connections, the LPFC can control broad aspects of motor behavior. Moreover, the LPFC modulates the flow of information in other areas of the central nervous system, in conforming to behavioral requirements, providing a resource for adaptive control of information flowing through cortical and subcortical structures (146). The PFC is thus situated at the center of large-scale information flow in the brain.

III. REGIONAL SPECIALIZATION WITHIN THE LATERAL PREFRONTAL CORTEX

A major debate regarding the LPFC has been whether this cortical region should be considered unitary or heterogeneous in function. Lesion studies in which behavioral deficits are examined following an ablation or acute inhibition or excitation of a restricted area in the PFC have provided important clues regarding functional specialization within the PFC (54). A consensus has developed that interprets the effects of lesions confined to the cortex in and around the principal sulcus (dorsal and ventral area 46) as deficits in behavior that require the processing of spatial information with a time delay between behavioral events such as between a spatial cue and a motor act or between successive motor acts in space (85, 86, 131, 149, 155). In contrast, ablation of the principal sulcus does not induce deficits in a behavioral task in which information on object identity must be handled such as in delayed match- (or non-match-) to-sample tasks (10, 156, 185). Thus the effects of lesions applied to the banks of the principal sulcus suggest its key involvement in processing spatial signals such as the spatial position of a cue and a motor act in space, but not in processing information on object identity.

Lesions in the ventral part of the LPFC lead to different deficits than those in the banks of the principal sulcus. Ventral prefrontal lesions cause deficits in behavioral tasks in which information on object identity plays a key role (156, 185, 277). An important observation is that animals with lesions in the ventral PFC could not perform a color-matching task, even if no delay was imposed (229), and that once the task was relearned, the animals could perform the task even with delay. Rushworth and co-workers (228, 229) suggested that the ventral PFC is not important for working memory, but may play a role in selecting attended objects. Bussey et al. (41) showed that ventral and orbital prefrontal lesions induce deficits in learning new visuomotor associations and retaining prelearned visuomotor associations. These findings point to the possibility that the ventral PFC plays an important role in processing multiple visual items or in associating visual signals with spatial motor acts (162, 189, 289). In fact, lesions in this area may also cause some deficits in spatial tasks (109, 224). Bussey et al. (41) also showed that prelearned strategies of repeat-stay and change-shift (repeating the same response when a rewarded cue was presented repeatedly and altering the response to the stimulus) were not retained after the lesion. Together with the perseveration tendency after lesions in the ventral PFC (109, 126), another important function of the ventral PFC would appear to be the implementation of behavioral strategies to optimize task performance (41).

Goldman-Rakic (89) proposed that the dorsal and ventral parts of the LPFC differ primarily with respect to the information domain, with spatial processes taking place in the dorsolateral PFC and feature processing taking place in the ventrolateral PFC. This hypothesis, based on anatomical connectivity exhibiting dorsoventral gradients in afferent and efferent projection patterns (see sect. n), was initially supported by reports of functional studies in humans (271, 272) and monkeys (179, 180, 288). However, subsequent functional studies were not necessarily consistent with this view. Rao et al. (213) examined LPFC neurons in monkeys during a task that involved processing of both what and where information. Neurons showing either object-tuned (what) or location-tuned (where) delay activity were distributed widely in both the ventral and dorsal parts of the LPFC. Furthermore, over half (52%, 64 of 123) of the PFC neurons with delay activity showed both what and where tuning, suggesting that their role in linking object information with spatial information was needed to guide behavior. In a study by Wilson et al. (288), 24 of the 31 delay-related neurons in the inferior convexity reflected visual objects, whereas 6 reflected the response direction. The existence of response-coding neurons, along with object-selective neurons in the ventral PFC, is consistent with the conclusions of lesion studies in that the ventral PFC plays a key role in associating visual information with motor responses. Furthermore, the passive viewing of stimuli presented on a screen (179, 180) can activate neurons responding to visual inputs, regardless of their relevance to the control of actions.

Spatially selective PFC activity is greatly influenced by behavioral factors such as the sequence of appearance (8, 22), probability of the direction of forthcoming movements (209), object identity (7, 210, 211), judgment diffi-
culty (51), saccade-direction judgment (116), and reward expectancy (117, 130, 217). Object selectivity of PFC neurons is also affected by such behavioral factors as go/no-go selection (233–236, 281, 282), category specification (66, 67), object quantity (171), object sequence and rank order (173, 174), task requirements or behavioral relevance (100), task rules (284), and an attended dimension of a visual object (shape versus color) (142). These reports stress the importance of the integrative processing of information within the PFC (189, 226, 229), rather than the simple reflection or retention of sensory information.

