The Orbitofrontal Cortex

David H. Zald, Ph.D., Suck Won Kim, M.D.

Since the famous case of Phineas Gage, investigators have speculated that dysfunction of the orbitofrontal cortex (OFC) plays an important role in neuropsychiatric illnesses. Recent neuroimaging and neurophysiological studies increasingly support this speculation and implicate the OFC in several neuropsychiatric conditions. This chapter reviews the current state of knowledge on the neurocircuitry and function of the OFC with the aim of providing a framework for understanding how dysfunction of this region contributes to psychopathological conditions.

ANATOMY OF THE ORBITOFRONTAL CORTEX

The OFC comprises the ventralmost regions of the prefrontal cortex. Several gyri constitute the OFC of humans, including 1) the gyrus rectus, which forms the boundary between the ventral and medial surface of the prefrontal cortex; 2) the medial orbital gyrus, which runs lateral to the olfactory sulcus; 3) a central region, which is disrupted by the arcuate or transverse orbital sulcus (the regions anterior and posterior to the transverse orbital sulcus are often labeled the anterior orbital gyrus and posterior orbital gyrus, respectively, but some anatomists refer to this area more generally as the middle orbital gyrus); 4) a lateral orbital gyrus; and 5) the orbital portion of the inferior frontal gyrus on the lateral boundary of the ventral prefrontal surface (in some cases, there is no clear division between the lateral orbital gyrus and the inferior frontal gyrus pars orbitalis). The specific shapes of the orbital gyri and sulci vary substantially across individuals. Indeed, although prominent medial and lateral sulci usually can be identified in human brain samples, the common presence of additional or free-standing sulci, and the variability in the degree to which the gyri connect with the transverse orbital sulcus, often leads to confusion in labeling this region. Because of this, some neuroanatomical atlases generically label everything between the olfactory sulcus and inferior frontal gyrus as orbital gyri and label all of the sulci by the generic term orbital sulci.

Several different parcellation schemes exist for designating the different regions within the OFC. The most widely used parcellation scheme is that of Brodmann, who divided the OFC into two major regions (area 47 and 11) (see Figure 4-1). Unfortunately, Brodmann's system treats regions with substantially different cyto- and chemoarchitecture as if they were homogeneous. Other researchers who used classical histologi-
The frontal lobes and neuropsychiatric illness

![Diagram of the human orbitofrontal cortex (OFC) according to Brodmann.](image)

**Figure 4-1.** Left: Ventral view of the human orbitofrontal cortex (OFC) according to Brodmann. Right: The parcellation of Beck, in which area 11 is restricted to the anterior portion of the medial orbital gyrus and area 13 is defined in the posterior portion of the gyrus.

Note the wide area of the OFC that Brodmann treats as homogeneous. Additionally, Brodmann's area 47 has been subdivided into anterior and posterior regions based on the transition posterior-anterior gradient of granulization. Beck's system was never widely accepted but shows greater similarity to Walker's system in the macaque and shows a rough correspondence to Hof's chemoarchitectural parcellation.

Architectural techniques defined far more regions within the OFC. The precedence of Brodmann's system, combined with the significant individual differences in the specific topography of the OFC and the transitional nature of OFC architectural features, limited widespread acceptance of more detailed parcellation schemes in humans. However, the human OFC has several clearly definable features that allow reliable parcellation with greater precision than with Brodmann's system. At the most general level, the area consists of three broad zones, with a posterior agranular region, middle dysgranular region, and anterior granular region (see Figure 4-2). Using modern cyto- and chemoarchitectural techniques, Hof and colleagues recently provided a general parcellation scheme based on reliable and statistically definable divisions between OFC subregions. This system divides the OFC into anteromedial, posteromedial, medial-orbital (central), anterolateral, and posterolateral segments. As can be seen in Figure 4-2, the chemoarchitectural boundaries defined by Hof et al. do not map exactly to the agranular-dysgranular and dysgranular-granular boundaries. Parcellation systems that take into account additional chemoarchitectural subdivisions that have been defined in the monkey OFC are currently under development.

The nonhuman primate OFC shares many features in common with the human OFC, and much of what is known about the neurocircuitry of the OFC derives from studies in nonhuman primates. Walker divided the OFC into five separate areas in the macaque, which he numbered 10, 11, 12, 13, and 14 (Figure 4-3). Walker's system appears to correspond well with many of the features of Hof's parcellation of the human OFC. Table 4-1 lists the human OFC regions with their corresponding regions in the macaque. The cytoarchitectural features of the medial OFC regions appear extremely similar across primate species. Over the years, there has been greater disagreement on the extent to which the more lateral sections of the OFC reflect architecturally homologous regions across species, but the lateral segments of the OFC in human and nonhuman primates clearly share many features in common. Specifically, Walker's area 12 in the macaque shares homologous features with the inferior frontal gyrus and lateral orbital gyrus in humans. Some neuroanatomists now refer to this inferior frontal gyrus/lateral orbital gyrus area as 47/12 to highlight this commonality across primate species.
FIGURE 4-2. Parcellation of the human orbitofrontal cortex (OFC) by Hof et al.9
Large dots represent divisions between major chemoarchitectural areas. Thin dashed lines represent the transition points between agranular (posterior), dysgranular (middle), and granular cortex (anterior). Note that the chemoarchitectural divisions defined by Hof et al. do not match the architectonic transitions between the dysgranular and granular zones, and in some cases, transitions cannot be defined precisely but represent prototypical transition points. AL = anterior lateral; AM = anterior medial; FP = frontal pole; MO = medial orbital (central); PL = posterior lateral; PM = posterior medial; SO = sus orbital; OLF = olfactory tubercle. Arrow 1 = olfactory sulcus. Arrow 2 = MO sulcus. In this brain, the MO sulcus merges with the transverse orbital sulcus, which runs horizontally between the PM and MO sections (some anatomists refer to the sulcus labeled by arrow 2 as a PM branch of the transverse orbital sulcus because of its continuity with the transverse orbital sulcus). As is frequently the case, the lateral end of the transverse orbital sulcus joins with a perpendicular running sulcus, which is typically labeled as the lateral orbital sulcus. The labeling of the sulci in the AM and MO regions is less clear in this brain sample and displays some of the idiosyncratic features that can be observed in this region (arrow 3).

