



Anatomic Basis of Cognitive-Emotional Interactions in the Primate Prefrontal Cortex

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BARBAS, H. *Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex.* NEUROSCI BIOBEHAV REV 19(3) 499–510, 1995. — Recognition that posterior basal and medial parts of the prefrontal cortex belong to the cortical component of the limbic system was important in understanding their anatomic and functional organization. In primates, the limbic system has evolved along with the neocortex and maintains strong connections with association areas. Consequently, damage to limbic structures in primates results in a series of deficits in cognitive, mnemonic and emotional processes. Limbic cortices differ in their structure and connections from the eulaminate areas. Limbic cortices issue widespread projections from their deep layers and reach eulaminate areas by terminating in layer I. By comparison, the eulaminate areas receive projections from a more restricted set of cortices and when they communicate with limbic cortices they issue projections from their upper layers and terminate in a columnar pattern. Several of the connectional and neurochemical characteristics of limbic cortices are observed as a transient feature in all areas during development. Anatomic evidence suggests that limbic areas retain some features observed in ontogeny, which may explain their great plasticity and involvement in learning and memory, but also their preferential vulnerability in several psychiatric and neurologic disorders.

Macaca mulatta primates Memory Limbic system Plasticity Learning Schizophrenia Epilepsy
 Orbitofrontal cortex Medial prefrontal cortex

OVERVIEW

THE frontal cortex in human and nonhuman primates is a vast cortical expanse which extends from the central sulcus to the frontal pole. The caudal half of the frontal lobe includes the primary motor and premotor areas. The rostral half has been referred to as the prefrontal cortex, to distinguish it from the general term "frontal" which includes the premotor and motor cortices as well. In macaque monkeys the posterior border of the prefrontal cortex is marked by the anterior bank of the arcuate sulcus. In both human and nonhuman primates the prefrontal cortex includes all lateral, medial and orbital areas rostral to the premotor cortices.

The prefrontal cortex is a heterogeneous and complex region both structurally and functionally. Its physiological and functional attributes are not easily amenable to the conventional analyses which have been applied to the sensory cortices. The direct linkage of sensory cortices with the sensory periphery has provided a basis for a detailed study at the anatomic, physiologic, and functional level. Investigation of the functional organization of prefrontal areas must, on the other hand, be inferred initially by their relationships with the rest of the cortex and subcortical structures, or by the deficits observed after their damage. Here I review patterns of the connectional organization of prefrontal cortices, and discuss

their functional implications for normal and some pathologic states.

A major advance in the study of the prefrontal cortex was made when it was recognized that it had a limbic component. The medial aspect of the prefrontal cortex in the vicinity of the corpus callosum was classified with the limbic system first by Broca (28) and then by Papez (106). The borders of the limbic system were later expanded further to include the basal surface of the cerebral hemisphere as suggested by Yakovlev (149) and Nauta (100).

Recognition that some prefrontal areas are limbic has been important from several perspectives. From a functional point of view, this implies that the prefrontal cortex, which was classically conceptualized as an integrative center for high-order cognitive processes, is also involved in emotional processes, previously thought to be the exclusive domain of the cingulate cortex and a set of subcortical limbic structures. Information obtained from comparative and connectional studies has necessitated a revision of ideas about association and limbic areas, and it has become increasingly apparent that it is impossible to separate the cognitive from the emotional or mnemonic processes in the nervous system. Comparative studies have shown that limbic areas are not regressive, but rather are progressive in evolution (6). In primates, the cortical limbic system has evolved along with the association corti-

ces and maintains strong connections with them. In concert with the linkage of the limbic system with the association cortices, its damage results in a series of deficits associated with cognitive, mnemonic, and emotional processes.

From an experimental point of view, identification of the limbic portions of the prefrontal cortex proved to be key for studying the entire architectonic organization of the prefrontal cortex, its connections, and some of its neurochemical features, as will be outlined below. For example, parcelling of prefrontal areas proved to be difficult when investigators relied only on the subtle architectonic differences among its subdivisions, as is apparent by the discrepancies in the areal borders in classic studies (29,140,143). However, architectonic parcelling became somewhat easier after Sanides, expounding on the comparative studies of Abbie (1) and Dart (35), proposed a systematic approach based on a theoretical framework (121-123). Sanides observed that the cortex is composed of a series of areas which exhibit gradual changes in laminar definition from limbic to eulaminate areas. Unlike the eulaminate cortices, which have six layers, transitional (or limbic) cortices in the prefrontal cortex have only three or four layers. In limbic cortices layer IV is either lacking, or is poorly developed. Limbic prefrontal cortices can thus be defined with accuracy at the structural level. Beyond the limbic areas are the eulaminate areas. However, even eulaminate areas show a progressive increase in the definition of their six layers in a direction away from the limbic areas (20).

I will review evidence which indicates that the structural architecture of prefrontal areas appears to be the best indicator of their anatomic pattern of communication with the rest of the neuraxis. There is a set of connectional features consistent with the idea that limbic prefrontal areas are involved in the plastic processes of learning and memory. However, the very characteristics which may be responsible for the plasticity of limbic areas may also render them preferentially vulnerable in neurologic and psychiatric disorders.

