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Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices

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ABSTRACT: Distinct domains of the prefrontal cortex in primates have a set of connections suggesting that they have different roles in cognition, memory, and emotion. Caudal lateral prefrontal areas (areas 8 and 46) receive projections from cortices representing early stages in visual or auditory processing, and from intraparietal and posterior cingulate areas associated with oculomotor guidance and attentional processes. Cortical input to areas 46 and 8 is complemented by projections from the thalamic multiform and parvocellular sectors of the mediodorsal nucleus associated with oculomotor functions and working memory. In contrast, caudal orbitofrontal areas receive diverse input from cortices representing late stages of processing within every unimodal sensory cortical system. In addition, orbitofrontal and caudal medial (limbic) prefrontal cortices receive robust projections from the amygdala, associated with emotional memory, and from medial temporal and thalamic structures associated with long-term memory. Prefrontal cortices are linked with motor control structures related to their specific roles in central executive functions. Caudal lateral prefrontal areas project to brainstem oculomotor structures, and are connected with premotor cortices effecting head, limb and body movements. In contrast, medial prefrontal and orbitofrontal limbic cortices project to hypothalamic visceromotor centers for the expression of emotions. Lateral, orbitofrontal, and medial prefrontal cortices are robustly interconnected, suggesting that they participate in concert in central executive functions. Prefrontal limbic cortices issue widespread projections through their deep layers and terminate in the upper layers of lateral (eulaminate) cortices, suggesting a predominant role in feedback communication. In contrast, when lateral prefrontal cortices communicate with limbic areas they issue projections from their upper layers and their axons terminate in the deep layers, suggesting a role in feedforward communication. Through their widespread connections, prefrontal limbic cortices may exercise a tonic influence on lateral prefrontal cortices, inextricably linking areas associated with cognitive and emotional processes. The integration of cognitive, mnemonic and emotional processes is likely to be disrupted in psychiatric and neurodegenerative diseases which preferentially affect limbic cortices and consequently

disconnect major feedback pathways to the neuraxis.
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There is a commonly held view that the frontal cortex in humans holds a privileged position within the nervous system with regard to thought and reason. This view stems, in part, from the classic neurological literature which has provided evidence that the frontal cortex, and its anterior (prefrontal) component, in particular, has a role in cognitive processes and central executive functions (for reviews see [57,63,127]). Recent functional imaging studies in humans have in some ways corroborated these views of the prefrontal cortex as a cognitive processor (e.g., [39,41,107,113]). There is now evidence that the prefrontal cortex in primates selects sensory and other information to guide behavior, though the mechanism on how this is achieved is not clear. However, we are beginning to appreciate the wealth of information that is necessary to carry out even a simple cognitive task, such as remembering temporarily a telephone number, a street address, or words spoken in casual conversation. To select relevant information for action the prefrontal cortex must have access to the sensory and spatial aspects of the environment, mnemonic information acquired through experience, and linkage with motor control structures. In addition, decisions and actions taken in behavioral settings are inextricably embedded within the context of the internal, or emotional, environment of the individual, commonly expressed as one's point of view.

The prefrontal cortex does not receive direct input from the sensory periphery and must obtain all information it processes through its connections with other cortical or subcortical structures. The following is an overview of the circuits through which distinct sectors of the prefrontal cortex gain access to the

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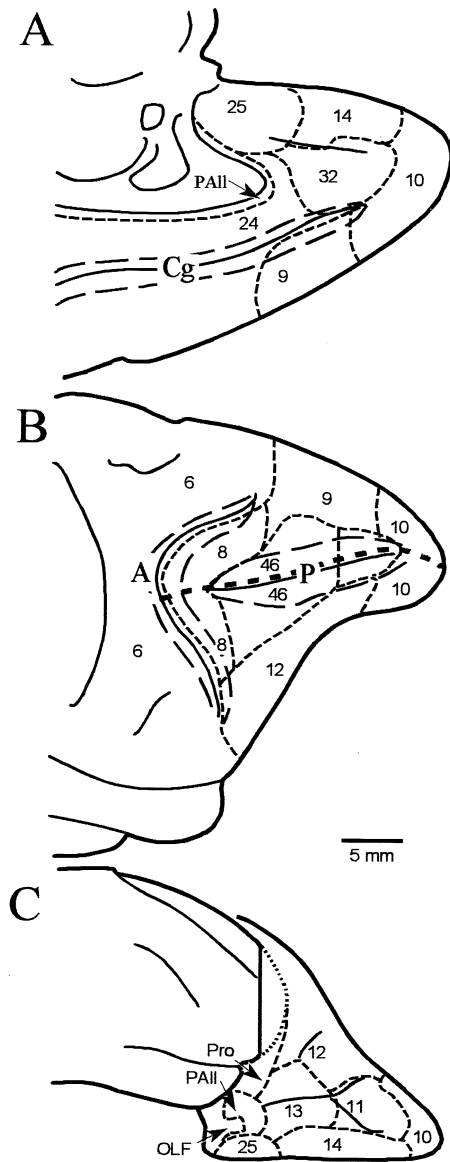