Based on detailed investigations of the cyto- and chemoarchitectural features of the OFC, Carmichael and Price\textsuperscript{13} divided Walker's areas into a series of subregions (Figure 4–4). This system labels the posterior agranular portion of the medial wall of the olfactory sulcus as area 13a. Just anterior to this lies a dysgranular region labeled 13b. The posterior third of the area between the medial and lateral orbital sulci forms area 13 proper. Carmichael and Price further subdivided this region into a lateral (13l) and a medial (13m) segment. Walker's area 12 is also subdivided into several separate subregions. The posterior orbital portion of area 12, which has only a thin, light, granular layer, forms area 12o. The more anterior regions of area 12 are composed of a rostral granular region (12r) and lateral and medial granular regions labeled 12l and 12m. Carmichael and Price also subdivided the band of agranular cortex at the posterior boundary of the OFC into five separate subregions, including a medial (lam), intermediate (lai), lateral (lal), posterior-lateral (lapl), and posterior-medial (lapm) segments. This region lies continuous with the insula, and they refer to it as an insular subregion. In this chapter, we use the term posterior agranular OFC to refer to this band of cortex. However, in referring to the specific subregions, we retain the nomenclature of Carmichael and Price.

Each of the subregions defined by Carmichael and Price in the macaque has a corresponding homologous subregion in the human brain.\textsuperscript{10} Although the exact boundaries of these subregions remain under study in humans, they show a relatively similar layout to that seen in the monkey. Human areas 13a, 13b, 13m, and 13l occur within the posterior-medial sector defined by Hof (refer to Figure 4–2), with areas 13m and 13l falling between the olfactory and the medial orbital sulci. Areas 11m and 11l lie anterior to this, with the division between 11m and 11l falling about halfway between the olfactory and the medial orbital sulci. Area 47/12m occupies much of the area between the medial and the lateral orbital sulci (Hof's postero-lateral and central areas), with 12r falling anterior to this in part of Hof's anterolateral area. Area 47/12l

---

**TABLE 4–1.** Correspondence between human and macaque parcellation systems

<table>
<thead>
<tr>
<th>Hof et al. (human)</th>
<th>Walker (macaque)</th>
<th>Brodmann (human)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontopolar</td>
<td>10</td>
<td>10, 11</td>
</tr>
<tr>
<td>Anteromedial</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Medial-orbital</td>
<td>12, 13</td>
<td>11</td>
</tr>
<tr>
<td>Posteromedial</td>
<td>13, 14</td>
<td>11</td>
</tr>
<tr>
<td>Posterolateral</td>
<td>13</td>
<td>11, 47</td>
</tr>
<tr>
<td>Sus-orbital sulcus</td>
<td>10, 11</td>
<td>12</td>
</tr>
</tbody>
</table>
appears mostly lateral to the lateral orbital sulcus. The homologue to the macaque 12o in monkeys falls posterior to this and appears buried in the rostral extension of the superior limiting sulcus, where it extends into the frontal lobe.

Unfortunately, the vast majority of studies reviewed in this chapter predate Carmichael and Price’s parcellation system in monkeys and its recent extension to the human OFC. Wherever possible, we use Carmichael and Price’s terminology because of its exquisite detail, but in situations in which such precision is lacking, we use Walker’s more general parcellation scheme. Many studies actually encompass more than one of Walker’s regions. The lack of specificity frequently results because the transition points between different cytoarchitectural regions in the OFC are often gradual, and substantial intra- and interspecies differences exist in the location of these transition points. Investigations often involve either a broad medial or a broad lateral segment of the OFC. Studies of the medial OFC generally encompass Walker’s area 13 and, to a greater or lesser extent, also may include part of area 14 and/or the medial part of area 11. Such investigations often focus on the posterior agranular-dysgranular portion of this area. The lateral OFC is generally viewed as consisting of the lateral portion of Walker’s area 11 and most or all of area 12. Although there exist marked differences in some of the innerva-
tion characteristics of areas 11 and 12, functional studies rarely distinguish between the two areas. Instead, lesion studies often involve a strip of cortex known as the inferior convexity. The inferior convexity includes the lateral part of area 11 and most or all of area 12 and, depending on the species and the cytoarchitectural system used, often intrudes on the ventral segment of area 46 along the inferior boundary of the principal sulcus. Unfortunately, the involvement of multiple regions in inferior convexity lesions frequently makes it difficult to determine the extent to which area 11, area 12, and ventral area 46 individually relate to many functions.

### SENSORY INNERVATION OF THE ORBITOFRONTAL CORTEX

The development of all prefrontal cortex areas in mammalian species derives from two prime moieties: a paleocortical moiety that evolved from a primitive olfactory core and an archicortical moiety that developed from hippocampal archicortex.\(^{14,15}\) These two moieties are distinguishable on both cytoarchitectural and functional grounds throughout the cerebral cortex. At a broad level, structures within the archicortical trend support functions related to the localization of stimuli in space, whereas structures within the paleocortical trend support stimulus recognition functions.\(^{15}\) Walker's areas 11, 12, and 13 derive exclusively from the paleocortical moiety. The primary source of sensory input into the OFC derives from cortical regions that also evolved from the paleocortical core. These connections provide the OFC with substantial sensory input from cortical regions involved in the recognition of stimuli. In contrast, the gyrus rectus forms a transition to portions of the medial prefrontal cortex that derive from hippocampal archicortex.

The OFC receives well-processed unimodal and polymodal, exteroceptive and interoceptive sensory information from every sensory modality (see Table 4–2). These afferents tend to follow a general pattern: more highly differentiated sensory association cortices project to the more differentiated regions of the OFC, whereas the more cytoarchitecturally primitive sensory association regions direct their projections to the agranular or dysgranular cortices in the more posterior OFC.\(^{5,6,16-19}\) This pattern provides the OFC with multiple parallel sensory projections originating from association cortices of different phylogenetic age.

