

Specialized Elements of Orbitofrontal Cortex in Primates

HELEN BARBAS

*Department of Health Sciences, Boston University, Program in Neuroscience,
Boston University, Boston, Massachusetts, USA*

ABSTRACT: The orbitofrontal cortex is associated with encoding the significance of stimuli within an emotional context, and its connections can be understood in this light. This large cortical region is architectonically heterogeneous, but its connections and functions can be summarized by a broad grouping of areas by cortical type into posterior and anterior sectors. The posterior (limbic) orbitofrontal region is composed of agranular and dysgranular-type cortices and has unique connections with primary olfactory areas and rich connections with high-order sensory association cortices. Posterior orbitofrontal areas are further distinguished by dense and distinct patterns of connections with the amygdala and memory-related anterior temporal lobe structures that may convey signals about emotional import and their memory. The special sets of connections suggest that the posterior orbitofrontal cortex is the primary region for the perception of emotions. In contrast to orbitofrontal areas, posterior medial prefrontal areas in the anterior cingulate are not multi-modal, but have strong connections with auditory association cortices, brain stem vocalization, and autonomic structures, in pathways that may mediate emotional communication and autonomic activation in emotional arousal. Posterior orbitofrontal areas communicate with anterior orbitofrontal areas and, through feedback projections, with lateral prefrontal and other cortices, suggesting a sequence of information processing for emotions. Pathology in orbitofrontal cortex may remove feedback input to sensory cortices, dissociating emotional context from sensory content and impairing the ability to interpret events.

KEYWORDS: orbitofrontal connections; laminar patterns of connections; emotions; inhibitory systems; sequential pathways; emotional memory; temporal structures; intercalated amygdalar neurons; anxiety disorders

Address for correspondence: Helen Barbas, Department of Health Sciences, Program in Neuroscience, Boston University, 635 Commonwealth Ave., Room 431, Boston, MA 02215. Fax: 617-353-7567.

barbas@bu.edu

<http://www.bu.edu/neural>

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OVERVIEW

The orbitofrontal cortex has been associated with emotional processing in general and specifically with encoding the significance and value of stimuli. As such, stimuli gain or lose relevance based on their association with reward, and the responses of neurons in orbitofrontal cortex reflect this flexibility and paramount regard for context. The anatomic features of the orbitofrontal cortex are best understood within the framework of its salient functional features, and the detailed circuitry, in turn, can inform behavioral and functional studies. A holistic view of the structure and function of the orbitofrontal cortex is necessary to understand its complex organization. This short review focuses on the essential structure and principal connections that underlie the functions that distinguish the orbitofrontal cortices, and which are frequently disrupted in psychiatric diseases.

EXTENT OF ORBITOFRONTAL CORTEX

The orbitofrontal cortex in primates is a large and heterogeneous region, and both its extent and architectonic areas have been variously described. In rhesus monkeys, the basal surface of the prefrontal cortex includes area 13, the orbital part of area 12, the rostrally situated area 11, and the basal part of area 10, which are shown in nearly all maps of the region in macaque monkeys and humans.¹⁻⁶ One map distinguishes two other regions in the posterior part of the basal surface of the rhesus monkey (areas OPAll and OPro),² and in another map area 13 has been subdivided into several sectors.³ In a previous study,² all these areas have been considered to be the basal part of the basoventral series of prefrontal areas (FIG. 1B). The ventral extension of this series includes the ventrolateral prefrontal cortices² (FIG. 1C). References to orbitofrontal cortex here pertain to the basal areas (FIG. 1B).

The orbitofrontal areas are distinct from the series of areas on the medial wall of the prefrontal cortex, which are considered part of a mediadorsal series of cortices.² The medial component of this region includes all medial prefrontal areas (FIG. 1A), which are anatomically continuous with dorsolateral prefrontal cortices.² The medial prefrontal region can be subdivided into an anterior sector, which includes areas 10, 9, and 14. The posterior part includes the anterior cingulate areas 32, 24, 25, and MPAll. In rhesus monkeys, areas 14 and 25 have a small basal component² whose connections are similar to the areas in the anterior cingulate and are part of the mediadorsal series of prefrontal areas. The basal part of area 25 is called caudal area 14 in some maps (e.g., Ref. 3). There is general agreement that the medial areas (including the basal components of areas 14 and 25) have sets of connections that distinguish them from the areas found on the basal surface, as will be described briefly later.