Based on a series of lesion studies in monkeys (193, 195) and on brain imaging studies in humans (181, 196), Petrides (192, 194) proposed that the dorsal part of the LPFC was involved in the monitoring and manipulation of retrieved information in the planning and execution of behavior. The ventral part of the LPFC, in contrast, was proposed to be involved in active encoding and retrieval of specific information held in visual, auditory, and somatosensory association areas, allowing selection, comparison, and decision processes based on such information.

This process-specific model of the functional organization of the LPFC has been influential and essentially constitutes an antithesis to the domain-specific model, although some issues remain to be answered. If behavioral monitoring is indeed a critical process that depends on the integrity of the dorsal LPFC, it is unclear why lesions in this area cause impairments in simple tests of spatial delayed response tasks that do not depend on monitoring (131). It is also unclear whether lesions in the banks of the principal sulcus, in addition to those in the more dorsal part of the LPFC, would give rise to deficits similar to those reported by Petrides (192).

Ninokura et al. (174) recorded neuronal activity while monkeys received three visual objects presented successively and reproduce the temporal order of their appearance by touching them in the presented order. They found that neuronal activity in the middle part of the dorsal LPFC, corresponding to the area that Petrides (194) proposed as a critical area for monitoring, preferentially represented the rank-order of the appearance of the objects, rather than object identity. Hasegawa et al. (96) recorded neuronal activity while monkeys performed a self-ordered task that required them to perform three steps. They found that neurons in the dorsal LPFC primarily reflected task progress, rather than object identity. These two studies suggest that the dorsal LPFC is involved in encoding the task phase or task progress, but is less involved in representing the identity of objects, which are amply represented in the ventral LPFC. This functional dichotomy is consistent with the pattern of anatomical connectivity, suggesting that the dorsal LPFC preferentially receives processed information, rather than the relatively more direct modality-specific sensory information reaching the areas in the orbitoventral network. The dichotomy also suggests that the interaction allowed by the intrinsic connections between the dorsal and ventral networks allows the dorsal LPFC to execute the monitoring and manipulation of retrieved information, which itself is preferentially represented in the areas of the orbitoventral network.

Hoshi and Tanji (102) compared neuronal activity in the dorsal and ventral LPFC by designing experiments to detect neuronal activity reflecting the process of receiving and retaining two sets of visual information, retrieving their behavioral meaning, and integrating the two to plan subsequent actions. Ventral LPFC neurons were preferentially involved in detecting and retaining spatial information contained in visual cues for subsequent use, whereas dorsal LPFC neurons were predominantly involved in a more advanced stage of sensorimotor processing, the retrieval of task-relevant information, and the integration of the two sets of information to construct instructions for actions to be planned. This observation demonstrating the progression of information transfer taking place along the direction from the ventral to dorsal LPFC suggests neuronal mechanisms that could explain the validity of the aforementioned two-stage hypothesis. Lebedev et al. (129) showed that neuronal activity reflecting a memorized location (more remote location) tended to be located in the dorsal LPFC, whereas activity reflecting an attended location (more recent location) was primarily located in the ventral LPFC. This can be viewed as showing that more processed information is represented dorsally. A recent report demonstrating the preferential role of the dorsal LPFC in more conceptual aspects of behavioral planning is also consistent with the process-specific theory (250).

There is sufficient evidence to reveal functional heterogeneity within the LPFC. As long as behavioral tasks do not require much information processing, neuronal activity may primarily represent the information received from sensory signals. However, if the behavioral conditions are demanding, properties that characterize specific processes that take place in individual portions of the LPFC are likely to emerge, even if cooperation between multiple areas belonging to different networks is necessary to allow the functioning of the LPFC at a high level of operation. From a separate point of view, a caveat against the process-specific theory is the possibility that some aspects of specific processes may also rely on domain-specific use of sensory information.