STRUCTURAL DEFINITION OF PREFRONTAL CORTICES

We used Sanides's approach (121) to track gradual changes in the laminar organization from limbic to eulaminate areas (20). We identified two groups of prefrontal limbic cortices. One is situated in the posterior orbitofrontal region near the anterior olfactory nucleus and the olfactory tubercle, and the other is found around the rostral tip of the corpus callosum. From the orbital limbic area it was possible to trace gradual changes in the number of layers and their delineation extending in a radial direction rostrally on the orbital surface, and then ventrolaterally through rostral and then caudal lateral areas towards the ventral limb of the arcuate sulcus. Similarly, from the medial limbic areas there are gradual changes in laminar definition towards the rostro-medial tip of the frontal pole and then onto the dorsal surface in a direction towards the upper limb of the arcuate sulcus. Using this approach it was thus possible to divide the prefrontal cortex into two large sectors, designated as basoventral and mediodorsal to describe their anatomic location (20; see also Fig. 1).

The above architectonic analysis provided the framework to investigate the pattern of corticocortical and subcortical connections of the prefrontal cortex. When we look at the cortex from the above point of view we can ask how much or how little does a particular area resemble anatomically the limbic cortices. The ones with the highest similarity receive the heaviest input from cortical and subcortical limbic structures and share a cluster of other connectional features. At the other

end of each axis, those eulaminate cortices which show the clearest laminar definition have the sparsest connections with limbic structures, and show a different set of anatomic characteristics.

SEGREGATION OF FUNCTIONAL STREAMS OF INPUT TO PREFRONTAL AREAS

Early ablation-degeneration studies indicated that prefrontal cortices are richly connected with other areas (31,79,103). One may then ask whether the connections of the prefrontal cortex show a certain degree of organization. For example, can basoventral (Fig. 1A) and mediodorsal (Fig. 1B) areas, parcelled on the basis of their structural features and intrinsic connections (20), be differentiated by other criteria, such as their connections with other cortices, or their behavioral or physiological attributes? Clues that sensory projections to the prefrontal cortex were topographically organized emerged from a series of studies which showed specific fiber degeneration in prefrontal areas after lesions of sectors of unimodal sensory association areas (31,79,103). In addition, behavioral studies which described deficits in specific tasks after selective ablations of prefrontal cortices, and physiological studies on neuronal properties are consistent with the view that there may be some degree of functional organization within the prefrontal cortex (for reviews see 11,42-44,54,109).

With the introduction of retrograde tracers it became possible to look at the entire profile of afferent projections directed to individual prefrontal areas. The organization of visual input to prefrontal cortices presents the clearest example, because the visual cortical system has been studied and parcelled into functional subdivisions more thoroughly than any other. Figure 2 summarizes the sources of visual input to prefrontal cortices. The information presented in Fig. 2 was obtained from detailed anatomic experiments which suggest that mediodorsal and basoventral prefrontal cortices receive visual input from cortices which analyze different aspects of the visual environment (10). Mediodorsal prefrontal areas receive projections primarily, though not exclusively, from dorsal and medial visual areas which have been implicated in visual spatial functions (10). This conclusion is based on the following findings: The majority of visually related neurons directed to mediodorsal prefrontal areas originate in dorsal and medial visual and parietal cortices associated with spatial aspects of vision. These include projections from areas MT and MST, which are involved in visual motion, and from visual cortices which process stimuli from the peripheral visual field (10,17), such as medial area V2 or area PO (32,51); the latter are excellently suited for the analysis of motion and spatial relationships but not of pattern (91,98). On the other hand, basoventral prefrontal areas receive projections mostly from neurons in inferior temporal cortices or ventral occipital areas (10,12) which appear to be involved in the analysis of the features of objects and their memory (39,50,55,128). Earlier (41,49) and more recent (146) physiological findings on the properties of single neurons in prefrontal areas are consistent with the anatomic data.

Projections from auditory and other modality specific cortices are not easily amenable to an analysis comparable to the one conducted for the visual, because they have not been parcelled into easily identified functional streams. However, there is information which suggests that projections from the motor cortical system to basoventral and mediodorsal prefrontal cortices may be segregated along functional lines as well. Dorsal prefrontal areas are connected primarily with dorsomedial premotor areas which have been associated with