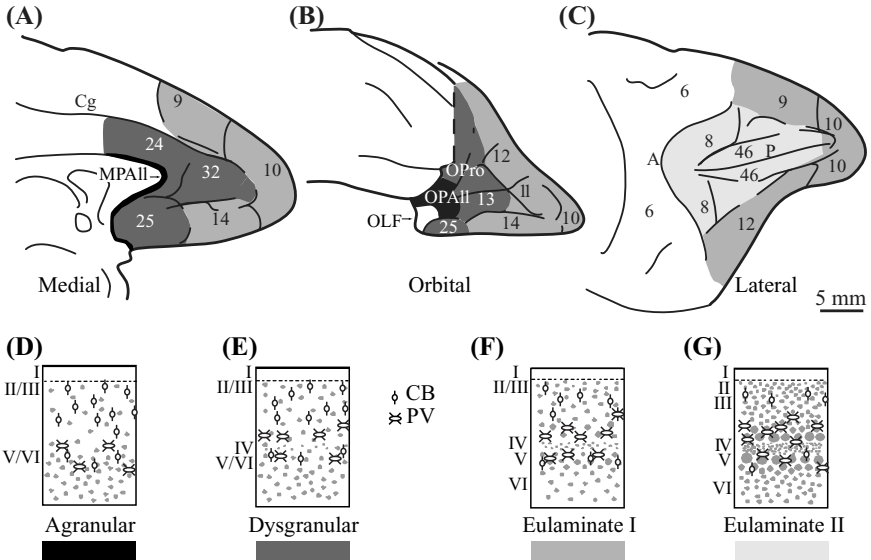


FIGURE 1. The three surfaces of the prefrontal cortex in the rhesus monkey: **(A)** the medial surface; **(B)** the basal surface showing the orbitofrontal cortex; **(C)** the lateral surface. **(D-G)** Cartoon showing differences in the type of cortex: D, agranular; E, dysgranular; F, G, eulaminate. There is an increase in the density of neurons (grey dots) in the direction from agranular (D) to eulaminate II (G) areas, and a concomitant decrease in the density of the neurochemical class of inhibitory neurons labeled with calbindin (CB), and an increase in the density of parvalbumin (PV) inhibitory neurons. Type is depicted in different shades of gray. Numbers designate architectonic areas; Abbreviations: A, arcuate sulcus; Cg, cingulate sulcus; MPAll, medial periallocortical area; OLF, olfactory area; OPAll, orbital periallocortical area; OPro, orbital proisocortical area; P, principal sulcus.

ARCHITECTURE OF ORBITOFRONTAL CORTICES

To Lump or to Split?

Situated on the basal surface of the frontal lobe, the orbitofrontal cortex has several architectonic areas that have been variously subdivided (reviewed in Ref. 7). Since the classic map of Walker,¹ some investigators have parcellated this region into relatively broad areas,^{2,5,8} while others have proposed finer architectonic subdivisions based on novel markers beyond the classical tools of cytoarchitecture and myeloarchitecture.³

Disagreements in placing architectonic borders seem to be based on the tendency of some investigators to split areas at points of subtle differences in architecture, which others consider to be parts of one area. One way to increase agreement among investigators is to use unbiased quantitative approaches to determine the density of specific markers that are sensitive in showing

architectonic borders. Quantitative data then can be used for different analyses. For example, the density of neural markers that are differentially expressed across areas, and are thus sensitive in showing architectonic borders, can be used to construct “fingerprints” of areas. If adjacent areas look different using quantitative measures, then the border is justified; if they appear to be similar, then they can be considered to be one area.

FIGURE 2 shows examples of the use of unbiased quantitative methods to construct fingerprints of some key orbitofrontal areas, using the density of all neurons, as well as specific neurochemical classes of inhibitory neurons that express the calcium-binding proteins parvalbumin (PV) or calbindin (CB), which are useful architectonic markers,^{3,9-12} as shown in the cartoon in FIGURE 1D–G. Differences in the shape of the triangular plots reflect differences in architecture among the areas. Quantitative data can also be used to carry out multi-dimensional analyses by taking into consideration many architectonic features simultaneously, a task that cannot be easily accomplished by serial observations. Multiple independent analyses can be employed to determine whether they yield the same results. FIGURE 3A shows the results of multi-dimensional analysis of architectonic data in the prefrontal cortex of rhesus monkeys using 17 parameter dimensions.⁹ The closer the areas are in the two-dimensional space, the more similar they are in their architectonic features. An independent cluster analysis shows a similar ordering of areas (FIG. 3B).

Architecture and Function

Structure frequently provides important insights on function. The primary visual cortex (area V1) in gyrencephalic primates, for example, has the most recognizable cortical architecture and a readily identified architectonic border with area V2. In early-processing visual cortices, the architecture coincides with detailed maps of the entire sensory periphery in each area. In progressively rostral higher-order visual association areas, however, the borders of areas are more difficult to define and so are the physiological properties of neurons.

Do the functions of the orbitofrontal cortex coincide with architectonic borders? Neurons in the orbitofrontal cortex that show responses to particular stimuli, or fire in distinct aspects of a behavioral task, are not restricted within architectonic areas (reviewed in Ref. 13). Additionally, functional imaging studies in behaving humans have recorded activation within relatively broad areas that encompass several architectonic areas or subareas.¹⁴ This is hardly surprising in view of findings that the responses of orbitofrontal neurons to sensory stimuli depend on behavioral context. For example, in a behavioral task, neurons that respond to a triangle serving as a positive stimulus associated with reward, but not to a square not associated with reward, switch their responses when the association of the stimuli with reward is reversed.^{15,16}