IV. WORKING MEMORY

The term working memory was proposed to refer to a multicomponent system capable of both storing and
manipulating information that plays a central role in complex cognitive activities required for the control of various aspects of behavior (12). Although the “central executive” part of this model has remained largely unspecified by experimental studies until recently, the “short-term storage of information” part of the model has received much interest in experimental studies. Neurophysiological studies have provided a great deal of evidence that PFC cells exhibit sustained type of activity throughout the delay period after the termination of visual (57, 71, 76, 148) or auditory (28) cue signals. Romo and co-workers (220–222) later revealed that the frequency of somatosensory signals was retained in cellular activity during a period of short-term storage, in a parametric manner. Goldman-Rakic (88, 89) proposed the hypothesis that the PFC mediates working memory, defined as the short-term storage of information pertinent in the performance of upcoming tasks. The delay-period activity in the PFC was viewed as essential in keeping memorized information on line. It was further proposed that the PFC is a collection of areas with a specialized mnemonic function and that the multitude of granular prefrontal areas differ from one another, not in the functions they perform, but rather more in the nature of the information they process (domain specificity hypothesis, Refs. 87, 89). Although attractive as a theory characterizing the functions of the dorsal and ventral parts of the LPFC, the working-memory theory of their account and the theory of domain-specific regional specialization have some problems. The theory has difficulty in accounting for some of the impairments observed in monkeys with PFC lesions (80, 154, 187). Furthermore, the results of ablation studies of the dorsolateral PFC on oculomotor delayed responses (72) have been inconclusive. Although the data have been interpreted as supporting a spatial working memory hypothesis, postoperative saccades were generally directed close to the correct direction of saccades to be remembered. Delay-period activity in the dorsolateral PFC has also been interpreted in terms of the maintenance-memory theory (51, 71). However, as revealed by recent studies, the delay-period activity could be interpreted with non-memory functions (e.g., selective attention or preparation of action), as we discuss in subsequent sections in this review. Evidence arguing against the domain-specific regional specialization theory is accumulating (see sect. III). Furthermore, brain-imaging studies in humans supported the memory-maintenance theory at first (53), but subsequently have resulted in questioning the substantial participation of the LPFC in working memory storage (204). It seems that the capacity of simple storage of information for a short term may not be of primary importance for the functional role of the LPFC. Instead, the contribution of this area to working memory function is more likely to be in controlling behavior in processes operating at a level that is abstracted from the processing of individual sensory signals. Attentional control, transformation of mnemonic representations from their encoded state, response selection, abstraction across trials of stimulus patterns with which to guide behavioral set, or mediation of the effects of interference in working memory are among capacities in which the LPFC is likely to be crucially involved.

V. ATTENTION for ACTION

To initiate an action to achieve what is intended, subjects first search for information to construct the schema of the action and its goal. Neuronal mechanisms that mediate perceptual selectivity required in this attentive process have long been known to involve the LPFC (30, 31, 57). Recent studies have provided evidence that the PFC is critical for attentional function to code information of specific relevance to current behavior, filtering out unwanted signals (56, 137, 147). The finding that cellular activity in the LPFC exhibits strong filtering of visual signals demonstrates the way in which focused attention can achieve the selection of behavioral targets versus non-targets (63). These findings are consistent with the view that top-down attention that results from signals emanating from the frontal cortex biases posterior areas to favor the channel of information relevant to the intended behavior (145, 191). The role of the LPFC in the attentional selection of objects, rather than the maintenance of object information, has been reported in event-related functional magnetic resonance imaging (fMRI) studies on human subjects (127, 225). A recent neurophysiological study attempted to examine whether the delay period activity of PFC neurons after the presentation of a positional cue signal represented a remembered location or the target of an attended location (129). In the study, monkeys attended to a stimulus marking one location while remembering a different, unmarked location: both locations served as potential targets of a saccade. Lebedev et al. (129) found that LPFC neurons predominantly represented attended locations, but not remembered ones, although the task made intensive demands on short-term memory. The findings showed that short-term memory functions cannot account for most delay-period activity in the LPFC, pointing to a more general role for the LPFC than proposed by the maintenance-memory theory (43, 147, 260, 267), including the top-down control of selective attention. Numerous studies using event-related fMRI have reported the participation of multiple cortical areas in attentional processes, but it has been difficult to localize various aspects of attentive behavior (165). However, attempts to fractionate attentive control processes are progressing. In a recent report, for instance, subjects voluntarily worked out which object was the target in a stimulus set of two faces and two buildings, and feedback...
was given once after two consecutive choices (94). With the use of this experimental design, which sorted out such behavioral factors as response reversals, stimulus change, stimulus-response mapping change, and changes in the dimension of stimulus, it was found that the ventrolateral PFC was involved in switching attention between stimulus dimensions (extradimensional shifts), whereas the posterior parietal cortex mediated changes in stimulus-response mapping.

VI. RESPONSE INHIBITION

A cardinal characteristic of the impairment observed in “frontal” patients, i.e., the higher rate of perseveration error, is usually explained as a failure in the inhibition of the central set or the need for a supervisory system to be involved in the inhibition of prepotent schemas (248). Using marmoset monkeys, Dias et al. (58) found that damage to the LPFC caused a loss of inhibitory control in attentional selection (failure of extra-dimensional shift), whereas lesions in the orbitofrontal cortex led to a loss of inhibitory control in affective processing (failure of intra-dimensional shift). In human subjects, damage to the LPFC is associated with impairment on the Wisconsin Card Sort Test (WCST) (151, 186). With the use of event-related fMRI, a transient activation focused in the LPFC was found in humans (33, 52, 124, 230, 258) and monkeys (166) during cognitive set shifting in the WCST. Miyashita and colleagues (125) further found that the active area during set shifting coincided with an area that was active during the performance of a go/no-go response, suggesting that the ventral LPFC (right hemisphere in humans) is commonly involved in the inhibition of different targets such as the go response during the performance of a go/no-go task and the cognitive set during the performance of the WCST. In a later study, however, a different area was found to be active when the WCST task was modified to temporally isolate the inhibitory processes of the cognitive set (123). Under such conditions, the dorsal LPFC (left middle frontal gyrus near the superior frontal sulcus) was activated. These findings indicate the presence of multiple inhibitory mechanisms in the LPFC. Indeed, when the WCST was modified to reveal the inhibition of prolonged proactive interference from a previous set, the participation of the anterior part of the LPFC was detected (122). A recent proposal that the right inferior frontal cortex of humans could be a focal structure to exert inhibitory control (6) awaits further confirmation.