FIG. 1. Map of the prefrontal cortex in the rhesus monkey showing architectonic areas on the: (A) medial, (B) lateral, and (C) basal surfaces. Abbreviations: A, arcuate sulcus; Cg, cingulate sulcus; OLF, olfactory cortex; P, principal sulcus; Architectonic areas indicated by letters: PALL, orbital (C) or medial (A) periallocortex (3-layered cortex); Pro, orbital proisocortex (4-layered cortex). All other architectonic areas are indicated by numbers. (Adapted from [25].)

external and internal environments, a rich variety of mnemonic information, and motor control systems. This review is not comprehensive in scope, but rather focuses on the principal sources of connections that may underlie the function of the prefrontal cortex as a central decision and command center in behavior. There seems to be a division of labor among distinct prefrontal cortices in processing information underlying cognition, emotion and memory, illustrated below by comparing the connections of caudal lateral (Fig. 1B) and orbitofrontal (Fig. 1C) cortices. The roles of these distinct prefrontal cortices in complex behavioral settings appear to be complementary and inextricably linked.

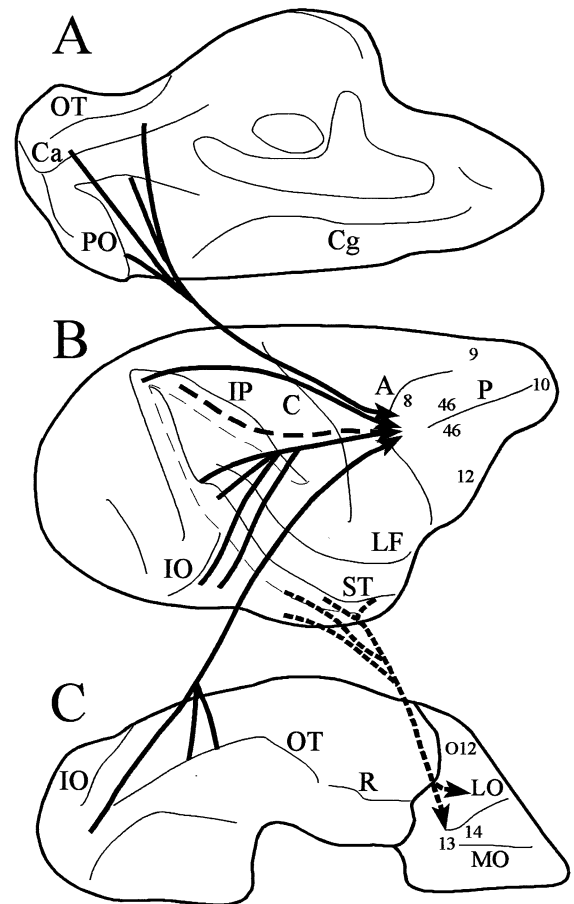


FIG. 2. Summary of the different sources of projections from visual cortices directed to area 8 (B) and to caudal orbitofrontal cortices (C) in rhesus monkeys. Area 8 in the concavity of the arcuate sulcus receives projections from occipital and caudal inferior temporal visual cortices (A–C, solid arrows), and from the intraparietal visuomotor cortex (B, segmented arrow). Orbitofrontal areas receive projections from anterior inferior temporal cortices (C, dotted lines). Abbreviations: A, arcuate sulcus; C, central sulcus; Ca, calcarine fissure; Cg, cingulate sulcus; IO, inferior occipital sulcus; IP, intraparietal sulcus; LF, lateral fissure; LO, lateral orbital sulcus; MO, medial orbital sulcus; OT, occipitotemporal sulcus; P, principal sulcus; PO, parietooccipital sulcus; R, rhinal sulcus; ST, superior temporal sulcus.

SENSORY INPUT TO THE PREFRONTAL CORTEX

The prefrontal cortex is distinguished as recipient of sensory information emanating from visual, auditory, somatosensory, gustatory, and olfactory cortices. The prefrontal cortex, however, is not a homogeneous region, but rather is composed of a series of areas that vary in their structure and connections. Regional variations in connections ultimately underlie distinct functional attributes within different sectors of the prefrontal cortex, which extends expansively on the medial, lateral and orbital surfaces (Figs. 1A–C). To illustrate these regional variations, the section below focuses on projections from sensory cortices to caudal lateral and orbitofrontal cortices in macaque monkeys.

Lateral prefrontal cortices appear to rely predominantly on input from visual, auditory, and somatosensory cortices (for reviews see [14,16]). Moreover, projections from sensory association cortices are not equally distributed within the lateral prefrontal

cortex but target preferentially, though not exclusively, specific areas. For example, the cortex within the anterior bank of the concavity of the arcuate sulcus (area 8) is distinguished as a target of robust projections from visual association cortices assessed in quantitative analyses (e.g., [13,22]; Fig. 2). Input from visual association cortices also reaches the posterior part of area 46 within the principal sulcus and adjacent area 12 [13,22,23,30,37,76,84,87,104,120,148,175]. Although auditory projections partially overlap with the visual, the preferential targets of auditory cortices are distinct from the visual, and include rostral area 8 at the tip of the upper limb of the arcuate sulcus, the central and dorsal part of area 46, and area 10 at the frontal pole [13,20,22,23,37,145]. Somatosensory cortices project heavily to the central portion of the principal sulcus (ventral area 46) and the adjoining area 12 on the ventrolateral convexity of the prefrontal cortex [13,23,37,87,133]. Although the above lateral prefrontal cortices cannot be considered unimodal by virtue of their connections, there is a bias in the distribution of sensory-specific projections within the lateral prefrontal cortex in macaque monkeys.