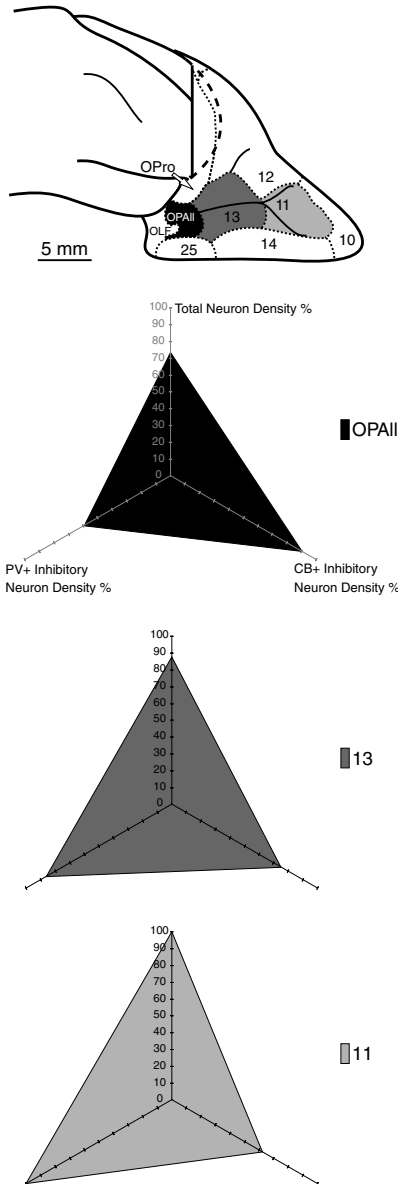


FIGURE 2. Fingerprints of some architectonic areas of the orbitofrontal cortex. The fingerprints were constructed from normalized quantitative data showing the density of all neurons and the density of PV and CB inhibitory neurons, which aid in parcellating architectonic areas. Differences in the shape of the triangles reflect differences in the architecture of these areas along the three parameter dimensions. The depicted orbitofrontal areas are shown on the basal surface (top), and include (from top to bottom), areas OPAIL (agranular, type 1), area 13 (dysgranular, type 2) and area 11 (eulaminate, type 3). Scale gradations and labels in central and bottom triangles are as in the top triangle.

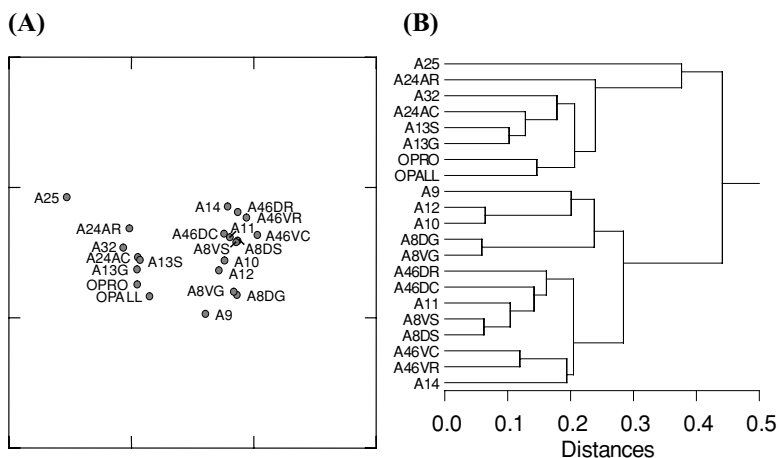


FIGURE 3. Sorting prefrontal architectonic areas by multiple architectonic features. **(A)** Multi-dimensional analysis using 17 parameter dimensions shows that limbic areas (agranular and dysgranular areas) segregate on the left. Orbitofrontal areas are seen at the bottom left (areas 13, OPRO, and OPALL), and anterior cingulate areas are seen at the top left (areas 25, 24, and 32). Eulaminate areas sort to the right. **(B)** An independent cluster analysis shows similar relationship of prefrontal areas to each other as in the multi-dimensional analysis. Reprinted from Ref. 9, with permission.

Architecture and Connections

In some cases architectonic areas coincide with specific connections. The well-defined V1 area in primates, for example, is linked in a highly specific pattern with the thalamic dorsal lateral geniculate nucleus, with cortical area V2, and with area MT. In many cases, however, the connections of cortical areas do not respect architectonic borders. The connections of the orbitofrontal cortex, in particular, are highly distributed. For example, the thalamic connections of orbitofrontal cortex include over 25 nuclei and their subdivisions, even though about half of all thalamic projection neurons are found in the mediodorsal nucleus (for discussion and references see 17, 18). Abrupt disappearance of connection fields close to major anatomic landmarks, such as the depths of sulci, reflect the mechanics of folding of the cortex rather than changes in architecture.¹⁹

It's clear that neither the function nor the connections coincide with architectonic borders in the orbitofrontal cortex. These findings are consistent with the flexible responses of orbitofrontal neurons within a behavioral context. Below follows a discussion of special aspects of the architecture and connections of orbitofrontal cortex, demonstrating that broader subdivisions of this region are a better match of its anatomic and functional organization.

Global versus Local Architecture and Connections

A different approach to architecture is to group areas by cortical type.^{2,8,20} The methods of parcellating by architecture and by type share some features but also have key differences. Architectonic areas are mapped on the basis of local features, such as the shape or size of neurons in different layers, which vary among areas and give each area its unique architectonic signature. Architectonic differences can be seen in Nissl-stained sections, which show all neurons, or in tissue stained for markers that label distinct groups of pyramidal neurons or inhibitory interneurons (e.g., Ref. 3). The fingerprints in FIGURE 2 were constructed using three markers for different architectonic areas of the orbitofrontal cortex.