Failure on the WCST or related tests may not necessarily mean the presence of perseverative response selection or the lack of inhibition of the prepotent cognitive set. Poor performance on the WCST could also be explained as the failure to reject prevailing behavioral rules, or alternatively, as the inability to think beyond the originally applied behavior-guiding principle. By designing a set of new sorting tests, Delis et al. (55) found that patients with lesions of the PFC also had problems in spontaneously generating rules, using abstract or explicit cues to guide sorting, identifying rules they had used to accurately sort, and identifying rules used by the examiner to sort. With these findings, Delis et al. (55) uncovered evidence of impairment in the use of behavior-guiding rules and also of deficits that included concept formation and abstract thinking. We address these behavioral aspects below.

VII. PREPARATORY SET AND REGULATION OF CROSS-TEMPORAL CONTINGENCY

Fuster (74) reemphasized the long-standing, traditional concept (110, 152, 207) that the general function of the LPFC is the temporal organization of behavior. Upon the initiation of actions, networks involving the PFC are viewed as providing representations of the schemas of the behavioral structure and the plan and program outlining actions. The preparatory set is a prospective function specifying the occurrence of a forthcoming action with a proper timing and order. It also regulates temporal relationships between the occurrences of events and actions, namely, the regulation of cross-temporal contingencies. A good example of neuronal activity representing cross-temporal contingencies was presented in a study that also required the cross-modal association of sensory signals (77). Fukushima et al. (70) found that the delay-period activity preceding the selection of the forthcoming cascade target shifted when a centrally positioned cue instructed a target shift, indicating that the representation of temporal contingencies could be updated in accordance with instructions. Furthermore, Genovesio et al. (82) revealed that two separate groups of neurons in the PFC represented either previous goals or future goals.

Rainer et al. (212) recorded neuronal activity from the LPFC while monkeys were performing a paired associate task and showed that activity of PFC neurons reflected not only a given visual signal, but also a visual object associated with it in the paired association task. Because similar patterns of activity were reported in the inferior temporal cortex (158, 169, 237), the interaction between the PFC and inferior temporal cortex is in no doubt crucial in retrieving associated visual objects from long-term memory (61, 93, 95, 269). Furthermore, it is shown that the interaction between the PFC and the inferior temporal cortex plays crucial roles in associating a visual stimulus with an action in a conditional visuomotor task (40) and in strategy implementation in which the subject could maximize a reward gain by making a choice of objects in a scheduled manner (79).

These reports indicate that the PFC plays a central role in forming the cross-temporal contingency of rele-
VIII. ACTION SELECTION AND DECISION MAKING

Although the involvement of the LPFC in the selection of action has long been inferred from studies in humans (e.g., Ref. 68) and monkeys (97, 106), it has been controversial whether the cortical activity during the behavioral action selection process, often involving working memory tasks, reflected the maintenance of memorized information or the selection of manual, verbal, or oculo-motor responses. Rowe et al. (226) used fMRI to study prefrontal activity in a behavioral condition that distinguished the maintenance of spatial items from the selection of an item from memory to guide a response. They revealed that selection, but not maintenance, was associated with activation of area 46. The LPFC was also found to be active during a self-initiation task in which a timing selection was required (111).

Action selection takes time to form when no instruction for action specifies a target or no associative learning has been established to prompt the selection of an action. One example of such behavioral conditions is a case of double-rule decision making in which the selection of a target should be made in accordance with two rules imposed simultaneously. Hoshi et al. (101) trained monkeys to select a reach target in accordance with two concurrent rules. Initially, a sample cue (triangle or circle) appeared at one of three possible locations (top, right, or left) on a touch screen. After a delay period, one of two choice cues appeared. In the first, either three circles or three triangles occupying the three locations solicited the monkeys to select a target by matching the locations of the sample-choice cues (location-match rule). In the second, a circle and a triangle at two of the three possible locations required the monkeys to select a target by matching the shapes of the sample-choice cues (shape-match rule). Thus neither the sample nor choice cues themselves instructed the target to be selected; the information specifying the target to be selected had to be generated internally. Under both behavioral rules, it was found that the information for target selection emerged promptly in neuronal activity in the LPFC within 300 ms after the appearance of the choice cue. This finding, along with the effects of transient inactivation of the LPFC by local application of GABA agonist (101), suggests that the necessary information was generated, at least in part, in the LPFC or in a neuronal circuit involving the LPFC, providing a case for the generation of information for decision making (266).