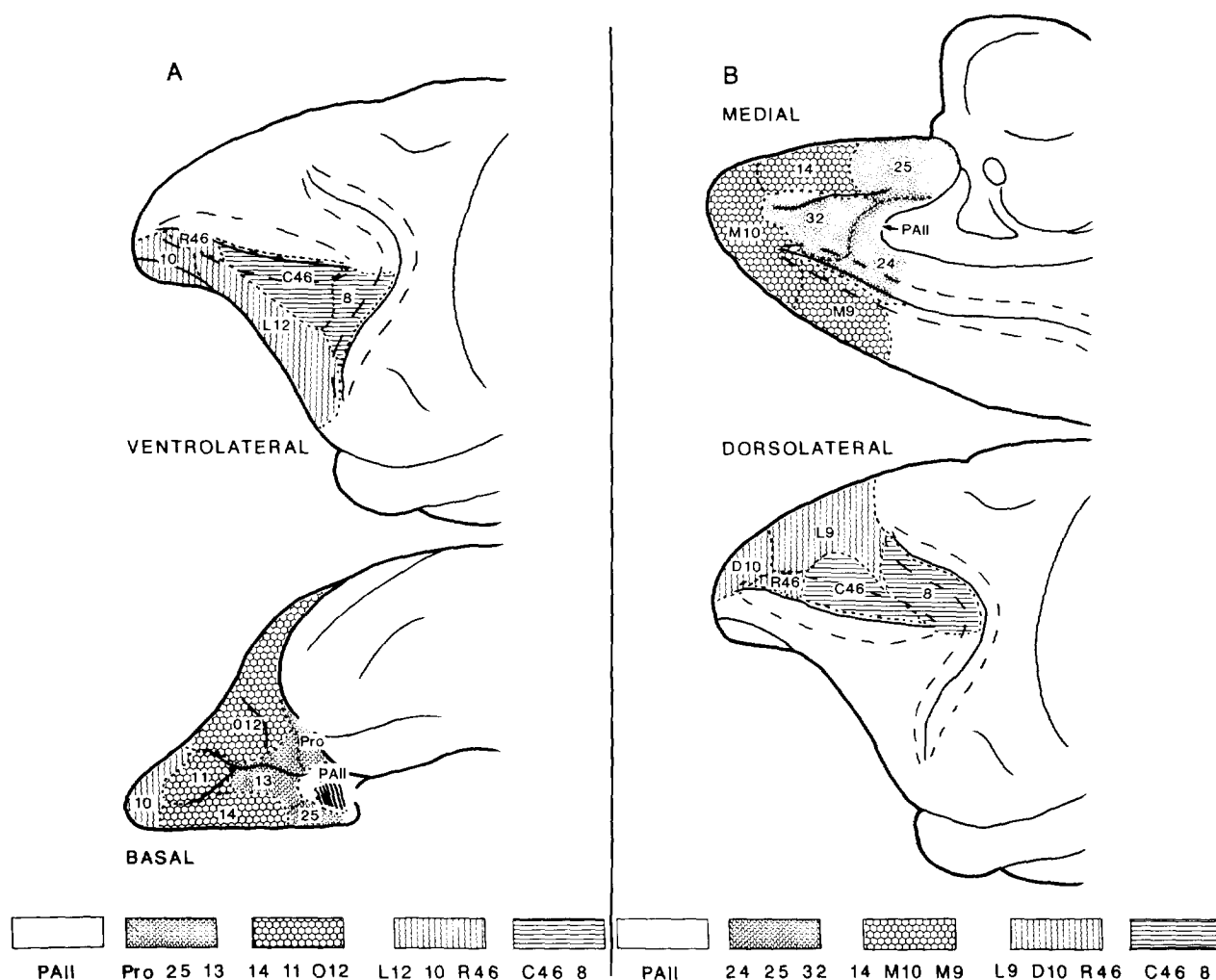


FIG. 1. Diagrams showing architectonic stages within the (A) basoventral and (B) mediadorsal prefrontal sectors. The basoventral axis begins at the basal limbic cortex (PAll), an agranular type of cortex which has only 3 layers (white area), and proceeds to the adjacent dysgranular areas Pro, 25 and 13 (cuboidal pattern) and then to eulaminate areas 14, the orbital part of area 12 (O12) and area 11 (honeycomb pattern); further differentiation of cortical layers is observed in lateral area 12 (L12), ventral area 10 and the rostral part of area 46 (R46; wavy pattern), and finally in the caudal part of area 46 (C46) and ventral area 8 (horizontal stripes). The mediadorsal axis (B) can be traced from the medial agranular area PAll around the rostral tip of the corpus callosum (white area), to dysgranular areas 25 32 and 24 (cuboidal pattern), and then to isocortical areas medial 14, 10 (M10), and 9 (M9) (honeycomb pattern); further differentiation of cortical layers is observed in dorsal area 10 (D10), the lateral part of area 9 (L9) the rostral part of area 46 (R46) (wavy pattern), and finally in the caudal part of area 46 (C46) and dorsal area 8 (horizontal stripes). Within each sector gradual changes in laminar differentiation are observed in a direction from the agranular area PAll to caudal area 46 and area 8, which are eulaminate areas with the most distinct laminar borders among prefrontal cortices. "Limbic" or "transitional" refers to all agranular and dysgranular cortices (areas shown in white or cuboidal pattern). Reprinted with permission from Barbas, H.; Panday, D. N. *Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey*. J. Comp. Neurol. 1989; Wiley-Liss, a division of the John Wiley & Sons, Inc. (20).

postural mechanisms and the intentional aspect and initiation of movement. In contrast, basoventral prefrontal areas are connected with ventral premotor cortices which appear to be involved in motor responses to sensory stimuli (for discussion and references see 19).

The segregation of sensory or motor-related functional streams directed to the two major sectors of the prefrontal cortex, however, appears to be partial (Fig. 2), as is also the case within the visual cortical system (for review see 92). In addition, within the prefrontal cortex the mediadorsal and basoventral sectors are interconnected at certain points (20). These connections, which may be described as "lateral" solely

on the basis of their topography, are also observed at specific points between dorsal and ventral sensory and motor cortices (for reviews see 92,104). Thus, whereas caudo-rostral pathways link functionally related visual cortices (8,97,131) and remain largely segregated in their projection to the mediadorsal and basoventral prefrontal sectors (10), interconnections between the functionally distinct pathways have also been observed. It is thus conceivable that information about space and motion, on one hand, and about features, on the other, may be integrated at different levels within the cortex via "lateral" pathways, as shown diagrammatically in Fig. 3. There is no information on the degree of integration of signals between