### TABLE 4–2. Overview of primary and major secondary targets of sensory input to the orbitofrontal cortex

<table>
<thead>
<tr>
<th>Modality</th>
<th>Principal recipient regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory</td>
<td>Iam, Iapm, 13a, 13m</td>
</tr>
<tr>
<td>Gustatory</td>
<td>I1, Iapm, 13l</td>
</tr>
<tr>
<td>Visual</td>
<td>12l, 11</td>
</tr>
<tr>
<td>Auditory</td>
<td>12r, 12m, 11l</td>
</tr>
<tr>
<td>Somatosensory</td>
<td>12m, 13l</td>
</tr>
<tr>
<td>Visceral</td>
<td>Iapm, I1, 13a</td>
</tr>
</tbody>
</table>

*Note. See text for details.*

### Olfactory

The primary (pyriform) olfactory cortex and the anterior olfactory nucleus project extensively to the posterior agranular portions of the OFC. Areas Iam and Iapm receive the heaviest input from primary olfactory regions, but significant direct afferents also reach areas 13a, I1, and I1, and lighter projections directly reach areas 13m and Iapl.\(^{19,20}\) Although area 13m receives only a light direct projection from the primary olfactory cortex, it receives heavy indirect olfactory projections via the mediodorsal nucleus of the thalamus, pars magnocellularis (MDmc),\(^{21-24}\) and projections from areas Iam and Iapm.\(^{25}\) Together, these OFC regions act as a cortical association area for the olfactory system. Neurophysiological studies indicate that cells in olfactory recipient regions of the OFC show robust and often highly selective responses to olfactory stimuli.\(^{26-29}\) In fact, many if not most of the olfactory responsive cells in the OFC show far greater stimulus selectivity than is observed in the pyriform cortex and olfactory bulb. Lesions to the OFC in humans damage olfactory discrimination, identification, and recognition memory without altering olfactory detection thresholds.\(^{30-32}\) Olfactory identification abilities show relatively equal levels of deterioration following left and right OFC lesions. In contrast, olfactory recognition memory and discrimination appear specifically sensitive to right OFC lesions. Recent positron-emission tomography (PET) studies in humans also indicated that the OFC shows significant increases in activity during exposure to odorants.\(^{33-35}\) The right OFC is more consistently involved in olfactory processing, although the left OFC shows a substantial involvement in some olfactory tasks. For instance, the left OFC has activated during exposure to odorants with strong appetitive or aversive properties.
Gustatory

Rolls and colleagues\textsuperscript{36,37} identified a secondary taste association area within a caudally located dysgranular portion of the OFC, which appears to most closely correspond to area 13l. This region receives projections from both the frontal opercular taste cortex and the insular taste cortex.\textsuperscript{38} The agranular posterior regions lApr and lAl receive substantial gustatory information and project this information to dysgranular areas 13l and 13m.\textsuperscript{18,25,38} Area 13 differs dramatically from other gustatory cortical areas in that it lacks direct innervation from the thalamic taste region (ventral posterior medial nucleus). Instead, its thalamic input derives from the MDmc.\textsuperscript{24} The OFC taste region has both unimodal (gustatory) and polymodal (gustatory/olfactory and gustatory/visual) responsive cells.\textsuperscript{36,39,40} The convergence of olfactory and gustatory modalities in these regions distinguishes the OFC from primary taste areas that lack significant olfactory input. This suggests that the OFC provides an interface zone through which olfactory and gustatory information interact to determine the perception of flavor. As in the olfactory modality, gustatory responsive cells in the OFC show a high level of stimulus specificity. Many of the OFC gustatory cells respond to only one or two tastes.\textsuperscript{37} This differs dramatically from the responsivity to multiple gustatory stimuli that occurs in earlier gustatory processing stages. Functional neuroimaging studies have repeatedly confirmed the presence of a gustatory responsive area in the human OFC. However, the location of these responses often appears more anterior than the secondary gustatory area defined in the monkey.\textsuperscript{41}

Auditory

Well-processed auditory information arrives via the rostral superior temporal gyrus and the neighboring rostral auditory parabelt.\textsuperscript{12,46-50} This input principally innervates rostral-lateral (Walker’s area 12) sectors of the OFC, but auditory responses have been observed in both the lateral and the medial OFC. As is typical of OFC sensory processing, auditory-responsive cells in this region appear to have a high level of stimulus specificity, but information on this subject remains scarce. Specifically, the cells show a high degree of frequency selectivity.\textsuperscript{42} These cells occur close to cells responsive to other modalities, and many of the cells show bimodal responses.\textsuperscript{40,45} The nature of auditory processing in the areas projecting to the OFC suggests that the OFC may receive information about certain types of vocalizations. PET studies have found a clear involvement of the OFC in music perception.\textsuperscript{51,52}

Visual

Visual input reaches multiple subregions of the OFC through projections from inferior temporal visual association areas.\textsuperscript{17,18,42} These association areas represent the last stages of the ventral visual processing pathway dedicated to object recognition.\textsuperscript{43,44} The most prominent of these projections derives from area TE (VA2) in the inferior temporal lobe, which projects to area 12l and the adjacent ventral portion of area 46 (Figure 4–5).\textsuperscript{18} In contrast, more medial orbital areas (11 and 13) receive input from VA3, which occupies a more anterior portion of the inferior temporal cortex. VA3 represents a later stage in the ventral visual pathway than the area projecting to lateral area 12. Only a few studies have examined the visual properties of OFC cells. Cells in area 12l and ventral area 46 (which also reciprocally connects with area 12l) appear to have response properties similar to those of the inferior or temporal cortices that project to them. These cells respond best to foveal stimulation with complex stimuli such as objects or patterns.\textsuperscript{45,46} The medial OFC also possesses many visually responsive cells.\textsuperscript{47} As in the olfactory and gustatory domains, visually responsive cells appear in close proximity to cells responsive to other sensory modalities, and many of these cells show bimodal responses.\textsuperscript{40,47} To the extent to which they have been studied, visually responsive cells in the OFC also show a high level of stimulus specificity.