By comparison with lateral prefrontal areas, the orbitofrontal cortices on the basal surface of the frontal lobe appear to be polymodal. Caudal orbitofrontal areas, in particular, receive projections not only from visual (Fig. 2), auditory, and somatosensory cortices, but also from gustatory and primary olfactory cortices [15,36,116]. Within the entire cortical mantle perhaps only the rhinal region in the temporal lobe rivals the orbitofrontal with regard to the wealth of cortical sensory information it receives [81,144,161,165,167].

SENSORY INPUT FOR COGNITION AND EMOTION

An intriguing question centers on the role of sensory information in prefrontal cortices. Another question is how the prefrontal cortex uses sensory information in comparison with other high-order association cortices, such as the parietal cortex (for review, see [121]). One way to begin to address the above questions is to examine the topography, and by extension nature, of sensory input to prefrontal cortices. Prefrontal cortices differ remarkably with regard to the origin of visual information they receive. To illustrate these differences, below we consider the topography and nature of visual input directed to two areas of the prefrontal cortex, namely a dorsolateral area (the frontal eye field [FEF] within area 8), and the caudal orbitofrontal region.

The FEF and Visuomotor Functions

Dorsolateral area 8, in general, and its FEF component, in particular, is a focal target of projections from visual association cortices (Fig. 2). Projections to area 8 originate from a variety of visual cortices, most of which represent relatively early stages of visual processing, including areas V2, V3, V4, TEO and MT [13,22,49,148,175]. Visual input directed to area 8 appears to contain considerable detail about the visual environment and is comparable to what unimodal visual areas receive.

Moreover, there is a bias in the origin of visual input to area 8 and adjacent lateral prefrontal areas based on the heavy projections from dorsomedial occipital cortices associated with visual spatial analysis [13]. In this regard, area 8 resembles the ventral intraparietal visuomotor region, with which it is robustly connected (e.g., [9,13,22,76,129,153,158]; Fig. 2B). In fact, there are several functional similarities between the intraparietal visuomotor region and the FEF in primates. In both areas visual input appears to be used to guide the eyes to visual targets using saccadic eye movements. Damage to either the FEF or the parietal region results in visual inattention and impairs visual search mechanisms (e.g., [97,98,102,132]; for reviews see [78,100]). In both areas neuronal re-

sponses to visual stimuli are dependent on behavior, manifested by accentuated activity when the monkey is required to attend to a stimulus in a behavioral task (e.g., [35,62,180]).

Nevertheless, there are also differences in the neuronal responses in the FEF and the intraparietal visuomotor areas. One difference is that enhancement of a visual response in the intraparietal visuomotor cortex is not necessarily dependent on an oculomotor response, but in the FEF it is contingent on eye movement (for review, see [179]). Thus, in the FEF, responses to visual stimuli are closely tied to the actual motor response, in this case within the oculomotor domain. This is one example where the response properties of prefrontal neurons are intricately linked to their executive functions. Another difference involves the nature of the visual receptive fields in the two regions. In the FEF, neurons have large visual receptive fields which always include the fovea [115], suggesting that they have a panoramic view of the visual environment, whereas neurons in the parietal region appear to specialize in processing preferentially, though not exclusively, peripheral aspects of the visual field (e.g., [182]).

The task of guiding the eyes to behaviorally relevant stimuli depends on detailed sensory information and accurately timed oculomotor responses. Topographically specific sensory information and eye movement magnitude appear to be matched in area 8. For example, the rostral part of area 8, at the tip of the upper limb of the arcuate sulcus, is involved in large saccadic eye movements [141], and overlaps with an area that receives input from auditory cortices and from visual cortices representing predominantly peripheral visual fields [22]. Rostral area 8 may be suited for orienting to peripheral visual and auditory stimuli. In contrast, caudal area 8 at the junction of the upper and lower limbs of the arcuate sulcus is concerned with small and medium size saccades [34,141], and coincides with an area that receives robust projections from visual cortices, including substantial input from areas representing central visual fields [13,22]. Caudal area 8 appears to be well suited for scanning central parts of the visual field using small saccades. The coupling of sensory topography with oculomotor features enables area 8 to execute precisely timed eye movements in a behavioral setting [150].

Orbitofrontal Cortices and Emotion

In contrast to lateral prefrontal cortices, orbitofrontal areas receive sensory information that is qualitatively different from that of the FEF. Within the visual cortical system projections originate from anterior inferior temporal cortices, where the visual environment is globally rather than locally encoded [47]. Orbitofrontal cortices receive input from inferior temporal cortices that are at a considerable distance from the visual periphery and specialize in processing features of the visual environment and their memory ([47,68]; for review see [67]; Fig. 2). In addition to visual input, the orbitofrontal cortex receives robust projections from cortices associated with every other sensory modality, as noted above. By virtue of its connections, the orbitofrontal cortex appears to trade the specificity of sensory input seen in the FEF for a global overview of the external environment.