Grouping architectonic areas by type, on the other hand, relies on global structural features that are common among several areas, such as the number of identifiable layers, the presence or absence of layer IV, neuronal density, and others. For example, areas that have fewer than six layers are different in type than areas that have six layers. To use an analogy, grouping by cortical type is like grouping people by similar height or weight. The people in each group have in common height or weight, though individuals within the group differ in facial features. Grouping areas by type is possible because large cortical systems, such as the prefrontal, visual, auditory, somatosensory, etc., vary gradually and systematically in cortical structure (reviewed in Ref. 21). Limbic areas fall into two major types (agranular and dysgranular), and eulaminar areas can be grouped into two or more types, depending on the structure of the region and by how fine the divisions one wishes to make.

The orbitofrontal cortex can be classified into three types of cortex, as shown in FIGURE 1. The area depicted in black in the posterior orbitofrontal cortex is agranular in type, with only three identifiable layers and a lower neuronal density than the other areas. This area is situated close to the olfactory areas. The adjacent orbitofrontal areas (depicted in dark grey), are dysgranular in type, differing from the agranular by the presence of a poorly developed layer IV. These two types of cortices describe limbic cortices. The anterior part of the orbitofrontal cortex consists of eulaminar cortex (depicted in FIG. 1B in light grey), meaning that it has six layers, including an identifiable granular layer IV. These three types of cortices have also been described for the human orbitofrontal cortex.²²

Cortical Type and Patterns of Connections in Orbitofrontal Cortex

The significance of type in understanding cortical organization emerged from observations that areas with similar structure are interconnected. Most cortical connections occur between neighboring regions, coinciding with similarity in structure. In the prefrontal cortex, areas are robustly connected with

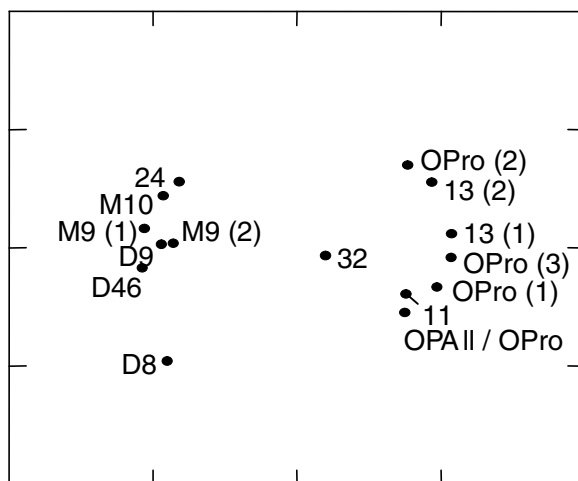


FIGURE 4. Sorting of prefrontal cortices by the entire complement of their connections with other prefrontal cortices. Cases with injection of tracers in orbitofrontal areas sort to the right and cases with injections in medial and lateral prefrontal areas sort to the left. The closer the areas, the greater the similarity in their sets of connections. Numbers in parentheses show results from injection of retrograde tracers in different experiments. Adapted from Ref. 23, with permission.

their immediate neighbors and a neighbor plus one.² Connections beyond that are sparser, except for areas that belong to the same structural type.²³ Dysgranular area 32 on the medial surface, for example, is robustly connected with dysgranular posterior orbitofrontal areas, even though they are not close neighbors and differ in their local architecture. FIGURE 4 shows the relatedness of several prefrontal areas by the pattern of their connections with other prefrontal cortices seen after a multi-dimensional analysis.²³ Orbitofrontal cortices cluster to the right by virtue of their similar connections.

Moreover, cortical type underlies the laminar pattern of corticocortical connections.²⁴ The structural model for connections emerged with the observation that certain areas of the cortex have similar laminar patterns of connections. Limbic areas, for example, which are either agranular or dysgranular in type, project to the six-layered eulaminar areas mostly through their deep layers regardless of their position in the cortex.²⁰ In contrast, eulaminar areas project to limbic areas mostly through their upper layers. The principal determinant of the laminar pattern of connections is the relative difference in structure between linked areas, as seen in various systems and species.^{10,11,25,26} In this model, each area is categorized by cortical type and given a numerical rating based on its structure (1–4 for cortical types D–G in FIG. 1). According to the structural model, feedforward projections, which originate in the upper layers and innervate the middle layers, describe those that link areas with either more

layers or higher neuronal density than the area of termination. Feedback connections, which originate in the deep layers and terminate in the superficial layers, link areas with fewer layers or lower neuronal density than the site of termination. Lateral connections, which originate in layers II-III and V-VI and terminate in all layers, link areas with similar structure. Moreover, since the structure of areas within a cortical region, such as the prefrontal, is graded,² the relative difference in the structure of areas is also graded, and so is the relative distribution of connections within cortical layers.²⁴

Accordingly, the connections of neighboring orbitofrontal areas with similar structure show a columnar pattern of efferent connections. Further predictions can be made on the basis of the relative differences in the type of linked orbitofrontal areas. Broad grouping of areas into structural types of cortex, therefore, can be used to distill complex connections into a few patterns. Further, this approach makes it possible to predict the laminar pattern of connections in humans on the basis of cortical structure.