Somatosensory

Somatosensory projections innervate the OFC from the parietal operculum (including both SI and areas 1 and 2), the inferior parietal lobule (area 7b), and the posterior granular insula.\textsuperscript{13,15,24,53} These projections focus most strongly on area 12m, with additional projections reaching areas 13m and 13l. These projections convey somatosensory information for the orofacial area and the digits of the hand. Little is known about the nature of somatosensory coding in the OFC. Interestingly, the information about the orofacial area converges with gustatory information in area 13l and appears to convey information about the texture of food.\textsuperscript{54}

Viscerall

The OFC has long been known to receive interoceptive (somatovisceral) sensory information. As early as
1938, stimulation of the vagus nerve was reported to produce alterations in electrical potentials in the OFC of cats. The OFC probably receives viscer al information through multiple sources. The most substantial source involves projections from the ventral posterior medial nucleus of the thalamus (parvocellular division) to posterior agranular regions, specifically areas LPM and IAI. These regions in turn project to agranular and dysgranular regions of the OFC, including all subdivisions of areas 13 and 12. A second source of information involves a projection through the submedial nucleus of the thalamus. This projection relays information from the spinal cord and appears to provide the primary route through which visceral nociceptive information reaches the OFC. In lower mammals, the areas of the OFC receiving submedial inputs respond to visceral nociceptive information. To date, nociceptive responses in primates have not been examined. However, the projection of the submedial nucleus to the OFC is retained in primates and focuses on area 13a. Intralaminar and midline nuclei of the thalamus may additionally augment the visceral and autonomic information reaching the OFC. The submedial nucleus also appears to relay information from the trigeminal nerve. The function of this projection has received little attention, but it may relate to the burning sensation of trigeminal irritants and could provide a source for integrating olfactory and trigeminal coding of airborne chemicals. A final potential source of information on visceral states derives from connections with area 25, which is situated just above area 14c on the posterior medial wall. This area appears to represent a cortical center for the visceral motor system and possesses afferents and efferents directly associated with autonomic functions. The gyrus rectus (especially area 14c) and, to a lesser extent, areas IAI and 13a, connect with this region.

**Polymodal**

The OFC’s innervation by multiple sensory modalities implicates it as a critical convergence zone capable of integrating diverse sources of information. In general, each modality projects to specific subregions of the OFC. However, the pattern of interconnections between OFC subregions allows for substantial multimodal sensory integration. Cells in much of areas 13 and 12 have access to different combinations of olfactory, visceral, gustatory, somatosensory, visual, and auditory information depending on their specific connections. Additionally, the OFC receives polymodal information via projections from heteromodal areas of
the temporal pole and insula. Areas 13a, 1ai, and 12o also receive prominent projections from polymodal regions of the superior temporal gyrus. As already noted, the OFC possesses many bimodal and polymodal cells. The stimulus specificity of bimodal cells in the OFC has not been thoroughly examined. However, at least some of these cells show a high degree of stimulus selectivity across sensory domains. For instance, Thorpe et al. observed a cell that responded to both the sight and the taste of a banana but did not respond to either the sight or the taste of other foods.

ASSOCIATIONS

Medial Frontal Lobe and Cingulate Cortex

Because of its position at the boundary between the orbital and medial surface of the frontal lobe, investigators have often disagreed on whether to consider the gyrus rectus as part of the orbital or medial frontal cortex. In terms of its connections, the gyrus rectus has far more intimate connections with other medial frontal areas than with the OFC, indicating that if a categorization has to be made, then the gyrus rectus should be considered as part of a medial frontal network. However, the gyrus rectus has significant connections with the immediately neighboring medial OFC regions (13a and 13b). Areas 13a and 12o (which are themselves heavily interconnected) provide a critical interface between the medial and the orbital prefrontal cortex. These two areas have substantial, often bidirectional connections with both medial and orbital regions, indicating that they integrate or coordinate both medial and orbital activity. Three other areas on the orbital surface (11m, 10o, 1ai) connect primarily with the medial prefrontal cortex rather than with other OFC structures. Each of these three regions has strong connections with area 12o and/or 13a, further highlighting the importance of 12o and 13a in medial and orbital prefrontal cortex integration. Interestingly, areas 12o and 13a, along with area 1ai, show substantially different patterns of connections than other orbital regions. These differences include an exclusive input from polymodal regions of the superior temporal gyrus, as well as unique amygdala and thalamic projections.

Multiple portions of the cingulate cortex reciprocally connect with the OFC. The most prominent connections with the anterior cingulate (Walker's area 24) involve areas 12o laterally, area 1ai posteriorly, and areas 13a, 13b, and especially area 11m in the medial OFC. The posterior cingulate area also projects to the more granulated area 11m.

Dorsolateral Prefrontal Cortex and Posterior Parietal Cortex

The OFC has reciprocal connections with both the dorsolateral prefrontal cortex and the frontal eye fields. Dorsolateral prefrontal cortex connections derive primarily from the lower bank of the principal sulcus and the region ventral to the principal sulcus and are heavily associated with the more rostral and lateral granular areas of the OFC. The heaviest connections focus on area 12l. In the medial OFC, area 13a also receives a significant dorsolateral prefrontal cortex projection. Associations between the frontal eye fields and the OFC appear limited to the more granular portions of area 12. The spatial processing functions of the dorsolateral prefrontal cortex closely reflect its intimate reciprocal connections with the posterior parietal lobe. Similarly, the attention-related functions of the frontal eye fields appear highly dependent on the frontal eye field's connections with an adjacent area of the posterior parietal lobe. It is interesting to note that the parietal lobes have restricted connections with the lateral granular OFC and that these connections lie directly adjacent to dorsolateral prefrontal cortex and frontal eye field-labeled bands of the lateral OFC.

Orbitofrontal Cortex, Temporal Pole, and Insula

Mesulam and colleagues use the term paralimbic to describe the OFC, temporal pole, and insula. These three regions evolved as a series of concentric rings deriving from olfactory paleocortex (Figure 4-6). The rings consist of agranular cortex surrounding the olfactory core, granular cortex farthest from the core, and dysgranular cortex in between. Each ring within the OFC continues uninterrupted into the insula and temporal pole. Given this shared evolution, it is not surprising that the three regions have tight reciprocal connections. Specifically, the agranular-dysgranular portions of the posterior OFC show their strongest associations with the agranular and dysgranular sections of the temporal pole and insula, whereas more anterior granular portions of the OFC are primarily associated with granular regions of the temporal pole and insula. The three areas also show similar patterns of connections with other structures in the paleo-
cortical moiety. Specifically, the agranular-dysgranular regions in the OFC, temporal pole, and insula have a closer relation to limbic structures such as the amygdala, whereas granular regions show greater associations with structures that act as higher-order association cortices.