The orbitofrontal cortex in primates has another prominent feature, robust connections with the amygdala [8,19,116,131], a set of nuclei in the temporal lobe which have a key role in emotions (for reviews see [42,45,99]). The orbitofrontal cortex and the amygdala may be part of a network involved in emotions (Fig. 3), an idea supported by the striking similarity of the connections of the two structures and the consequences observed after each is damaged. Like the orbitofrontal cortex, the amygdala receives robust projections from all sensory cortices [15,36,70,116,164]; Fig. 3). In both structures sensory projections arise most promi-

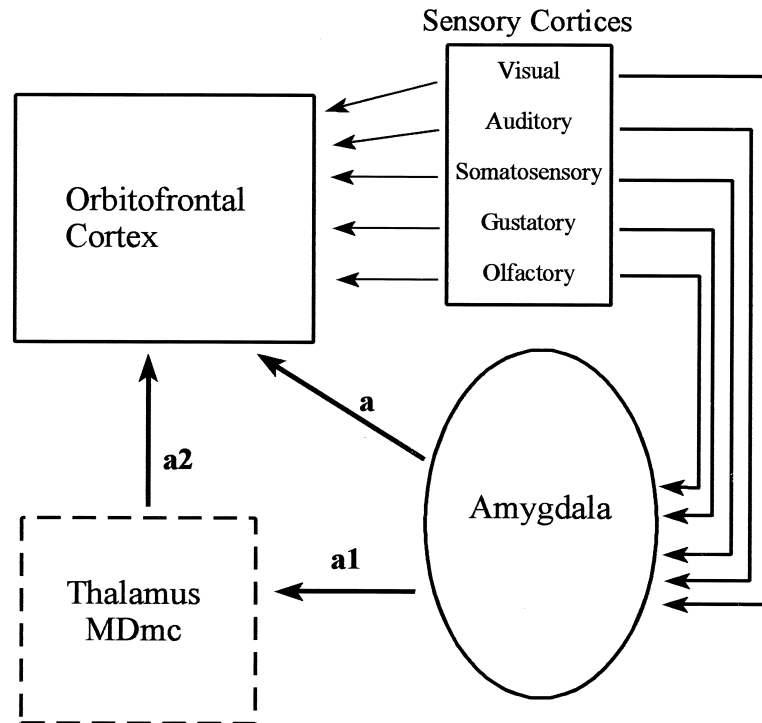


FIG. 3. Direct and possible indirect projections associated with sensory processes and emotion to orbitofrontal cortices in rhesus monkeys. Orbitofrontal cortices receive direct projections from visual, auditory, somatosensory, gustatory and olfactory cortices and possible indirect sensory input through the amygdala (a). Projections from the amygdala reach the orbitofrontal cortex directly (a) and possibly indirectly through the thalamic MDmc (a2), which receives projections from the amygdala (a1). MDmc, magnocellular mediodorsal nucleus.

nently from areas where processing appears to be concerned with the significance of features of stimuli and their memory (for review, see [16]). Damage to the orbitofrontal cortex or the amygdala leaves monkeys bereft of appropriate emotional responses necessary for communicating with their conspecifics and consequently disrupts their social interactions (for review, see [92]). Changes in personality and inappropriate social affect have been well documented in humans with orbitofrontal lesions (for review, see [44]). Likewise, damage to the amygdala in humans impairs their ability to appreciate the emotional expression of human faces (e.g., [2]).

The above discussion indicates that the orbitofrontal cortex receives robust sensory input from the cortex directly, and heavy projections from the amygdala. The orbitofrontal cortex is thus capable of sampling the entire external and internal environment and may act as an environmental integrator. Moreover, sensory input to the orbitofrontal cortex arrives not only directly from sensory cortices, but indirectly through the amygdala (Fig. 3). The combination of direct and indirect sensory input may enable the orbitofrontal cortex to capture the emotional significance of events. In short, these pathways may serve to place sensory stimuli in the appropriate context for action.

MEMORY AND THE PREFRONTAL CORTEX

Lateral Prefrontal Cortices

Damage to lateral prefrontal cortices does not render humans or monkeys amnesic but rather impairs their performance on cogni-

tive tasks. The accomplishment of even a simple cognitive task is based on the ability to keep information temporarily in mind and to monitor self-generated responses (for reviews see [57,63,127]). Lateral prefrontal cortices have been associated with this role since the now classic demonstration that their damage, and in particular an area around the principal sulcus, impairs the ability of monkeys to remember after a few seconds delay where a food reward was hidden ([83]; for reviews see [56,63,64]). Physiologic data corroborate the role of lateral prefrontal cortices in this task by the discovery of a set of neurons that fire during the delay period [54,55,88,95,96,174] and appear to be involved in holding information in memory. These “delay” neurons appear to bridge the gap between the initial presentation of the food reward and the required response after the delay.

Moreover, dorsolateral prefrontal cortices participate in working memory tasks within the domain of their specialization, so that cognitive tasks with different requirements engage different prefrontal cortices (e.g., [53,54,126–128]). For example, periarculate and periprincipal cortices participate in oculomotor delayed response tasks, encoding in temporary memory the spatial location of visual targets [54]. Damage to these areas results in deficits not in oculomotor responses, per se, but in remembering the place of a visual target within a behavioral context.