We have seen that unique connections do not describe specific architectonic areas on the orbitofrontal cortex, but sets and patterns of connections are seen for groups of areas. Below we explore how antero-posterior division of the orbitofrontal cortex based on cortical type provides useful insights on the connectivity and function of the region.

DISTINCTIVE FEATURES OF ORBITOFRONTAL CORTEX

Antero-posterior Orbitofrontal Divisions by Cortical Type

Connections that differentiate orbitofrontal cortices occur along an antero-posterior division, consistent with changes in cortical type (FIG. 1B). The posterior orbitofrontal areas (black and dark gray in FIG. 1B) differ in their connections not only with cortical but also with subcortical structures^{8,27,28} (reviewed in Refs. 7, 29, 30). The posterior orbitofrontal cortex is strikingly multi-modal, perhaps the most so among all cortices. It receives projections from primary olfactory areas, the gustatory cortex, and high-order visual, somatosensory, gustatory, and auditory association areas. The latter originate in the superior temporal gyrus and in the lower bank of the lateral fissure,^{10,27} which are connected with earlier-processing auditory cortices (reviewed in Ref. 21) and respond to auditory stimuli in macaque monkeys.³¹

The most distinctive feature of posterior orbitofrontal cortex is its prominent connection with the olfactory areas,^{27,32} which lie adjacent to posterior orbitofrontal cortex (FIG. 1B, OLF, white area). Olfactory input to posterior orbitofrontal cortex originates from the piriform cortex and the anterior olfactory nucleus,²⁷ which are primary olfactory areas (reviewed in Ref. 33), a feature it does not share with its rostral neighbors. Interestingly, the primary olfactory areas are thought to represent high levels of processing (for discussion see

Shepherd, this volume³⁴), perhaps comparable to the highly processed inputs originating from high-order sensory association and polymodal cortices that also project to orbitofrontal cortex.

Connections of Orbitofrontal Cortex with the Amygdala

The posterior orbitofrontal cortex is further distinguished by its connections with the amygdala. The amygdala has widespread connections with the entire prefrontal cortex (e.g., Refs. 8, 35–44), but its connections with posterior orbitofrontal cortex and the anterior cingulate are considerably denser.⁴⁵ Axons from the amygdala terminate densely in bands within layers I-II of many prefrontal cortices.^{35,39} However, only the limbic prefrontal areas in the posterior orbitofrontal and anterior cingulate areas receive amygdalar projections in their middle layers as well, or in columns that span the entire cortical thickness.⁴⁵ Moreover, unlike other areas, the prefrontal limbic areas issue significant projections to the amygdala from layers II and III, in addition to the predominant projections from layer V.⁴⁵

Specificity of the Connections of Posterior Orbitofrontal Cortex with the Amygdala

The posterior orbitofrontal cortex has a unique pattern of connections with the amygdala, sending projections that terminate in a U-shaped pattern around the borders of the magnocellular basolateral nucleus (FIG. 5). The heaviest terminations in this projection target the intercalated masses of the amygdala,⁴⁶ which are entirely inhibitory in primates,⁴⁷ as well as in several other species. These small inhibitory neurons project to the central nucleus of the amygdala,^{47–52} which sends inhibitory projections to hypothalamic and brain stem autonomic structures.^{46,53,54}

The heavy and unique projection to the intercalated masses is unidirectional and originates exclusively from posterior orbitofrontal cortex. The dynamics of this pathway have yet to be investigated at the physiological level. Nevertheless, as shown in FIGURE 6, this pathway has specific functional implications, namely, a net effect of suppressing activity in the central nucleus and removing its inhibitory influence on hypothalamic and brain stem autonomic centers, and may thus increase autonomic drive in emotional arousal.⁵⁵ In addition, there is a lighter direct pathway from the posterior orbitofrontal cortex to the central nucleus of the amygdala,^{40,46} whose activation would be expected to have the opposite effect, inhibition of autonomic centers (FIG. 6). This pathway potentially can suppress central autonomic drive and help return the system to autonomic homeostasis as circumstances change.

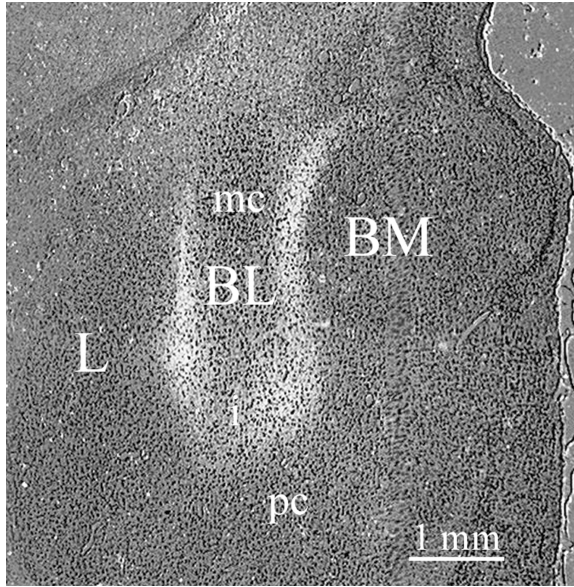


FIGURE 5. The unique innervation of the amygdala by posterior orbitofrontal cortex. Darkfield and brightfield (double exposure) photomicrograph of a coronal section through the amygdala, showing the termination of axons from posterior orbitofrontal cortex in the amygdala. Axons from posterior orbitofrontal cortex terminate heavily (white grain) onto the inhibitory intercalated masses of the amygdala, which are interposed between nuclei of the amygdala, separating the lateral (L) from the basolateral (BL) and basomedial (BM, also known as accessory basal) nuclei. mc and pc refer, respectively, to the magnocellular and parvicellular sectors of the basolateral nucleus. Adapted from Ref. 46.