Based on commonalities in the connections and the effects of stimulation and lesions in these three regions, Mesulam and Mufson argued that these regions evolved as an integrated functional network engaged in integrating sensory information with inner motivational states.

**Amygdala-Orbitofrontal Interconnections**

The functions of the OFC are critically intertwined with the functions of the amygdala. A substantial literature implicates the amygdala in the process of evaluating the affective or behavioral significance of stimuli. The OFC and medial wall of the prefrontal cortex are the only regions of the prefrontal cortex that have strong connections with the amygdala. Amygdalar projections to the OFC focus on the agranular band in the posterior OFC; areas 13a, 13b, and 12c; and the gyrus rectus. Few amygdalar fibers reach area 13 proper or area 11, and only light projections reach the more anterior and lateral portions of area 12. Amygdalar fibers reaching the OFC derive largely from the basolateral nucleus of the amygdala, with additional projections arriving from the basolateral nucleus and to a lesser extent the dorsomedial part of the lateral nucleus (Figure 4–7). Retrograde tracing data further indicate that different sections of the basolateral nucleus project to different subregions of the OFC based on the subregion’s level of connection with the medial prefrontal cortex.

Studies of the afferent, efferent, and intrinsic connections of the amygdala have identified a critical pathway through which information proceeds through the amygdala. The lateral nucleus acts as a crucial zone of sensory input, whereas the central nucleus is the major source of efferents to brain stem and hypo-
thalamic structures controlling a spectrum of endocrine, autonomic, and involuntary behavioral responses.\textsuperscript{74,75,80} The vast majority of information flow from the lateral nucleus travels through the basolateral and basal accessory nucleus before reaching the central nucleus (Figure 4–8). As a recipient of lateral, basolateral, and accessory basal innervation, the OFC receives information from the critical input and sensory/response interface zones of the amygdala. In return, the OFC sends prominent projections back to the basolateral and basal accessory nuclei of the amygdala.\textsuperscript{77,80} The majority of the OFC-amygdala interaction involves this sensory/response interface zone. However, the caudal OFC also projects directly to the central nucleus of the amygdala, providing a route through which the OFC may exert a direct influence on the amygdala’s output.\textsuperscript{81}

A less substantial amygdala projection derives from the medial and anterior cortical nuclei of the amygdala. These nuclei represent the “olfactory amygdala” because they retain afferents from the primary olfactory cortex and/or the lateral olfactory tract.\textsuperscript{22} They primarily project to the agranular areas in the posterior OFC (Ial and Iapm), with sparse projections reaching areas 13a, 13b, and 14c from the anterior cortical nucleus.\textsuperscript{66} A secondary pathway through the MDmc provides an indirect, but substantial, route through which the amygdala directs information toward the OFC.\textsuperscript{21,23,79} All regions receiving direct amygdalar input receive indirect input via the MDmc. In addition, areas 11 and 13 proper, which receive only sparse and patchy direct amygdalar input, receive input from regions of the MDmc that are innervated by the amygdala.\textsuperscript{23}

**Medial Temporal Lobe**

The OFC was once thought to lack prominent connections with the hippocampus. However, a region
near the border of the subiculum and the CA1/CA3 region of the hippocampus send a projection to the medial OFC (particularly areas 13a, 13b, and 14c, with lighter projections to 14r and 11m).⁷,⁶⁶,⁸²,⁸³ There is some controversy over whether the area sending this projection should be defined as CA1/CA1' or the subiculum, although its staining features appear more consistent with CA1/CA1' than subiculum. The OFC does not directly reciprocate these projections but instead sends fibers to the entorhinal, perirhinal, and parahippocampal regions, which in turn project to the hippocampus (Figure 4–9). The OFC’s reciprocal connections with the entorhinal cortex appear particularly important in this regard and largely focus on the agranular regions in the posterior OFC and medial areas 13a, 13b, 14c, and 11m.⁷,⁶⁶,⁸⁴ The reciprocal parahippocampal connections largely overlap with the medial regions receiving direct hippocampal projections.⁶⁶,⁸⁵ In contrast, the reciprocal perirhinal projection to the OFC primarily involves the posterior agranular OFC and areas 13m and 13l.⁶⁶,⁸⁴

**FIGURE 4–9.** Schematic of the orbitofrontal cortex’s (OFC’s) interconnections with the hippocampal complex. lai = intermediate; lal = lateral; lam = medial; lapm = posterior-medial.
Hypothalamus and Brain Stem

In addition to its connections to the amygdala, the OFC projects to several areas critically involved in the coordination of autonomic and behavioral responses to emotional stimuli. The lateral hypothalamus represents a major output channel for the limbic system. The lateral hypothalamus, and to a lesser extent the medial hypothalamus, send nonselective projections to much of the OFC. In contrast, posterior and medial areas of the OFC selectively innervate the lateral hypothalamus. The densest frontal lobe projections to the hypothalamus derive from structures along the ventromedial wall (especially area 25). Areas on the orbital surface that are heavily connected with the ventromedial wall, such as the gyrus rectus and areas 13a and 1a, provide a dense projection to the hypothalamus. Lighter projections also reach the hypothalamus from other sectors of the OFC, including 12o and the other subregions of area 13. This pattern of connections indicates that the OFC (particularly the posterior and medial OFC) can directly influence hypothalamic output channels.

The OFC subregions that send strong projections to the lateral hypothalamus also innervate the ventrolateral column of the periaqueductal gray. Taken together with its hypothalamic projections, these connections indicate that the OFC influences two of the most critical structures involved in activating visceral responses to emotionally salient stimuli. Interestingly, the same areas of the lateral hypothalamus and periaqueductal gray that receive OFC projections also receive projections from the central nucleus of the amygdala. Thus, the OFC not only interacts with the amygdala but also appears capable of directly manipulating some of the same output pathways as the amygdala. The caudal section of the OFC additionally sends a projection to the septal region. This may allow the OFC to influence processing within the septum, which has long been known to play a role in modulating certain types of aggression. Taken together with its lateral hypothalamic and periaqueductal gray connections, the OFC is thus well positioned to exert an influence over multiple areas involved in responses to emotionally salient stimuli.