Another example of a behavioral condition requiring problem resolution is related to decisions for the selection of actions under uncertainty. Using fMRI, Huettel et al. (105) found activity focused in the LPFC, as well as in the intraparietal sulcus, when subjects were engaged in a task in which uncertainty developed over short time scales as information was accumulated toward a decision. This finding is in contrast to a report that the activation of the frontomedial cortex reflected the degree of uncertainty for predictions induced in a long-term stimulus-response adaptation process (273).

IX. BEHAVIORAL PLANNING VERSUS MOTOR PLANNING

A. Motor Planning in the LPFC

The concept that a substantial proportion of prefrontal neurons takes part in the preparation of movement has received support from studies examining neuronal activity in the LPFC (27, 215, 233, 241). In a subsequent study, Funahashi et al. (73) recorded LPFC neurons in monkeys required to make saccades toward a remembered target and also toward a direction opposite to the remembered target. They found that 30 neurons coded the location of the visual stimulus memorized, whereas 13 neurons coded the direction of the impending saccade. Based on these data, they concluded that the cue location is represented more than saccade direction. However, in a study examining the LPFC of monkeys performing a manual response in a task condition requiring visuomotor memory (209), more neurons were found to specify the direction of forthcoming arm motion than those to code the memorized visual information. For these motion-coupled cells, the slope of acceleration of their firing during the delay period was proportional to the degree of probability with which the monkey could predict the direction of the forthcoming manual response. In later studies, Takeda and Funahashi (262, 263) found that neuronal activity in the PFC signaling memorized sensory signals was replaced with the activity signaling the direction of forthcoming saccade, during a delay period. Thus, until recently, it had been thought generally that neurons in the LPFC play a considerable role in preparing or planning an intended movement.

B. Task or Rule Dependency of Preparatory Activity

A separate group of experiments casts some doubt on the notion that the LPFC codes for a planned move-
ment, thus participating in the specification of motor variables constituting the intended movement (e.g., choice of body part or parameters such as direction, amplitude, or speed of forthcoming movement). Hoshi et al. (100) examined neuronal activity while monkeys were preparing and executing reaching movements to objects that appeared on a video screen. They found that 36% of LPFC neurons that were active during the preparation and execution of arm reaching differed depending on whether the object to reach was circular or triangular. Furthermore, the neuronal activity preceding arm-reach movements differed greatly depending on whether the monkeys were performing the motor task to match the shape of a response object with a sample object or to match the location of the response object with the sample object. The former finding raised the possibility that neuronal activity signified the objective of the action (i.e., to capture a circle or a triangle). The latter finding may be interpreted as the expression of the task rule: achievement of a motor task in conforming to a task rule (i.e., shape-match or location-match rule). Alternatively, the findings suggest the possibility that neuronal activity related to the preparation or execution of motor acts is strongly modulated by behavioral objectives or behavioral rules. White and Wise (284) designed experiments to test more explicitly whether the rule of the behavioral task is represented in neuronal activity. By presenting instructional cue signals, they required monkeys to perform arm reaching in accordance with two behavioral rules: matching to a sample rule or a spatial match rule. They found that movement-related activity of LPFC neurons, as well as activity responding to visual signals or during the delay period, was profoundly modulated by the rule. The rule dependency of activity during the preparation or planning of motor responses was also reported in a study incorporating behavioral rules of either match or non-match to sample objects (275). In human subjects, neural substrates for behavioral rules have been reported in a number of studies (32, 35–38, 182, 238, 239).