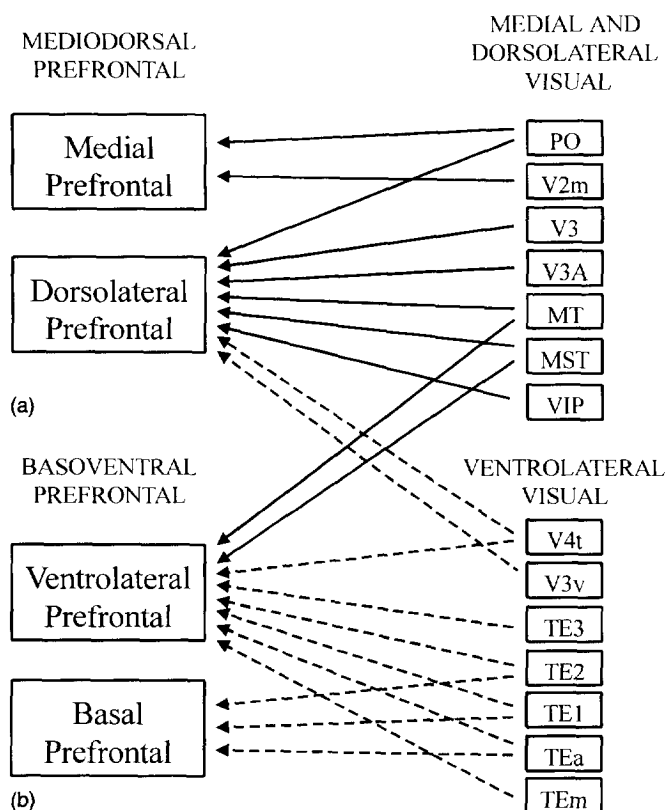


FIG. 2. Diagram showing that projections from visual cortices to the (a) mediodorsal and (b) basoventral prefrontal sectors are largely, though not completely, segregated topographically and perhaps functionally. Abbreviations for visual areas: MST—medial superior temporal; MT—middle temporal motion area; PO—parietooccipital; TE1—rostral part of the inferior temporal cortex; TE2—intermediate part of the inferior temporal cortex; TE3—caudal part of the inferior temporal cortex; TEa—inferior temporal cortex in the inner part of the lower bank of the superior temporal sulcus; TEM—temporal cortex on the outer rim of the lower limb of the superior temporal sulcus; V2m—the medial part of visual area 2; V3—visual area 3; V3A—dorsal subdivision of visual area 3; V3v—ventral subdivision of visual area 3; V4t—transitional part of visual area 4; VIP—depths of the ventral bank of the intraparietal sulcus.

functionally specific streams, or the strength of connections within a stream as opposed to connections between streams. The functional significance of each type of connection may differ on the basis of the neurons it influences in different layers, or by its synaptic pattern. Differences in the strength or in the functional attributes of connections may help explain why damage to specific cortices in humans eliminates some aspects of feature or motion analysis, but leaves others unaffected (34,133,150).

PREFRONTAL LIMBIC AREAS ARE MULTIMODAL

The above discussion suggests that there is some degree of organization in the projections from visual and motor cortices to prefrontal areas. However, unlike the sensory specific cortices, which appear to specialize in processing input from one sensory modality, the prefrontal cortex is linked with cortices

representing each of the sensory modalities and polymodal areas (5,10,12,17,18,25,31,77,79,96,103,105,110,114). The question then arises as to whether all prefrontal areas are multimodal, or to what degree its subareas are multimodal.

Anatomic studies have indicated that prefrontal cortices are connected with other areas in a manner that can be predicted, to a certain extent, on the basis of their structure. For example, prefrontal limbic cortices are interconnected widely with sensory, polymodal, and other limbic cortices. Among prefrontal areas the most diverse cortical and subcortical input is directed to limbic cortices in the posterior orbitofrontal region (areas PAII and Pro in reference 12; see also Fig. 1). The above areas receive robust projections from limbic, polymodal and premotor cortices, in addition to input from areas associated with the modalities of olfaction, vision, audition and somatic sensation (12,96). Moreover, classic physiologic studies have implicated the posterior orbitofrontal cortex in autonomic responses (37). As the recipient of input from both exteroceptive and interoceptive modalities, the posterior orbitofrontal region is thus in a position to integrate multiple aspects of the environment.

In contrast, those eulaminate prefrontal areas which show the highest degree of laminar definition, such as caudal areas 46 or 8, have only sparse links with limbic cortices and receive projections from areas associated primarily with one or two modalities (10,17; for review see 11). A prime example of the latter is caudal area 8 in the arcuate concavity. We have shown that the majority of afferent neurons from sensory cortices which distribute to caudal area 8 originate in visual or visuo-motor cortices and very few are found in limbic cortices (10,17). Areas between the above extremes, show a projectional pattern which falls somewhere in the middle with respect to the modalities represented and the relative preponderance of neurons from limbic cortices directed to them (18). The above evidence suggests that projections to prefrontal limbic cortices are not only topographically dispersed, but they also emanate from areas which represent several sensory modalities. The tendency for diverse projections from sensory cortices thus appears to decrease as laminar definition in the prefrontal cortex increases. However, no cortical area appears to be strictly unimodal in its inputs within the prefrontal cortex.