Lateral prefrontal cortices do not have significant connections with the hippocampus or the rhinal cortices, which have been associated with long-term memory (for reviews see [7,17,184]). The most notable monosynaptic interaction of lateral prefrontal cortices with limbic cortices appears to be with the cingulate

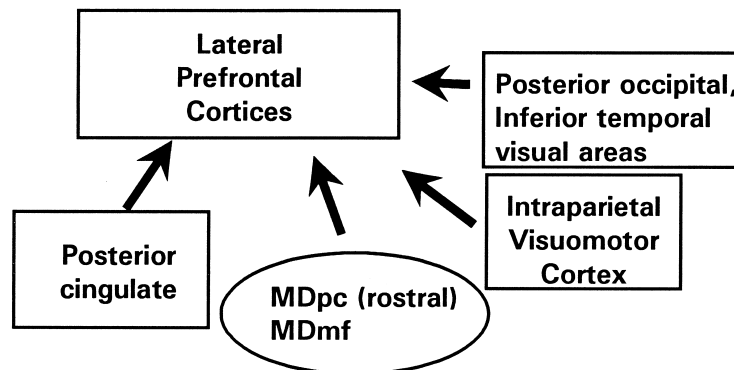


FIG. 4. Circuits associated with oculomotor guidance and attentional processes in cognitive tasks. Connections of caudal lateral prefrontal cortices with principal visual, visuomotor, and posterior cingulate cortices, and with the thalamic MDpc and MDmf nuclei, associated with visuomotor and attentional processes. The diagram is simplified and shows only unidirectional projections to prefrontal cortices, even though most connections are reciprocal. MDpc, parvocellular mediodorsal nucleus; MDmf, multi-form mediodorsal nucleus.

cortex, and particularly its posterior sector associated with attentional processes and eye movements ([18,111,112,170]; Fig. 4). These connections, coupled with a strong projection from intraparietal visuomotor regions (for review, see [14]), reinforce the idea that lateral prefrontal cortices have a role in attentional processes, which is prerequisite to remembering information on a short-term basis in behavioral tasks.

Orbitofrontal Cortices

The principal projections to the orbitofrontal cortices originate in areas with distinctly different mnemonic functions than those projecting to lateral prefrontal cortices. Anterior inferior temporal cortices, which project to the orbitofrontal cortex, appear to encode mnemonic information within the visual do-

main [59,114]. In addition, sensory input to orbitofrontal cortices is coupled with a strong projection from the perirhinal region (areas 35 and 36), the entorhinal cortex (area 28), the parahippocampal cortex (areas TF, TH) and the hippocampal formation all of which are themselves multimodal (e.g., [15, 146,166]). Moreover, the above medial temporal structures have been implicated in long-term memory (for reviews see [7,156, 157,184]). On the basis of their connections, the caudal orbitofrontal and their medial prefrontal neighbors are aligned with medial temporal structures in networks concerned with long-term memory (Fig. 5). In fact, damage or temporary interference of function in orbitofrontal cortices results in visual memory deficit comparable to what is seen after damage to anterior inferior temporal cortices (e.g., [11,173]).

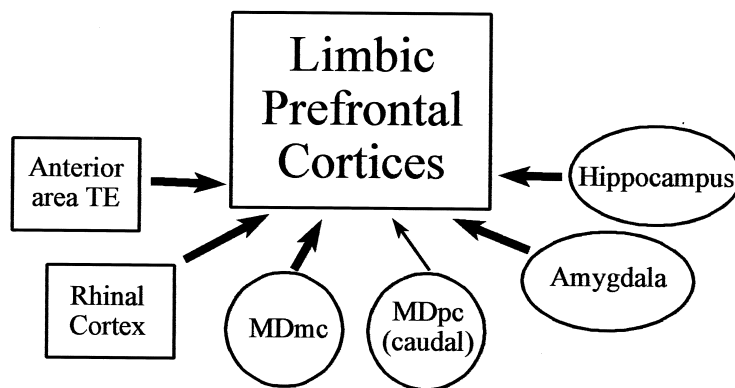


FIG. 5. Circuits associated with long term memory in macaque monkeys. Connections of prefrontal limbic cortices (posterior orbitofrontal and medial prefrontal areas) with principal memory-related structures of the thalamus (MDmc and MDpc, caudal part), the hippocampal formation, the rhinal cortices, the amygdala, associated with emotional memory, and anterior inferior temporal area TE implicated in visual memory. The strength of the projection is depicted by the thickness of the arrows. The diagram is simplified and shows only unidirectional projections to prefrontal cortices, even though most connections are reciprocal. MDmc, magnocellular mediodorsal nucleus; MDpc, parvocellular mediodorsal nucleus.

THALAMIC INPUT TO PREFRONTAL CORTICES RELATED TO COGNITIVE AND MNEMONIC PROCESSES

Lateral Prefrontal Cortices

The thalamic connections of specific prefrontal cortices appear to support their distinct roles in cognition, memory, and emotion. Projections from the thalamus to the frontal eye fields appear to be related to oculomotor functions. Thus, the principal thalamic connections of the FEF are with the lateral parvocellular sector of mediodorsal nucleus (MDpc), its multiform sector (MDmf; Fig. 4), the supragenulate and limitans nuclei [21,22], all of which receive projections from the superior colliculus and the lateral substantia nigra, both of which have been implicated in eye movement [29,71–74,79,80,101,178]. In addition, area 8 receives input from the upper parts of the central lateral and paracentral thalamic nuclei [21,22] which have visual and visuomotor properties [151, 152].