Orbitofrontal Cortex and the Thalamus

The mediodorsal nucleus is the primary source of thalamic input to the OFC. These projections derive primarily from the MDmc, which projects to the OFC in a topographically organized manner. Projections from the MDmc to areas 11, 12o, 12 proper, 13a, 13b, and 13 proper are reciprocated by significant projections from the OFC to the MDmc. Similar to their distinction in amygdala connections, areas 13a, 12o, and 1a connect with portions of the MDmc that primarily connect with the medial prefrontal cortex rather than with the rest of the OFC. Area 13a also receives projections from the submedial nucleus, which lies ventral to the mediodorsal nucleus. On the other hand, area 121 receives projections from the most medial edge of the parvocellular division of the mediodorsal nucleus, which is consistent with its close involvement with the dorsolateral prefrontal cortex.

Multiple structures project indirectly to the OFC via the MDmc. These structures include the amygdala; temporal pole; primary olfactory, entorhinal, and perirhinal cortices; substantia innominata (including the ventral pallidum); and lighter projections from the superior and inferior temporal gyri and the insula. It is unlikely that the MDmc acts as a simple relay station for these structures because all of these areas (with the exception of the substantia innominata) also project directly to the OFC (Figure 4–10). Although projections to the OFC and the MDmc appear to arise from similar cortical and subcortical regions, there appears to be a difference in the nature of the cells projecting to the MDmc and OFC, respectively. Direct projections to the OFC arise from numerous small cells, whereas projections to the MDmc derive from a few sparsely labeled large neurons with long, radiating dendrites. This suggests that the direct projections to the OFC may be more suited for carrying detailed information, whereas projections to the MDmc may carry more integrated information.

In contrast to the combination of direct and indirect projections that characterizes most input into the OFC, the substantia innominata (including the ventral pallidum) only influences the OFC via projections to the thalamus. Lacking direct projections to the OFC, this transthalamic projection appears to be the primary route through which basal ganglia functions influence the OFC.

The medial structures of the OFC, which receive projections from the subiculum, also receive a projection from the anteromedial nucleus of the thalamus. The same portion of the anteromedial nucleus that projects to the OFC also receives a projection from the subiculum. The triangular arrangement of the hippocampus, anteromedial thalamus, and OFC thus parallels the triangular arrangement of the amygdala, MDmc, and OFC. Some less significant projections
also reach the OFC from the pulvinar, midline, and intralaminar nuclei. The association with the pulvinar appears relatively limited to granular (visual recipient) OFC regions. In contrast, midline and intralaminar nuclei only project to the poorly granulated medial areas. These midline and intralaminar nuclei appear to transfer information related to noceptive, autonomic, and visceral functions and likely provide a transthalamic pathway through which the medial OFC receives interoceptive information.

Orbitofrontal Cortex–Basal Ganglia Loops

Both the lateral OFC and the medial OFC direct significant projections toward the basal ganglia. These projections contribute to a pair of segregated loops connecting the OFC, striatum, globus pallidus, and thalamus. In both cases, the flow of information follows a unidirectional course from the OFC to the striatum to the globus pallidus and then returns to the OFC via projections through the MDmc and, to a lesser extent, the ventral anterior thalamic nucleus. The lateral OFC loop originates with a projection from the lateral OFC to a ventral and central strip of the head and body of the caudate nucleus and a medial portion of the putamen (Figure 4–11). The same region of the striatum also receives projections from the superior and inferior temporal (auditory and visual) association cortices. In contrast, the medial OFC loop projects to a more extreme ventromedial segment of the caudate extending into adjacent portions of the putamen and other aspects of the ventral striatum (Figure 4–12). The ventral striatum consists of the nucleus accumbens, part of the olfactory tubercle, and the extreme edge of the ventral caudate. It primarily receives projections from limbic and paralimbic regions, including the basolateral nucleus of the amygdala; the anterior cingulate; and entorhinal, perirhinal, and temporal lobe structures. Thus, many of the key structures that interact with the lateral OFC project to the same region of the striatum that is innervated by the lateral OFC, whereas the key structures that interact with the medial OFC project to the same region of the caudate and ventral striatum that is innervated by the medial OFC.

The medial OFC targeting of the ventral striatum likely plays a critical role in its ability to influence motivation-related functions. A wealth of evidence implicates the ventral striatum, specifically the nucleus accumbens, in brain-reward mechanisms activated by habit-forming drugs, other reinforcers, and the initiation of behaviors aimed at gaining these reinforcers. The posterior agranular OFC (area 13/anterior insula) also sends a highly selective projection to the “striosomes” of the striatum. Along with the agranular medial prelimbic regions, these form the only prefrontal projections to the striosomes. This projection is of interest because the striosomes appear to project directly to the dopamine-containing cells of the substantia nigra or its immediate vicinity, allowing the posterior OFC to selectively modulate the firing of dopamine projections to the basal ganglia. This may allow the OFC to play a selective role in controlling the initiation of basal ganglia–controlled processes. These projections, along with the other OFC projections to the “matrix” compartments of the basal ganglia, also may allow the OFC to influence the initiation of routinized, sequential, or habit-based processes typically attributed to striatal functioning.

FUNCTIONAL CHARACTERISTICS OF THE ORBITOFRONTAL CORTEX

The anatomical characteristics of the OFC provide the basis for the OFC’s involvement in normal functioning and psychopathology. The area forms a critical convergence zone for exteroceptive sensory association cortices, interoceptive information, limbic regions involved in emotional processing and memory, and subcortical regions involved in the control of auto-
nomic and motor effector pathways. Sensory information is already well processed by the time it reaches this region, and the OFC codes this information with an exquisite level of stimulus specificity. Yet, it is clear that with the exception of the olfactory modality, the region is less involved in perception per se. Rather, the region is involved in the recognition of biologically significant stimuli and their associates and modulating responses to these stimuli based on the current motivational state of the organism.