CORTICAL AREAS WHICH HAVE COMPARABLE LAMINAR DEFINITION ARE INTERCONNECTED

The idea that the cortex can be parcelled by going to the limbic cortices and following gradual changes away from them, has been applied to understand the architecture of several cortical systems including the auditory, somatosensory, motor and the visual (for review see 104). This parcelling of the cortex has enabled us to observe yet another consistent feature in corticocortical connections. Prefrontal areas seem to be connected with sensory and premotor areas which have a comparable degree of laminar definition. Thus, with regard to visual input, orbital areas are linked with the most anterior inferior temporal visual cortices (10,12); the interconnected cortices show the lowest degree of laminar definition within their respective cortical system. Lateral prefrontal cortices, which have a better laminar definition than the orbital, are connected with caudal inferior temporal and occipital cortices, which have more distinct laminar borders than rostral inferior temporal areas. A similar pattern is observed in the connections of prefrontal cortices with auditory, somatosensory, motor, or parietotemporal cortices (for review see 11).

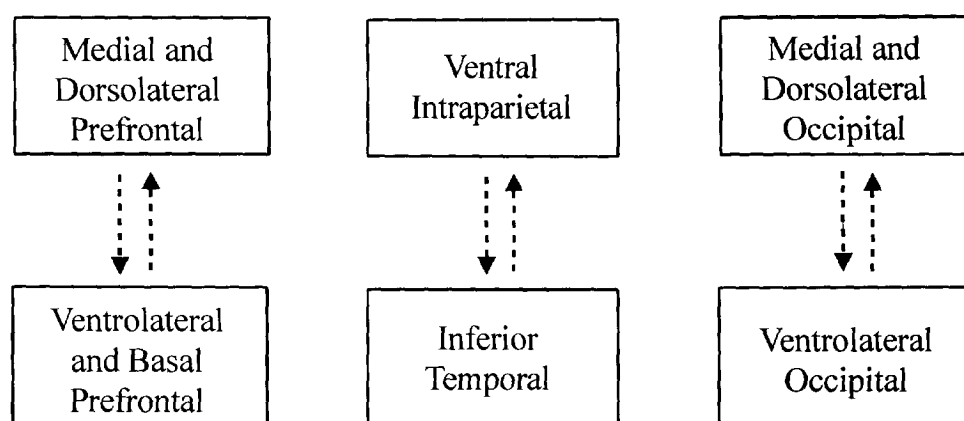


FIG. 3. Diagram showing that dorsal and ventral visual, parietal, inferior temporal and prefrontal cortices are interconnected at certain points via a system of lateral connections (dotted arrows).

HORIZONTAL AND COLUMNAR PATTERNS OF CORTICOCORTICAL CONNECTIONS

The above discussion suggests that there are consistent patterns in the topography of connections of prefrontal areas with the rest of the cortex. In addition, we also saw that cortices vary widely in their laminar organization, having from three to six cortical layers. In most eulaminate areas further subdivisions of layers III–VI have been made. With the introduction of retrograde tracers, which label neurons clearly, it has been possible to investigate the laminar origin of neurons which participate in corticocortical connections. The first observations were made in the visual system. Projections which originate in V1 and terminate in V2 or MT were found to arise predominantly from layer III. In contrast, neurons projecting in the opposite direction (i.e., from V2 to V1) were found mostly in the deep layers, even though some neurons from the upper layers participated in this type of projection as well (119,129). These projections have been referred to as “forward” and “backward” to describe their topographic relationships (89,119). Later, however, it was observed that projections between other visual areas such as MST and TE, or MT and V4, etc., did not fall clearly into the above two categories (89,132). Though projection neurons linking visual cortices were observed mostly in layers III, V and VI, they were distributed in different ratios in each of the layers. These projections were termed “intermediate.”

The above information provides an idea on how some sensory specific cortices communicate with areas of the same modality in a limited set of circumstances (for discussion see 80). The above studies do not indicate what principles govern “intermediate” connections. In addition, the “forward” and “backward” scheme does not address how information is conveyed from sensory cortices to association areas which are not unimodal, or between two different association or limbic cortices.

Some clues on the pattern of corticocortical connections outside the unimodal sensory cortices emerged with the observation that limbic cortices project to the prefrontal cortex primarily from their deep layers (17). In contrast, projections arising from areas which are close to the primary areas, such as V2, originate mostly in layer III. The most striking difference between the areas which project via their deep layers and those which project from layer III is the degree of their lami-

nar definition. The latter are eulaminate with a well-delineated six layer pattern, whereas the former are transitional and have only three or four layers. Because laminar organization is a structural attribute, it was easy to test whether cortical architecture can predict the laminar origin of corticocortical projection neurons. I thus examined the laminar origin of projections from various types of cortices to the frontal cortex and found that it varied in accordance with the laminar definition of the cortical regions that gave rise to such projections (9). Thus, when limbic areas project to the frontal cortex, the cells of origin are found mainly in layers V and VI. Projections from regions with increasing laminar differentiation arise progressively from layer III. Moreover, this pattern appeared to be general for all projections directed to frontal areas: it was observed in projections originating in visual, somatosensory, auditory, motor, and prefrontal cortical systems (see Fig. 1 in reference 9). Thus, as the cortical architecture within each system changes from limbic areas towards those eulaminate areas which have the clearest laminar definition, the origin of frontally directed projections shifts from predominantly infragranular, to predominantly supragranular layers in a graded manner.