C. What is Planned in the LPFC?

These reports raise a more fundamental question of whether movements themselves are planned or prepared in the LPFC. An alternative hypothesis is that behavioral factors not directly relevant to the selection of movements (or motor parameters) could be the primary components processed in the PFC, and this area may not be much concerned with the specification of how motor effectors would operate. To resolve this issue, monkeys were trained to move a cursor on a video monitor by operating two manipulanda with either hand (164). Supination or pronation of the manipulandum with the right or left hand was linked to the movements of the cursor in four directions (up, down, right, left). The directions of cursor motion were assigned to each of four different hand movements in three different ways. For the great majority of neurons, activity in the preparatory period reflected movement of the cursor (or the location of the cursor) on the monitor screen, but not the movement to be performed (use of the right/left hand or the direction of the movement). Thus PFC neurons primarily represented the movement of an object that will occur as a consequence of an intended limb movement, but not the movement per se. This finding raises the possibility that the planning of motor behavior in the PFC is generally executed in terms of the end result of a target object occurring as an outcome of a planned action, but not in terms of an intended movement. Averbeck et al. (8) recorded the activity of small ensembles of neurons in the LPFC while monkeys copied geometrical shapes shown on a screen. Monkeys drew the shapes as sequences of movement segments, and these segments were associated with distinct patterns of neuronal ensemble activity. Averbeck et al. (8) concluded that the neuronal ensemble activity observed during the time preceding the actual drawing reflected distinct segments of movements. However, it is also possible that the neuronal activity reflected the trajectories of the segments of the geometric figure planned to be drawn, rather than segments of limb movements, because these two behavioral factors were not dissociated in the experiment. The results may have indicated the representation of segments of shapes that were planned to appear as the outcome of the intended copying action.

X. BEHAVIORAL GOAL SELECTION

One of the cardinal problems characterizing frontal lobe patients is the neglect of behavioral goals (60, 141). During the performance of a variety of behavioral tasks that require such cognitive control as multistep tasks or concurrent execution of dual tasks, frontal patients often fail to achieve the behavioral goal, although they understand the requirements of the behavioral task (151, 175, 190). With the use of a Tower of Hanoi task (84) or a variant (65), the PFC has been implicated in resolving goal-subgoal conflicts. Clinical studies and reports on human subjects prompted an attempt to look for the representation of behavioral goal information in the PFC in experimental studies. Saito et al. (232) constructed a spatial maze task to induce monkeys to determine multiple behavioral goals to be attained in a temporal sequence. Monkeys were trained to move a cursor on the screen from a start position to a goal position in a maze by tracking a path with three steps of moves that were temporally separated. During a preparatory delay period after receiving an instruction signal, they were also re-
required to plan a path to take with the three motion steps while waiting at the start position for the first go signal to initiate the first step. Saito et al. (232) found that neuronal activity in the LPFC during the delay period first began to represent the final goal to be reached. Subsequently, during the later part of the delay period, the final goal representation was gradually substituted with the representation of an immediate goal that was planned to be reached (the first of the three goal positions to be acquired, in order). The second goal representation appeared after completion of the first step. This exhibits the way in which neurons in the LPFC take part in governing goal-oriented sequential behavior by temporally arranging representations for a goal and subgoals.

The term behavioral goal is sometimes used simply to refer to reward acquisition. Apparently, animal behavior is often oriented to obtain rewards. The potency of reward expectation, internal drive to acquire a reward, or reward reception in influencing neuronal activity everywhere in the brain has been described in the literature (e.g., Refs. 244, 245). Prefrontal neurons certainly reflect reward relevance or reward expectation, as we describe below. However, it is important to differentiate simple reward-seeking behavior, which is ubiquitous among animals, including unicellular creatures such as amoebae, from the kind of behavior requiring the regulation of temporal structures of action based on current and remembered information. We suggest the use of the term behavioral goal to refer to the latter category, but not to everything related to reward acquisition, at least when considering the involvement of the PFC in executive behavioral control.

XI. REWARD EXPECTATION AND REINFORCER-BASED CONTROL OF BEHAVIOR

Although the orbitofrontal cortex is the primary site representing primary reinforcers, for learning and reversing associations of audiovisual information to the primary reinforcers, and for controlling behavior based on reinforcers (218, 268), neurons in the LPFC also encode reinforcers (3, 172, 178, 223). Watanabe (280) found that the activity of LPFC neurons during a delay period reflected not only the expectancy of a reward or no reward, but also the nature of the reward. Neuronal activity reflected the object to be obtained as a reward and also reflected the preference for the expected reward. Furthermore, LPFC neurons reflected the discrepancy between the expectancy of a specific reward and the reward actually obtained. Thus neuronal activity in this area is likely related to the expectancy of the nature and preference of an anticipated reward or its magnitude (130). An alternative interpretation of the neuronal activity could be the alteration of attentive processes selectively connected to aspects of reward expectation or alteration of the general attentive state in preparing for the outcome of the behavioral action. Similar reward expectancy-related activity has been recorded in the orbitofrontal cortex (98).