Similarly, a close neighbor of FEF, area 46, which has been linked to remembering information over a short delay (for reviews see [56,57,63,64]), receives thalamic projections mostly from the parvocellular sector of MD [21], where neurons exhibit responses specific to delayed response tasks, like those in area 46 [58]. The above information suggests that the visual, visuomotor, and working memory functions associated with lateral areas 8 and 46 are matched by their thalamic connections with nuclei associated with these functions.

Orbitofrontal Cortices

In contrast to lateral prefrontal areas, the orbitofrontal cortex receives projections from a different set of thalamic nuclei. The thalamic midline nuclei, the magnocellular sector of MD (MDmc), and the caudal part of parvocellular MD (MDpc) project robustly to the orbitofrontal cortex ([21,46,60,65,116,137,163]; Fig. 5). The above thalamic nuclei are unified by their common role in long-term memory, manifested by the classic amnesic syndrome when they are damaged [3,82] for review see [105]). It should be noted that whereas MDpc projects to a certain extent to all prefrontal cortices, it does so from its functionally distinct parts. Thus, the caudal part of MDpc, which has been implicated in long-term memory in both humans and monkeys [82,168,183], projects preferentially to orbitofrontal and medial prefrontal cortices, whereas the anterior part of MDpc projects to lateral prefrontal cortices, such as areas 8 and 46 [21,46].

The projection from MDmc to orbitofrontal cortices is particularly notable because MDmc receives an equally strong projection from the amygdala [4,131,147]. This circuitry provides yet another example where sensory signals, in this case concerning the emotional environment, reach the orbitofrontal cortices directly from the amygdala and indirectly through MDmc (Fig. 3). As noted above, the orbitofrontal cortex is similarly distinguished as recipient of sensory input from the cortex directly and from the amygdala indirectly (for review, see [16]; Fig. 3).

MEDIAL PREFRONTAL CORTICES

The above discussion has focused on two prefrontal regions to exemplify some of the ways the prefrontal cortex may use information in behavior. The above analysis can be extended to other prefrontal areas as well. One of these includes the pericallosal areas on the medial surface of the frontal lobe (Fig. 1A, areas PAll, 32, 25, 24), which along with caudal orbitofrontal areas (Fig. 1C, areas PAll, Pro, 13, 25) make up the limbic component of the prefrontal region as described in classic studies ([33,118,124,181]; for review see [16]). Pericallosal prefrontal cortices receive input

from the same thalamic, hippocampal, medial temporal, and amygdaloid structures as the orbitofrontal cortices, and share involvement in emotions and long-term memory. For example, rupture of the anterior communicating artery in humans, which supplies medial prefrontal areas [40], results in anterograde amnesia comparable to the classic amnesic syndrome seen after hippocampal lesions [6,162].

However, there are some differences in the connections of orbitofrontal and medial prefrontal cortices, suggesting that there is functional specialization within the limbic sector of the prefrontal cortex. For example, the hippocampus projects more robustly to medial than to orbitofrontal cortices, while the opposite pattern is seen in the projections from the amygdala (for review, see [17]). Another difference concerns the multiplicity of input to the two structures. Medial prefrontal areas receive sporadic input from unimodal sensory cortices, differing from the orbitofrontal cortices which are enriched with sensory projections (for review, see [17]). Sensory input to medial prefrontal cortices emanates preferentially from anterior auditory association cortices [13,20,130,171], where neurons are broadly tuned [93] and respond best to complex species-specific vocalizations in monkeys [135,136]. In medial prefrontal cortices the nature of auditory input is consistent with their role in vocalization [89,117,155,159,160]; for reviews see [48,169], and is specialized within this domain in emotional communication, such as distress calls emitted by infant monkeys when separated from their mothers [103]. As in the orbitofrontal region, sensory input in medial cortices is embedded within an emotional context.

PREFRONTAL CORTICES AND EXECUTIVE CONTROL

The above discussion suggests that prefrontal cortices have different roles in cognitive, mnemonic, and emotional processes. Prefrontal cortices have in common direct access to motor control systems associated with their executive functions, albeit within the domain of their specialization. Below is a brief overview of the specialized motor connections of different prefrontal cortices.

Lateral Prefrontal Cortices Project to Brainstem Oculomotor Areas and to Premotor Cortices

The oculomotor functions of the frontal eye fields are associated with attentional processes and are effected through their projection to the superior colliculus (Fig. 6A) and brainstem oculomotor control systems (for review, see [149]). In addition, area 8 as well as neighboring areas 46 and 9 are robustly connected with the premotor cortices situated posterior to the arcuate sulcus (Fig. 6A) and in the cingulate region on the medial surface [10, 24,27,69,87,108,119,120,122,123,154], and thus have access to areas for head, limb and body movement.