The advantage of the above scheme is that it can be used to predict the connective relationship of two areas solely on the basis of their respective architecture. Thus, whereas the visual cortical system has been described as hierarchical on the basis of the laminar origin and termination of the connections between areas (134), the hierarchy can be described first and foremost in structural terms. On the other hand, within the “forward” “backward” “intermediate” scheme, position of an area in a hierarchy must be inferred post hoc after a connective relationship is established. In fact, the laminar origin of “forward” and “backward” connections is considerably more blurred in the sensory systems of lissencephalic primates (147), which have an overall less differentiated laminar organization than the gyrencephalic macaques. The latter observation suggests that structure can be used to predict the pattern of connections in sensory as well as in other association cortices.

The termination of efferent connections within the cortex also appears to be tightly linked to the architectonic features of cortical areas. Some of the first clues about the pattern of efferent connections came from the sensory cortices, which was also described within a directional framework. Thus, axo-

nal projections proceeding in the forward direction (i.e., from V1 to V2) terminate in and around layer IV more or less in a short columnar pattern. In contrast, axonal projections going in the opposite direction (i.e., from V2 back to V1) terminate as a strip in layer I (119).

Though there is less information on the pattern of termination of projections from distant sensory cortices to association areas, we have made some observations on how efferent fibers from one prefrontal area terminate in another prefrontal area. The laminar pattern of termination of efferent connections within the prefrontal cortex appears to be related to the laminar definition of the cortex of origin and its relation to the laminar organization of the site of termination (20). For example, axonal projections directed to cortices that have a less distinct laminar organization than the site of origin terminate primarily in columns and to a lesser extent in layer I. In contrast, axonal projections directed to cortices that have a more differentiated laminar organization than the site of origin terminate in layer I and to a lesser extent in a columnar pattern (see Fig. 14 in reference 20). Even though the pattern of efferent terminations in the prefrontal cortex is more blurred than what is observed in the sensory cortices, projections to layer I are comparable to the termination of "backward" axonal projections in the sensory systems. Conversely, the columnar pattern of termination in the prefrontal cortices resembles the "forward" pattern of fiber termination in sensory cortices. It should be noted that in the sensory systems "forward" connections always emanate from cortices with more, and terminate in areas with less distinct laminar borders. Conversely, "backward" connections always originate in areas with less, and terminate in cortices with more distinct laminar organization. Thus, the structural relationship appears to be the best predictor of termination of efferent fibers as well, both in sensory and in other association cortices.

SUBCORTICAL INFLUENCES ON PREFRONTAL CORTICES PARALLEL THE CORTICAL: INPUT FROM THE THALAMUS AND THE AMYGDALA

In classic studies the prefrontal cortex had been associated with the mediodorsal nucleus of the thalamus (for reviews see 78,86,99,116). With the use of modern tracing procedures, however, it became clear that several other thalamic nuclei, including medial, intralaminar, ventral, medial pulvinar, and to some extent the anterior issued projections to prefrontal areas (e.g., reference 81). One may ask whether there is a consistent pattern in the topography of projections from the thalamus to the prefrontal cortex.

The structural architecture of the prefrontal cortex has provided the framework to view the pattern of its connections with the thalamus as well. We recently noted that the organization of thalamic afferents directed to prefrontal areas followed a pattern similar to the corticocortical: Thus, lateral eulaminar prefrontal areas receive topographically restricted projections which emanate primarily from the mediodorsal nucleus. In contrast, the nuclear origin of projections to orbital and medial limbic cortices is more diverse within the thalamus (16,38). In fact, the three-layered agranular prefrontal cortex on the orbital surface receives projections primarily from midline and intralaminar nuclei and comparatively sparse projections from the mediodorsal nucleus (38).

Unlike the thalamus, the amygdala projects selectively to only some prefrontal cortices (4,76,111,112; for review see 36). The heaviest projections from the amygdala are directed to limbic orbital areas, followed by limbic medial areas (14).

The rest of the prefrontal cortex appears to have few, if any, links with the amygdala (14).

One may ask what type of signals are being transmitted from the thalamus and the amygdala to prefrontal cortices. The qualitative nature of signals conveyed from sensory specific thalamic nuclei to unimodal sensory cortices is comparatively easy to infer. In the sensory systems the pathways from the periphery to the thalamus and then to the cortex have been established with certainty. In contrast, thalamic nuclei which project to prefrontal cortices are not connected directly with the sensory periphery. Moreover, there are few studies on the physiological properties of thalamic nuclei which project to prefrontal areas (2,46). It is, therefore, difficult to decipher the possible nature of signals transmitted from the thalamus to prefrontal areas.

One way to circumvent the above difficulties is to ask what other inputs are directed to thalamic and amygdaloid nuclei which project to prefrontal cortices. While information in the literature is far from complete, some consistent relationships have emerged. For example, the anatomic, physiological and behavioral features of area 8 suggest that it has a role in visual and visuomotor functions (for review and references see 10). The thalamic projections to area 8 are also consistent with the above idea. Several thalamic nuclei, including the multiform subdivision of the mediodorsal nucleus, the supragenulate and limitans are recipient of projections from the superior colliculus and the lateral part of the substantia nigra which have been implicated in eye movement as well (21,61-64,70,71,148). In addition, the upper parts of the central lateral and paracentral nuclei have visual and visuomotor properties (125,126), and project to area 8 as well. It appears, therefore, that there is correspondence between the functional attributes of thalamic nuclei and cortical areas which project to the same prefrontal cortices.