Wallis and Miller (276) directly compared neuronal activity in the orbital and dorsolateral PFCs while monkeys were performing a reward preference task to choose between pictures associated with different amounts of reward. The neuronal activity in both areas reflected the reward amount, although reward selectivity arose more rapidly in the orbitofrontal cortex than in the LPFC. However, LPFC neurons encoded both the reward amount and the monkeys’ forthcoming response, whereas orbitofrontal neurons more often encoded the reward amount alone. These findings were consistent with the hypothesis that the orbitofrontal cortex primarily encodes the reward per se, whereas the LPFC uses this information to control behavior. Matsumoto et al. (143) also recorded neuronal activity from the medial frontal cortex and LPFC while monkeys performed a differentially cued, delayed go/no-go task in which two visual cues, two responses (go or no-go), and two reward conditions (reward + and −) were combined in eight different combinations. The cue responses were strongly modulated depending on whether they were associated with reward or no reward at the completion of the task. Furthermore, neuronal activity selective to either go or no-go responses was also modulated depending on whether the motor response would give rise to a reward or no reward. The latter neuronal activity appeared earlier in the medial frontal cortex than in the LPFC. These findings indicate the apparent involvement of both prefrontal areas in reward-based response selection or reward prediction (cf., Ref. 270).

Because both appetitive and aversive behavioral outcomes can reinforce animals’ responses, it is of interest to know whether information for the opposing reinforcers is processed in the LPFC. Kobyashi et al. (118) examined neuronal activity while monkeys performed a delayed saccade task in which a correct motor response led to three different outcomes: delivery of a liquid reward, avoidance of an air puff, or feedback with sound only. They found that aversive avoidance had clear effects on some prefrontal activity, although the effects of rewards were more common. Their results demonstrated that information about positive and negative reinforcers is processed differentially in the LPFC.

XII. TEMPORAL SEQUENCING OF MULTIPLE ACTIONS

Many purposeful behaviors are composed of sequences of actions, and the brain must gather information
concerning the sequence required before planning to execute that particular sequence. Neuronal activity reflecting sequence-specific information, reported in many areas in the frontal cortex (136, 163, 167, 208, 251), is viewed as constituting the neural elements necessary to construct the temporal structure of sequences (265). In the LPFC, Barone and Joseph (22) were the first to describe neuronal activity that was selective to the sequence of a visuospatial eye-hand task (reaching to three spatial targets located at the top, right, and left of a panel). During an instruction period, they described neuronal activity specific to the sequence of the three spatial targets to be captured. They also reported sequence selectivity of cells that appeared during the performance of sequential eye-hand movements. The performance of each sequence also required eye-hand movements with specific trajectories in space. Thus the selectivity of neuronal activity may have meant selectivity for the spatial trajectory of tracking movements (e.g., tracking targets at the top, right, and left versus top, left, and right). In more recent reports (173, 174), the involvement of the LPFC in the temporal organization of sequential actions was studied in a behavioral condition that eliminated the confounding factor of spatial trajectory. Monkeys were trained to plan a sequential capture of three objects that would appear at unpredictable locations on the screen (e.g., capture a circle, a cross, and a square in that order). During planning when the monkeys gathered information about a sequence of three-object captures, neuronal activity representing the rank order of each object (e.g., yellow circle appearing first or red cross appearing second) was detectable. During planning, LPFC neurons also represented the temporal order of objects that were planned to be captured, regardless of their spatial position. Fujii and Graybiel found that neuronal activity of the LPFC was preferentially active in the first and last parts of sequential saccadic eye movements.

**FIG. 2.** Activity of PF cells selective for a category of sequences during planning and their recording sites in the prefrontal cortex. A: Raster displays and peri-event histograms illustrating the cellular activity selective for the “paired” category. The discharges are aligned on the appearance of the GO signal for the first of memorized movements. B: Activity selective for the “alternate” category. C: “Four-repeat” category selective activity. D, Top: recording sites of category-selective cells plotted on the surface maps of the prefrontal cortex of two monkeys. The size of the circle is proportional to the number of selective cells at each site. Bottom: a cortical surface map showing the surveyed area. PS, principal sulcus; ARC, arcuate sulcus.[From Shima et al. (250).]
and suggested that these types of activity reflect the action sequence boundaries (69).

These findings are compatible with those of clinical studies that report disturbances in the temporal ordering of events (150, 197, 252) and with those of brain imaging studies (42, 196), which report activity in the LPFC during behavioral tasks that require the temporal structuring of visual information. In a recent study (9), monkeys were trained to produce a series of eye movements according to a sequence that changed unpredictably from one block of trials to the next. Ensemble neuronal activity in the LPFC predicted the sequence in a manner that changed gradually from the sequence that had been correct in the previous block to the sequence that was correct in the current block. Based on this dynamic property of neurons to action sequences, Averbeck et al. (9) proposed prefrontal involvement in representing subjective knowledge of the correct action sequence. Finally, in a very recent report, information on the behavioral sequence was represented at a higher order of abstraction: the categorization of behavioral sequences (250). This is described below.