Orbitofrontal and Medial Prefrontal Cortices Project to Autonomic Effector Structures

The motor connections of the orbitofrontal limbic cortices in the rhesus monkey lie in the realm of the expression of emotions through descending projections to hypothalamic visceromotor centers [138]. This pathway is unique for caudal orbitofrontal and caudal medial prefrontal cortices, distinguishing them from lateral prefrontal cortices which do not issue significant projections to the hypothalamus ([138]; Fig. 6B). Thus, the orbitofrontal cortex not only receives ascending projections from the amygdala, but also issues robust projections to hypothalamic autonomic centers, suggesting that the orbitofrontal cortex can change cardiac and respiratory responses in emotional situations. In fact, damage to the

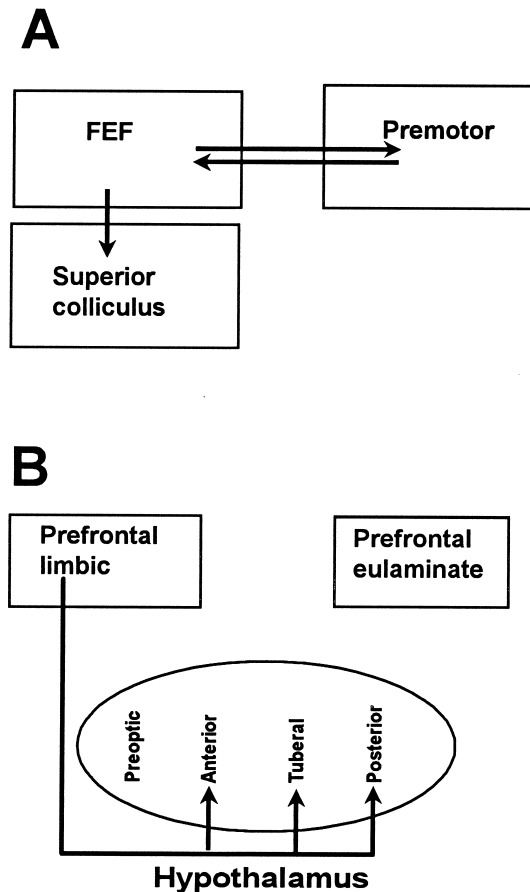


FIG. 6. Access of prefrontal executive cortices to motor control systems. (A) The frontal eye field (FEF) projects to premotor cortices and to brainstem oculomotor structures (e.g., the superior colliculus). (B) Prefrontal limbic (caudal orbitofrontal and medial prefrontal) cortices have direct access to hypothalamic visceromotor centers implicated in the expression of emotions.

orbitofrontal cortex in humans impairs their ability to initiate autonomic responses in emotional situations [28,43]. Patients with orbitofrontal lesions retain cognitive function but make poor decisions, suggesting that cognitive processes become disconnected from emotionally driven autonomic responses.

Medial prefrontal cortices, which appear to specialize in emotional communication, share with the orbitofrontal a descending and even stronger projection to hypothalamic visceromotor centers [138]. Furthermore, medial prefrontal cortices have additional projections to brainstem structures which innervate laryngeal muscles necessary for phonation (for reviews see [90,169], consistent with the role of these areas in emotional communication. Taken together, the above evidence suggests that all areas of the prefrontal cortex have access to specialized motor control systems, consistent with their specific role in central executive functions.

Indirect Projection of the Basal Ganglia to All Prefrontal Cortices

In addition to their connections with specialized motor control systems, all prefrontal cortices receive indirect projections from the basal ganglia. Although the basal ganglia receive projections from all cortical areas, they project selectively to the frontal cortex,

which includes the posterior cortical motor and premotor systems, and the prefrontal cortex (for reviews, see [5,66,85]). The prefrontal cortex gains access to information from the basal ganglia through a relay in the thalamic MD and VA nuclei (e.g., [21,46,91]; for reviews see [85,86]). Moreover, functionally distinct prefrontal areas are influenced by the basal ganglia via partially parallel pathways [5,85], which may be associated with their specific roles in motor behavior.

SYNERGISTIC ROLE OF DISTINCT PREFRONTAL CORTICES IN COGNITION, MEMORY AND EMOTION

The above discussion suggests that prefrontal cortices have distinct and perhaps complementary roles in cognition, memory, and emotion. However, purposive behavior requires the recruitment of diverse signals about the internal and external environments and retrieval of information from memory accumulated through experience. Prefrontal areas with distinct specializations must participate in even simple behavioral tasks by tapping into different sources of external and internal sensory and mnemonic information. One way diverse information could be orchestrated to guide behavior is through the rich interconnections between prefrontal areas (e.g., [13,15,25]; for reviews see [14,121]). Information reaching distinct prefrontal cortices thus may be transmitted to another prefrontal area through intrinsic connections.

The laminar pattern of intrinsic connections of prefrontal cortices is highly ordered and can be predicted on the basis of the structure (or type) of the interconnected cortices [12,26]. In this context, cortical structure is defined on the basis of the number of cortical layers and their definition and transcends cytoarchitecture, which focuses on the unique cellular or molecular features of neurons within layers in each area. By classifying areas by cortical type, structurally similar areas can be grouped together. For example, areas situated either on the caudal orbitofrontal or the caudal medial surfaces of the frontal lobe have only three or four identifiable layers and are collectively called limbic [25]. Prefrontal limbic cortices differ from eulaminar areas, which have six layers. The usefulness of parceling the prefrontal cortex by cortical type is apparent when we consider the laminar pattern of connections between different types of cortices [26]. For example, when a eulaminar area that has 6 well-delineated layers projects to a limbic area, projection neurons originate mostly in the upper layers (2–3) and their axons terminate predominantly in the deep layers (4–6). Connections proceeding in the opposite direction, from limbic to eulaminar areas, originate predominantly in the deep layers (5–6) and their axons terminate mostly in the upper layers (1–3) [26]. The significance of the above observations is based on the functional implications of specific patterns of connections, since distinct populations of neurons in different layers have different functions. For example, in the sensory cortices, projection neurons from deep layers have been ascribed a feedback role (e.g., [50,106,142,143]). By analogy, limbic cortices may provide feedback to the entire cortex. The degree and temporal sequence of recruitment of distinct prefrontal areas in behavior may be affected by the pattern of their intrinsic connections. Functional studies are necessary to address this issue.