There is less information on the physiological properties of neurons in nuclei which project to prefrontal limbic cortices. However, some topographic relationships of the thalamic projections offer some clues about their functional significance. For example, the rostral parts of the mediodorsal nucleus project to the lateral prefrontal areas, whereas its caudal parts project to limbic cortices on the medial and orbital surfaces (16,38). In this context it is interesting to note that mnemonic deficits in human and nonhuman primates follow damage of the caudal parts of the mediodorsal nucleus (74,137,153). Similarly, the cortical projections to orbitofrontal cortices arise from areas which have been associated with mnemonic aspects of sensory information. For example, rostral inferior temporal visual areas and the adjacent rhinal and perirhinal regions have been associated with mnemonic processes (3,47,66,67,93,154,155) and project to orbitofrontal limbic cortices (12,96). Orbital limbic areas thus appear to have a role in mnemonic processes on account of both their cortical and subcortical connections. In fact, there appear to be functional similarities between the anterior inferior temporal and orbitofrontal areas in visual discrimination and cognitive tasks in primates (7,41,45,48-50,66,107,141,142). The specific role of the limbic prefrontal cortices in memory is not known. Though deficits in some sensory specific memory tasks have been explored in the orbitofrontal cortices, as noted above, the polymodal nature of orbital cortices suggests that they may have multiple roles in mnemonic processes, which have remained hitherto unexplored.

The orbital limbic areas also receive robust projections from the amygdala. A major role of the amygdala along with the hippocampus in mnemonic processes that was proposed in

earlier studies (87,95,152) has recently been discounted (for review see 154). It appears that the role previously ascribed to the amygdala and the hippocampus can be attributed largely to the adjacent rhinal and perirhinal cortices, as had been suggested previously by studies in which the rostral temporal cortices were temporarily incapacitated by cooling (52,67). It is interesting to note that the entorhinal cortex, like the orbitofrontal, is a multimodal region (12,73,96,135).

The lack of a significant role of the amygdala in the types of memory that have been tested thus far in primates leaves unanswered the question of the nature of information conveyed by the amygdala to the cortex. To gain some clues we turn again to input directed to the amygdala from other areas. The amygdala receives robust projections from the sensory cortices which appear to be organized by modality to some extent (60,75,130). A comparison of the sensory input directed to prefrontal areas via corticocortical pathways, and the input from sensory cortices directed to amygdaloid nuclei which then project to the prefrontal cortex, reveals some striking parallels, as is summarized in Fig. 4. For example, prefrontal limbic areas, particularly those on the orbital surface, receive widespread projections from most sensory association cortices (10,12,96). Similarly, the amygdaloid sites which project to the prefrontal limbic cortices are themselves targets of input from the same sensory cortices. In contrast, eulaminate areas with a high degree of laminar definition receive cortical projections which are comparatively restricted with respect to the number of sensory modalities represented. For example, area 8 in the arcuate concavity receives projections primarily from visual and visuomotor cortices (10,17,68). Though amygdaloid projections to area 8 are sparse, they emanate exclusively from the dorsal part of the basolateral nucleus, which is a major target of projections from visual cortices as well

(60,75,130). Thus, there appears to be correspondence in the input reaching prefrontal areas from sensory cortices directly, and sensory input filtered through the amygdala to prefrontal areas indirectly. The significance of direct and possible indirect routes of sensory information to prefrontal areas is not known. Stimulation of the amygdala in humans has elicited memories of experiences with strong emotional significance (53,56). It is possible that mnemonic aspects of the amygdala may be related only to emotionally memorable events. Details of the perceptual images may be conveyed from the sensory cortices directly via corticocortical pathways.

INTEGRATION OF INPUT TO PREFRONTAL AREAS FOR ACTION

The connectional patterns discussed above suggest that sensory input to the prefrontal cortex is highly integrated with input from cortices associated with mnemonic and emotional processes. The potential for integration of the above processes appears to be particularly marked in the posterior orbitofrontal region, which receives information about all aspects of the external and internal environment, from thalamic nuclei involved in associative aspects of memory, and from the amygdala, which may enrich events with an emotional component (12,14,16,38,96). Projections from postRolandic sensory cortices to caudal areas 8 and 46, on the other hand, may provide more detailed information on the analytical aspects of the sensory environment.

Prefrontal areas, in general, appear to integrate sensory input for action (for discussion see 43,44). In this context it may be significant that prefrontal cortices have robust connections with premotor cortices and with a network of ventral thalamic nuclei and the magnocellular part of the mediodorsal nucleus (16,19,22,38,88,90), which are strong recipients of projections from the basal ganglia (70,71,84,101).