XIII. STRATEGIC or CONCEPTUAL BEHAVIORAL PLANNING

To achieve internal goals, behavioral planning often requires the ability to coordinate thoughts and actions at cognitive levels that go beyond the association of sensory information with action or the expectation of reward relevance. In complex behavioral tasks, patients with prefrontal damage use poor strategies, exhibit behavioral incoherence (249), and are impaired in organizing strategies to improve task performance (182). The involvement of the LPFC in encoding strategies has been substantiated by an event-related fMRI study (29) using a behavioral task that required strategic chunking of spatial sequences to remember. The organization of memory contents (spatial structures) into higher-level chunks was associated with increased prefrontal activity, even when the memory demand itself was decreased. In subhuman primates, the involvement of the PFC in the strategic organization of spatial-sequencing (50) or object-retrieval tasks (78) has been proposed. At the single-neuron level, Barraclough et al. (23) studied LPFC activity while monkeys were engaged in a mixed-strategy game against a computer opponent. Signals related to the conjunction of the animal’s previous decision and its outcome were processed differently in the PFC according to the type of decisions made by the animal, suggesting a role for the LPFC in optimizing decision-making strategies. Subsequently, Genovesio et al. (81) analyzed neuronal activity using a behavioral task in which monkeys learned to map visual symbols to saccade responses by trial and error. During learning, monkeys used two response strategies. According to the repeat-stay strategy, if a symbol repeats from a previous successful trial, the monkeys should stay with their most recent response choice. According to the change-shift strategy, the monkeys should shift to a different choice if the symbol changes. Many LPFC neurons exhibited activity selective for the strategy used, implying their contribution to the implementation of abstract response strategies.

A separate issue is behavioral planning based on the development of a generalized concept of a set of behavioral activities encompassing multiple events and actions. Behavioral planning in daily life often starts with the formulation of a general plan to achieve the aim of what is intended, followed by the determination of individual details involved in that general plan. An aspect of behavioral problems for patients with frontal cortex lesions is the failure to achieve an objective of goal-oriented behavior by performing a series of simple actions (39). Patients with frontal cortex lesion were also impaired in arranging a set of open-ended, simple tasks in an appropriate temporal order to achieve a behavioral goal (249). More recently, clinical reports have suggested that patients with prefrontal lesions are impaired in analyzing clusters of action sequences (294) or in formulating action plans that accord with managerial knowledge (253, 254). To investigate the involvement of the LPFC in formulating macrolevel plans that cover multiple actions, an experimental model was recently introduced to analyze neuronal activity in the LPFC during the formulation of a plan at the conceptual level, including categories of planned behavior (250). If subjects are required to remember a large number of complex motor sequences and plan to execute each of them individually, categorization of the sequences according to the specific temporal structure inherent in

FIG. 3. Diagram summarizing the flow of information requiring the executive function of the prefrontal cortex.
each subset of sequences serves to facilitate higher-order planning based on memory. On this basic assumption, monkeys were trained to remember 11 different sequences of performing 4 actions. Individual sequences of actions were designed in such a way as to belong to one of three categories: paired sequences containing two pairs of actions (e.g., AABB), alternate sequences composed of the alternation of two actions (e.g., ABAB), and four-repeat sequences (e.g., CCCC). Behavioral analysis revealed that the monkeys depended on the categorization of the sequences to remember each of the 11 sequences. LPFC cells selectively exhibited activity for a specific category of behavioral sequences, and categories of behaviors, embodied by different types of movement sequences, were represented in prefrontal cells during the process of planning (Fig. 2). Such cellular activity was viewed as the representation of the macrolevel structure of planned sequences, exemplifying the development of behavioral planning at a conceptual level in the LPFC. This proposed view is consistent with the hypothesis that structured event complexes are represented in the LPFC (291) and with an fMRI study reporting the involvement of the LPFC in action selection on the basis of the hierarchical structure of behavioral plans (119).

XIV. CONCLUSIONS

The LPFC is involved in broad aspects of executive behavioral control based on anatomical connectivity that enables communication with cortical association areas and subcortical areas (Fig. 3). Executive functioning that takes place in this area can be fractionated into component processes for the purposeful integration of behavior. Here, we critically assessed research reports on the involvement of the LPFC in each component.

Within the LPFC, regions are differentiated primarily according to the functional operations that they perform. The ventrolateral part is involved in first-order executive processes such as active retrieval and selection of information, whereas the dorsolateral part is more involved in higher-order executive components of behavioral planning, including monitoring, manipulation, and integration of multiple pieces of information.

The LPFC takes part in various aspects of executive behavioral control, including attention for action, retrieval and manipulation of relevant information, response suppression, behavioral planning of temporal structures of actions and events, behavioral-rule implementation, action selection and decision making, behavioral goal selection, reinforcer-based behavioral decisions, and strategic or conceptual behavioral planning. Recent developments in research on this topic increasingly stress the importance of the LPFC in providing novel information to cope with requirements imposed by environmental alterations or in formulating concepts that enable subjects to effectively deal with complex behavioral demands.

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