The Dialogue between the Amygdala and Orbitofrontal Cortex

The amygdala receives projections from the same sensory association cortices as the orbitofrontal cortex (reviewed in Ref. 56). Moreover, projections from auditory and visual association cortices innervate heavily the posterior half of the amygdala, the same parts that are connected with the orbitofrontal cortex.⁴⁶ This evidence indicates that the orbitofrontal cortex receives direct projections from sensory association cortices^{27,57} and potentially indirect sensory input through the amygdala.⁵⁶ Interestingly, projections from the amygdala target each layer of orbitofrontal cortex to a different extent, including significant projections to the middle layers.⁴⁵ By analogy with sensory systems, these unusual pathways to the middle layers may convey feedforward information from the amygdala to orbitofrontal cortex pertaining to the emotional significance of events. The strong interactions of the orbitofrontal cortex with the amygdala may help explain why neurons in the orbitofrontal cortex respond within the framework of behavioral context, encoding the value of

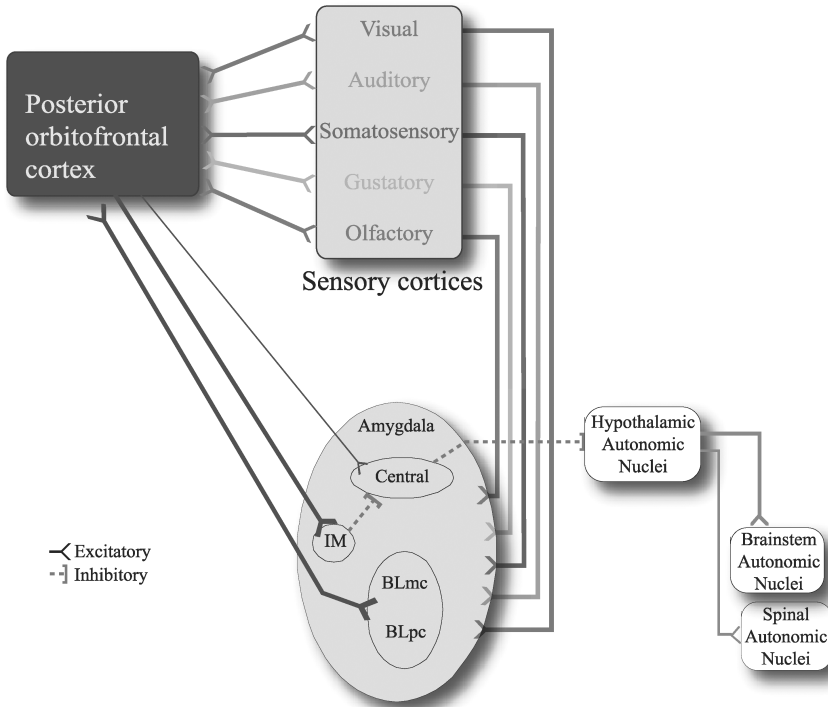


FIGURE 6. Summary of the connections of posterior orbitofrontal cortex. Bidirectional connections of cortices from every sensory modality give the orbitofrontal cortex its multi-modal features. The same sensory association areas project to the amygdala (most of these pathways are likely bidirectional, not shown). The posterior orbitofrontal cortex has robust bidirectional connections with the basal complex of the amygdala (only the basolateral, BL, nucleus is shown). The posterior orbitofrontal cortex also targets robustly the intercalated masses of the amygdala (IM), which project and inhibit the central nucleus of the amygdala, which inhibits hypothalamic autonomic centers; the latter innervate brain stem and spinal autonomic nuclei, which innervate peripheral organs. Activation of this pathway is expected to disinhibit the hypothalamus, allowing its activation in emotional arousal. A lighter pathway from the posterior orbitofrontal cortex innervates the central nucleus of the amygdala. Activation of this pathway is expected to inhibit hypothalamic autonomic centers, perhaps for return of the system to autonomic homeostasis.

stimuli, forming reward associations in cognitive tasks, and responding to stimuli when they are significant for the task at hand, but cease to respond when the reward contingencies change^{58–69} (reviewed in Refs. 70–72).