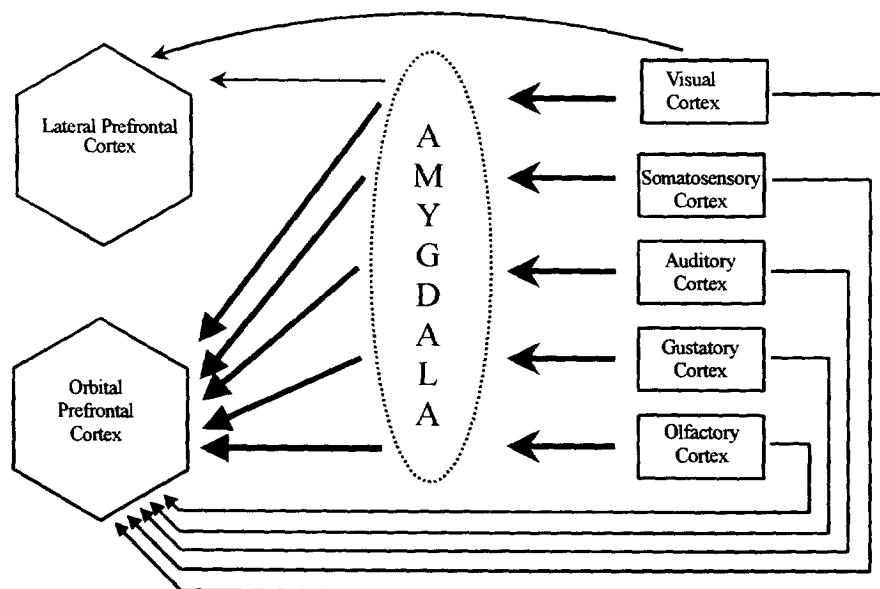


FIG. 4. Direct and possible indirect pathways of sensory projections to lateral and orbital prefrontal cortices. Lateral prefrontal areas, such as the frontal eye fields (top left), receive robust projections from visual cortices directly (top, right), and sparse projections from the visual-recipient part of the amygdala. In contrast, caudal orbitofrontal areas (bottom, left) receive projections from olfactory, gustatory, auditory, somatosensory and visual cortices, and robust projections from the amygdala which are also recipient of input from the same sensory modalities.

THE PLASTIC NATURE OF PREFRONTAL LIMBIC CORTICES

Prefrontal limbic cortices have several connectional and neurochemical features that are consistent with their involvement in learning and memory which require a certain degree of plasticity. In fact, some connectional and neurochemical characteristics observed in the limbic system in adult animals are observed universally during development when all neural structures are plastic. For example, the widespread connections of limbic cortices observed in adult animals are reminiscent of exuberant connections noted in development in all neural systems (33). In addition, in the thalamocortical system, where connections are largely ipsilateral (78), a small population of neurons in the contralateral thalamus in adult rhesus monkeys (5,113) project preferentially to prefrontal limbic areas (38). In contrast to the relative paucity of contralateral projections from the thalamus to eulaminate areas (38), contralateral thalamic projections are common during development (85,94,124,127). More recently, we noted that limbic cortices, in general, are more likely to issue widely divergent projections via branched axons than eulaminate areas in rhesus monkeys (13). While in adult animals divergent projections via branched axons are relatively rare, they are prevalent in eulaminate sensory cortices during development (30,72,102).

The parallels in the characteristics of limbic areas in adult animals and cortices undergoing development extend to their neurochemistry as well. Several molecular markers which are ubiquitous in the nervous system during development, in the adult are localized preferentially in limbic structures. One example is the protein GAP-43, which is widespread during development or after neural damage but in the adult is localized preferentially in limbic and associative cortices (for reviews see 23,120). The phosphoprotein DARPP-32, which is associated with intracellular signal transduction processes (58,59), is found in several cortical areas in newborn primates (24), but DARPP-32, as well as the related phosphoprotein, phosphatase Inhibitor 1, are concentrated preferentially in limbic structures in adult primates (15). Recently we have also noted that NADPH-diaphorase, which colocalizes with nitric oxide synthase, an enzyme necessary for the production of the novel neurotransmitter nitric oxide (27), which may have a role in synaptic plasticity (151) is also prevalent in prefrontal limbic cortices (40).

CONCLUSION

The type of information conveyed from limbic cortices to the rest of the neuraxis is not known. The preponderance of projections emanating from limbic areas suggests that they may have a tonic influence on the cortex. While some of these pathways may be excitatory, the distribution of intracellular signal transduction proteins in limbic structures suggests that several may have modulatory influences on the rest of the cortex and subcortical structures as well (15). In addition, the pattern of connection of limbic areas offers some additional clues on their possible functional significance. For example, limbic areas issue projections from their deep layers and terminate in layer I of eulaminate areas, a pattern which resembles the "backward" projections in the sensory systems. Backward projections in sensory cortices have been ascribed a feedback role (89,119), and by analogy, projections from limbic cortices may be considered feedback connections to the entire cortex. In fact, projections from subcortical limbic structures, including those from the olfactory bulb and the limbic thalamus terminate in cortical layer I as well (57,78,82,115,138,145). Feedback projections from limbic cortices may serve to compare the input and output necessary for the interpretation of events. The possible involvement of prefrontal cortices in schizophrenia (144) may be related to a breakdown of a massive feedback system issued from limbic areas, which may have a role in the integration of distributed pathways associated with sensory perception, associative mnemonic, and emotional processes. The connectional and neurochemical characteristics of limbic cortices suggests that they may retain some developmental features to a greater extent than other cortices. This would help explain the involvement of limbic structures in learning and memory, but also their preferential vulnerability in several neurologic and psychiatric disorders (26,53,65, 69,83,108,117,118,136,139,144) such as epilepsy, Alzheimer's disease, and schizophrenia.

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