**RECOGNITION OF REINFORCING STIMULI**

**Cellular and Behavioral Responses to Appetitive Reinforcers**

Food is a powerful reinforcer. The gustatory projections to the OFC provide specific information about the physical properties of food, whereas projections from other sensory areas provide information about stimuli associated with food. This convergence of information provides the ability to make cross-modal associations related to food reward. OFC cells that fire in response to visual presentation of reinforcing foods provide a clear demonstration of this capacity. These cells often show bimodal responses to both the taste and the sight of food. Cells that respond to the visual presentation of appetitive stimuli also exist in the lateral hypothalamus, the substantia innominata, and the amygdala. However, the cells in the OFC show a far greater level of stimulus specificity than do cells in these other regions. Cells with responses to visually presented food or aversive stimuli in the substantia innominata, lateral hypothalamus, and amygdala generally respond to multiple aversive or hedonic stimuli, whereas OFC cells have been observed to respond to as few as one appetitive stimulus.

A similar process of association occurs between olfactory and gustatory information in the OFC. The robust ability to associate odors with foods likely reflects the anatomical proximity of secondary taste
cortex and olfactory-dedicated areas of the OFC. Lesions of the OFC cause marked alterations in food preferences and impair the discrimination of food from nonfood objects.\textsuperscript{111–113} For instance, OFC-lesioned monkeys will eat foods such as raw meats that nonlesioned monkeys treat as unpalatable.\textsuperscript{111,113} These animals also show a hyperorality in which they both place nonfood objects in their mouths and show a readiness to eat nonfood items.\textsuperscript{112,114} This hyperorality resembles aspects of the Klüver-Bucy syndrome arising from bilateral temporal lobectomy (amygdalectomy).\textsuperscript{115} OFC-lesioned animals appear to treat these nonfood objects as if they had the same reinforcement value as food, and they will even perform operant responses at high levels in order to eat them.

By far, the most commonly used appetitive reinforcer in behavioral and neurophysiological studies is food. During the course of studies that use food reward, cells in the OFC frequently respond to the presentation of food reward or stimuli that signal upcoming food reward.\textsuperscript{47,116–118} This reinforcement-related activity occurs in both the lateral and the medial OFC. The OFC’s responsiveness to appetitive stimuli is not limited to food reward. Intracerebral self-stimulation has been widely used to map the neural network involved in reward.\textsuperscript{119} The only region of the neocortex in primates that reliably supports intracerebral self-stimulation is the OFC. Self-stimulation sites are primarily found in the posterior-medial OFC (area 13).\textsuperscript{119} These intracerebral self-stimulation sites are closely connected to intracerebral self-stimulation sites in the amygdala, lateral hypothalamus, and nucleus accumbens. Indeed, intracerebral self-stimulation of area 13 activates lateral hypothalamic cells, and intracerebral self-stimulation within the lateral hypothalamus or nucleus accumbens activates cells within the posterior OFC.\textsuperscript{119} Dopamine antagonists injected into the OFC dose-dependently attenuate the operant responding for intracerebral self-stimulation in the OFC.\textsuperscript{120} These OFC injections also significantly
decrease operant responding for intracerebral self-stimulation in the amygdala and the lateral hypothalamus. Thus, the OFC is intimately connected to other regions in the brain's reward network and appears to directly influence the ability of these regions to support intracerebral self-stimulation.

An important aspect of the OFC's cellular responses to food reinforcers and intracerebral self-stimulation lies in the reduction or cessation of these neuro-physiological responses when the motivational or affective value of these stimuli decreases. For instance, many OFC cells that show activity in response to specific foods when an animal is hungry become unresponsive or show substantially reduced responsiveness after the animal has been satiated on that specific food.\textsuperscript{121} Similarly, OFC cells that respond when a thirsty animal receives fluids show decreased firing when the animal is no longer thirsty. The gustatory processing that occurs in the OFC differs dramatically from what is seen in the earlier stages of the gustatory system, where activity occurs independent of motivational state.\textsuperscript{122-124}

Sensory-specific satiety also extends into the visual and olfactory domains. OFC cells that respond to the sight or taste of a specific food decrease or cease firing when the animal sees or smells the food after being fed to satiety.\textsuperscript{125} These findings indicate that the activity of these cells does not just reflect a process of cross-modal sensory integration but rather reflects the current motivational or reinforcement value of the gustatory stimuli.

In nonlesioned animals, the readiness to perform operant responses for food reward inversely relates to the animal's level of satiety. Animals without lesions significantly reduce their operant responding for food when satiated. In contrast, animals with lesions that include the OFC do not show as great a decrement in operant responses when satiated.\textsuperscript{126} These animals sometimes have seemingly insatiable appetites.\textsuperscript{126,127} Similarly, several case reports have noted the presence of voracious appetites in humans following OFC lesions.\textsuperscript{128-132} The exact focus within the OFC necessary to produce this effect is not clear, although some reports suggested that damage to the more anterior regions of the OFC or the frontal poles forms the critical focus in these cases.\textsuperscript{132}

Satiety not only decreases operant responses for food but also attenuates operant responses for intracerebral self-stimulation in the OFC and the lateral hypothalamus.\textsuperscript{133} This highlights the close linkage between reward and gustatory processing at the level of the OFC. Furthermore, it suggests that the OFC's modulation of the primary reinforcement value of food reward reflects a more general role in processing the reward value of appetitive reinforcers. Indeed, the OFC appears to process information about positively valenced stimuli in every sensory modality. Even in the somatosensory modality, greater OFC activity emerges during exposure to pleasant stimuli than during neutral stimulation.\textsuperscript{134} Thus, while responses to food-related stimuli provide one of the easiest to observe manifestations of OFC processing, it probably represents a more general process that affects all classes of appetitive reinforcers.

**Cellular Responses to Aversive Stimuli**

Some OFC cells respond to olfactory, gustatory, and visual stimuli that act as unconditioned or conditioned aversive reinforcers.\textsuperscript{28,47} The lateral hypothalamus, amygdala, and substantia innominata also have cells that respond to the visual presentation of aversive stimuli.\textsuperscript{107,108,110,135} As is the case in the processing of appetitive reinforcers, the cells in the OFC process aversive stimuli with greater specificity than do the cells in these other areas. Whereas cells in these other regions respond to multiple aversive stimuli, OFC cells respond to as few as one aversive stimulus. Studies examining aversive responses in the primate OFC have primarily focused on aversive gustatory stimuli (e.g., an aversive saline solution). However, data in lower mammals further indicate that OFC cells respond to somatovisceral nociception.\textsuperscript{57} Thus, both interoceptive and exteroceptive stimuli with aversive properties activate OFC cells.