Feedforward projections from the amygdala to orbitofrontal cortex may have additional functions. Activity in the amygdala increases in response to faces showing emotional expressions even when they are presented quickly and below the level of awareness.⁷³ In rats, a short subcortical loop connecting the

amygdala with the thalamus can support fear conditioning.⁷⁴ This evidence suggests that the circuits of the amygdala allow fast and fairly automatic processing for vigilance in emotional situations. It is possible that the robust and bidirectional interaction of the amygdala with the orbitofrontal cortex may be necessary for the conscious appreciation of the emotional significance of the environment. This view is consistent with the classic findings of Kennard,⁷⁵ who suggested that the cortex is necessary for conscious perception. The direct projections from sensory association cortices to orbitofrontal cortex may provide an overview of the content of the external environment, and the indirect sensory input through the amygdala may provide the emotional context necessary to interpret the significance of events.⁵⁶

The Orbitofrontal Cortex and Memory for Emotional Events

Animals learn to associate stimuli with reward in a large variety of tasks (for reviews see Refs. 76, 77). Neurons in orbitofrontal cortex reflect this ability by encoding in memory changes in reward contingencies in behavioral tasks.⁶⁹ Moreover, neurons in the orbitofrontal cortex respond to stimuli that predict reward.⁶⁴ What are the pathways that may mediate the process of remembering behaviorally relevant information? The connections of orbitofrontal cortex include a host of cortical and subcortical structures with a demonstrated role in long-term memory. At the cortical level, they include the entorhinal (area 28) and perirhinal (areas 35, 36) cortices.^{8,27,40,78} The projections from the orbitofrontal cortex to the entorhinal cortex may underlie the process through which information about the emotional significance of stimuli is remembered, since the entorhinal cortex innervates the hippocampus^{79–82} (reviewed in Refs. 83, 84).

Moreover, projections from the dysgranular orbitofrontal cortex terminate in the middle layers of the agranular entorhinal cortex,⁵⁷ consistent with the prediction of the structural model for laminar connections, which is based on the structural relationship of linked cortices.²⁴ Innervation of the middle layers is analogous to feedforward (or bottom-up) projections in sensory cortices. The question then arises, what type of information does the orbitofrontal cortex issue in a feedforward manner to the entorhinal cortex? The orbitofrontal cortex may synthesize its multi-modal input and the robust signals from the amygdala and send the information to the entorhinal cortex, possibly to store motivationally relevant information in long-term memory.⁵⁷ The impairment seen in associating objects with rewards after lesions of orbitofrontal cortex^{85,86} may be due to disruption of a feedforward pathway to the entorhinal cortex and a return projection from the hippocampal formation, including CA1 and the subiculum to orbitofrontal cortex.^{87–89}

Attention for Emotional Events

A striking feature of the innervation of orbitofrontal cortex by the amygdala is the dense projection to the superficial layers I and II of prefrontal cortices, where terminations intermingle with local inhibitory neurons labeled with calbindin.⁴⁵ Activity in these inhibitory neurons in prefrontal cortex, and other areas, is associated with focusing attention on relevant features for a task and suppressing distractors.⁹⁰ The pathway from the amygdala to orbitofrontal cortex may be engaged to focus attention on stimuli with emotional import,⁴⁵ consistent with the role of the amygdala in vigilance (reviewed in Refs. 91–94).

Further, the prefrontal cortex, in general, has a specialized interaction with the inhibitory thalamic reticular nucleus (TRN), which has a role in gating the bidirectional connections of cortical areas with the thalamus. Unlike sensory and motor cortices, which project topographically onto one sector of TRN, some prefrontal areas send widespread projections to the TRN.⁹⁵ These projections extend beyond the anterior (prefrontal sector) into the sensory sectors of TRN. In addition, the mediodorsal thalamic nucleus, which is the principal thalamic nucleus for the prefrontal cortex, has widespread bidirectional connections with TRN, including the parts connected with sensory thalamic nuclei. This circuitry suggests a mechanism through which behaviorally relevant stimuli may be selected and distractors filtered out early in information processing through the thalamus.⁹⁵ Orbitofrontal area 13 is one of the prefrontal areas with widespread projections to TRN, providing yet another pathway that may facilitate focusing attention on motivationally relevant stimuli.

SIMILARITIES AND DIFFERENCES IN THE CONNECTIONS OF MEDIAL AND ORBITAL AREAS

The discussion thus far has centered on the posterior orbitofrontal cortex (areas OPAll, OPro and 13 in FIG. 1B), which make up the orbital part of the prefrontal limbic region. These posterior orbitofrontal cortices overlap approximately with the posterior half of the “orbital network” of Price and colleagues (this volume).⁶ The discussion thus far did not include posterior medial areas in the anterior cingulate (areas MPAll, 25, 32, and 24 in FIG. 1A), which belong to the agranular or dysgranular types of cortices, like the adjacent orbitofrontal. These posterior medial prefrontal areas in the anterior cingulate are part of the prefrontal limbic system,^{96,97} and the first to be considered part of the great limbic lobe.^{98,99} These anterior cingulate areas correspond to areas 24, 32, 25, and 14c of the “medial network” of Price and colleagues,⁶ who do not differentiate between anterior and posterior sectors of medial or orbital networks. As discussed in this review, the division of orbitofrontal and medial prefrontal regions into anterior and posterior sectors is based on cortical type, which, in turn, can help explain their overall topography

and pattern of connections. The densest connections with the amygdala, for example, are found in posterior orbitofrontal and posterior medial (anterior cingulate) areas.⁴⁵