DISCONNECTION OF COGNITIVE, MNEMONIC AND EMOTIONAL PROCESSES IN NEUROLOGIC AND PSYCHIATRIC DISEASES

The above discussion suggests that distinct sectors of the prefrontal cortex have specific roles in cognition, memory, and emotion. Yet, these functions are linked in behavior, as they are linked anatomically through the widespread connections of prefrontal

limbic cortices with the neocortices in and outside the prefrontal cortex. Through a rich network of connections prefrontal limbic areas appear to exercise a tonic influence on the rest of the prefrontal cortex, intricately linking cognition and emotion. The widespread connections of prefrontal limbic cortices have important implications for behavior, in view of the preferential vulnerability of limbic cortices in several neurologic and psychiatric diseases in humans, including epilepsy, Alzheimer's disease, schizophrenia, obsessive compulsive disorder and Tourette's syndrome ([31,32,61,75,77,94,125,139,140,172,176]; for reviews see [134,177]). Preferential involvement of limbic areas in disease will attenuate or remove the influence of limbic areas on the neuraxis and lead to widespread repercussions on behavior.

One of the consequences of insult to prefrontal limbic areas is the likely disconnection of circuits underlying cognitive and emotional processes. Reduced activation of pathways connecting the amygdala with prefrontal limbic cortices will disrupt a circuit which is likely to have a role in the emotional coloring of events (Fig. 3a). Disruption of this pathway may account for the flattening of emotions and inappropriate affect in several diseases, including schizophrenia, psychopathic personality, or autistic behavior. This idea is consistent with observations that activity in prefrontal limbic cortices is reduced in some of these disorders, and is exemplified by inappropriate affect when orbitofrontal cortices are damaged (e.g., [42,43]).

Pathologic conditions with manifestations which are opposite to the ones noted above, seen in obsessive compulsive or anxiety disorders, may arise from overactivity of pathways connecting prefrontal limbic cortices with the amygdala (Fig. 3a). Increased activation of the orbitofrontal cortex in obsessive compulsive disorder is well-documented (e.g., [1,32]). The additional implication of the striatum in obsessive compulsive disorder [134] may represent the motor pathways activated in translating thought into action, such as washing the hands.

The memory deficits observed in Alzheimer's disease may be attributed, in part, to disconnection of prefrontal limbic areas from the thalamic MDmc and other nuclei associated with long-term memory. This idea is supported by evidence that the degenerative process is most prominent in the deep layers of orbitofrontal cortices [38], which issue the majority of corticocortical and subcortical projections in primates [12,26]. Limbic cortices are found at the bottom of cortical structural hierarchies, and thus may function as a feedback system to the neuraxis. Disruption of limbic cortices in several neurologic and psychiatric diseases is likely to affect preferentially a major feedback communication system, based on the pattern of corticocortical connections summarized above.

The role of the widespread feedback projections from prefrontal limbic cortices directed to other prefrontal, post-Rolandic, and subcortical structures is not known. As recipient of signals from all sensory modalities and from the amygdala, the prefrontal limbic areas may integrate complex internal and external representations to provide the appropriate context in a behavioral setting. One example of the intricate use of sensory information by prefrontal limbic areas can be seen for caudal medial areas, which are interconnected with auditory cortices (for review, see [17,169]). The circuits linking medial prefrontal and auditory cortices appear to have a role in monitoring inner speech and in distinguishing external auditory stimuli from internal auditory representations through distinct patterns of activation. Moreover, these specific functional relationships are altered in schizophrenic patients who experience auditory hallucinations [52,109,110]. In addition to their connections with auditory areas, prefrontal cortices on the medial surface, are heavily connected with dorsal superior temporal polar cortices, which are themselves limbic, and may encode

the emotional significance of auditory stimuli [20]. The strong interaction of medial prefrontal and dorsal temporal polar cortices may help explain why auditory hallucinations are emotionally charged (for review, see [51]).

In summary, based on the profile of their connections, specialized sectors of the prefrontal cortex appear to have a differential role in cognition, memory and emotion, and have access to different motor control systems. Distinct prefrontal cortices appear to have complementary roles in behavioral tasks requiring their synergistic engagement in executive functions. Damage to a specific sector of the prefrontal cortex may dissociate critical circuits underlying emotional or mnemonic processes and is likely to affect cognitive functions as well. Finally, the limbic prefrontal cortex is distinguished as a robust model feedback system exercising a tonic influence on all neocortices. The preferential involvement of prefrontal limbic cortices in several neurologic and psychiatric diseases suggests that malfunction of feedback systems may underlie the behavioral manifestations in all of these diseases.

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