There is general agreement that the two components of the prefrontal limbic system share robust connections with cortical and subcortical limbic structures, widespread connections with many thalamic nuclei, the amygdala, the hypothalamus, and memory-related medial temporal cortices. The limbic prefrontal cortices also show a similar laminar pattern of connections with other cortices, as discussed above. Further similarities include bidirectional connections with the basal forebrain and perhaps other neurotransmitter-specific brain stem structures. Other prefrontal areas, including the anterior orbitofrontal and anterior medial areas, receive, but do not send, projections to neurotransmitter-specific structures in primates.¹⁰⁰

The orbitofrontal and anterior cingulate components of the prefrontal limbic cortex have connectional specializations as well, which were reviewed previously¹⁰¹ and will be mentioned only briefly here. The two prefrontal limbic components diverge in their connections with sensory association cortices. In sharp contrast to the orbitofrontal cortex, medial prefrontal areas do not have significant connections with sensory association cortices, with the exception of robust connections with auditory association areas.^{10,25,102} In addition, although both posterior orbitofrontal cortices and anterior cingulate areas have dense connections with the amygdala (e.g., Refs. 38, 40), their patterns differ markedly,^{45,46} as discussed above. Medial and orbitofrontal cortices have some similar connections within the prefrontal cortex, but their entire complement of connections differs.^{2,103} These differences are exemplified in the multi-dimensional analysis of prefrontal interconnections (FIG. 4), which shows that cases with orbitofrontal injections of tracers cluster to the right and cases with medial and dorsolateral injections cluster to the left in the two-dimensional space.

Medial prefrontal cortices differ from the orbitofrontal by their stronger projections to hypothalamic autonomic centers and the spinal cord¹⁰⁴ and brain stem autonomic centers¹⁰⁵ (reviewed in Ref. 106). A pathway from area 32, for example, issues robust projections to hypothalamic autonomic centers, where they synapse through large boutons, suggesting efficient transmission of information.⁵⁵ In fact, the anterior cingulate areas have been called the emotional motor system.¹⁰⁷⁻¹⁰⁹

Based on the above differences in connections, there appears to be a division of labor within the prefrontal limbic system.¹⁰¹ The posterior orbitofrontal cortices (areas OPAll, OPro and 13 in FIG. 1B), which have robust connections with high-order sensory association cortices and specialized connections with the amygdala, may be the sensors of information pertaining to emotions. On the other hand, posterior medial prefrontal cortices in the anterior cingulate (areas MPAll, 32, 25, and 24), with their extensive connections with hypothalamic, brain stem, and spinal autonomic structures, may be the effectors for

emotional arousal. The anterior cingulate areas are connected with brain stem vocalization structures (for reviews see Refs. 7, 110) and have a role in emotional communication, which may help explain their robust connections with auditory association areas.

THE ORBITOFRONTAL CORTEX IN HEALTH AND DISEASE

The connections of the orbitofrontal cortex equip it with information that makes it possible to navigate in a complex social environment, pursuing rewarding goals and avoiding dangers. The posterior orbitofrontal cortex, in particular, appears to be key in these complex functions by its diverse and specialized connections. The posterior orbitofrontal cortex may be viewed as the primary cortical area for emotional processing by its specialized connections with primary olfactory areas, rich connections with high-order sensory association and polymodal cortices, and highly specialized connections with the amygdala and memory-related temporal cortices.

The posterior orbitofrontal cortex, however, must collaborate with the rest of the prefrontal cortex, including areas on the lateral surface that have been implicated in cognitive and executive functions, and can be engaged for action. The posterior orbitofrontal cortex has robust and bidirectional connections with anterior orbitofrontal cortices,^{2,103} which are, in turn, linked with lateral prefrontal cortices^{2,103} in a pattern that suggests sequential processing of information. The posterior orbitofrontal cortex is also robustly linked with anterior cingulate areas, which innervate autonomic centers and may have a key role in the expression of emotions.

Based on the differences in their sets and pattern of connections, orbitofrontal and medial prefrontal areas may be affected in distinct psychiatric diseases. The anterior cingulate region, for example, has been implicated in schizophrenia, consistent with pathology in specific classes of neurons¹¹¹ and hypoactivation in anterior cingulate areas that are connected with auditory association cortices (reviewed in Ref. 7).

The orbitofrontal cortex has been implicated in a wide variety of psychiatric diseases, including anxiety, phobias, obsessive-compulsive disorder, depression, and psychopathic personality disorder (e.g., Refs. 112–114 reviewed in Ref. 115). These diverse diseases likely affect different nodes in the complex pathways that link the orbitofrontal cortex with other cortical and subcortical structures. The pathway from the orbitofrontal cortex to the intercalated masses of the amygdala, which has the potential to allow increase in autonomic gain, may be abnormally active in diseases marked by anxiety.

Projections from structures associated with sensory, mnemonic, and emotional processing to orbitofrontal cortex provide a rich content of information. By virtue of their structure, posterior orbitofrontal areas send robust feedback projections to sensory and other association cortices. In several

systems, feedback projections are thought to influence task-related activity.^{116–119} Pathology in orbitofrontal cortex may remove feedback input to association areas, dissociating emotional context from sensory, cognitive, and mnemonic content and degrading the ability to interpret events.

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