Olfactory stimuli may possess unconditioned aversive properties. Some cells in the primate OFC respond to aversive odors.\textsuperscript{28} In a PET study of olfactory hedonics in humans, aversive odors produced significant increases in left posterior-lateral OFC activity, and the magnitude of the increase correlated significantly with ratings of aversiveness.\textsuperscript{33} Interestingly, this increase also correlated with activity in the left amygdala, indicating that humans retain the close functional relationship between the OFC and the amygdala seen in nonhuman primates. Aversive gustatory stimuli also have been observed to activate the OFC in humans.\textsuperscript{136} Surprisingly, this activation occurs far more anteriorly than the caudolateral OFC and thus appears to represent activity within a section of the OFC other than that described as secondary gustatory cortex by Rolls and colleagues.\textsuperscript{36-38}
STIMULUS-REINFORCER LEARNING

Amygdala–Orbitofrontal Cortex Interactions in Creating Stimulus-Reward Associations

In many cases, OFC neurons only respond to a sensory stimulus after it has become associated with an appetitive or aversive reinforcer. For instance, Thorpe et al. observed an OFC cell that responded to the visual presentation of a syringe only after the syringe had become associated with an unpleasant-tasting fluid. Many olfactory-responsive cells in the OFC have activity patterns that reflect stimulus-reinforcer learning. A recent neurophysiological study reported that approximately 35% of the olfactory-responsive neurons in the OFC depend on the association of odorants with a rewarding or aversive gustatory stimulus. Such neurons may code for incidental associations, such as the place where the rewarded odorants occur.

Lesions of the OFC impair the ability to directly associate visual stimuli with food reward (without relying on a secondary reinforcer). Lesions of the amygdala produce impairments of similar severity to those produced by lesions of the OFC. Similar impairments also arise following lesions of the MDmc. Thus, lesions at any point in the triangular circuit connecting the amygdala, OFC, and MDmc disrupt the ability to make direct stimulus-reinforcer associations.

Despite its involvement in directly associating visual stimuli with food reward, the OFC is not essential for the acquisition of numerous tasks involving reinforcement. Conditioning of operant responses and fear conditioning to contextual cues are both acquired at normal levels in the face of OFC damage. Similarly, OFC-lesioned animals perform tasks such as the positional response task and temporal reinforcement schedules at normal levels. Medial OFC lesions also leave many visual and auditory discrimination tasks unimpaired. Thus, despite the OFC’s critical participation in directly associating stimuli with reward, many tasks and conditioning paradigms can proceed without OFC involvement. This parallels findings from nonhuman primates with amygdala lesions, which showed intact learning of tasks that allow secondary or indirect associations with reward, despite impairments in direct stimulus-reinforcer learning.

Coding Changes in Reinforcement Contingencies

Many OFC cells show alterations in their firing pattern that coincide with alterations in reinforcement contingencies. For instance, on a go/no-go visual discrimination task, in which visual stimuli were associated with food reward and aversive saline, respectively, 71% of the cells (mainly lateral OFC cells) that selectively responded to the visual stimuli reversed their firing pattern when the visual-gustatory pairings were reversed. These changes occurred extremely rapidly (sometimes after only one trial) and usually coincided with or preceded behavioral reversal. Another 23.5% of the visually responsive cells showed extinction of differential responses after the reversal. In a similar paradigm involving the olfactory-responsive cells of the OFC (primarily medial OFC), 25% of the odor-responsive cells showed full reversal of their firing after reversal of the stimulus association, whereas 43% showed extinction of selective responding to the stimuli. These physiological and behavioral reversals and extinctions in the olfactory domain take substantially longer than the rapid reversals and extinctions in the visual domain.

In addition to possessing cells that show reversals and extinctions, the OFC has cells that fire when there is a discrepancy between the expected reward and the actual consequences of a behavior. For instance, Rosenkilde et al. observed “error detection” cells in the OFC that did not fire when a response was rewarded but fired vigorously after responses if the expected reward was withheld. After a few extinction trials, the firing decreased, suggesting that the cells were primarily involved in registering the absence of an expected reinforcer. A similar pattern of activity occurs in response to the removal of food or preferred objects. Most “error detection” or “reinforcer withdrawal” cells localize to the medial OFC, although a few error detection cells of this sort have been reported in the anterior cingulate. A subpopulation of reinforcement-sensitive cells in ventral area 46/lateral area 12 also appear sensitive to changes in reinforcement contingencies. These cells have been observed to respond to unreinforced trials with changes in firing activity opposite to their firing on reinforced trials.

Orbitofrontal Cortex Involvement in Extinction and Reversal

Error detection cells and cells that extinguish selective responding following changes in reinforcement contingencies likely play a critical role in the OFC’s ability to modify behavior when reinforcement contingencies
change. Lesions encompassing or focused on the medial OFC (especially Walker’s area 13) result in a marked tendency toward continued (perseverative) responding in extinction paradigms.\textsuperscript{114,126,143,151}

The medial OFC’s role in reversal learning is more complicated. Medial OFC–lesioned animals are not impaired in learning an initial reversal.\textsuperscript{148,151} However, these animals often have difficulty acquiring subsequent reversals.\textsuperscript{148,152} This deficit arises only after both stimuli have been associated with reward and nonreward. In such situations, a simple associative process alone cannot be used for determining which stimulus is the correct one to respond to because both stimuli have been associated with reward and nonreward. Rather, some mechanism for retaining or using information about the most recently reinforced object is required. The reliability and focus of this multiple reversal deficit remain in question. Restricted lesioning of the posterior medial OFC or more anterior OFC areas produce no impairment or only mild impairment on reversal tasks.\textsuperscript{151} The lesions that produce multiple reversal deficits appear more widespread than those that do not and may involve a more laterally placed area of the OFC. However, the perseverative pattern of errors typically observed following lateral OFC lesions was not observed in these animals.

In contrast, inferior convexity lesions produce severe impairments in the acquisition of spatial and object reversals and alternations.\textsuperscript{148,151,153–155} A major cause of this impairment has been traced to the strong tendency for inferior convexity–lesioned animals to perseveratively respond to stimuli.\textsuperscript{148,155} This perseverative behavior occurs on such a wide variety of tasks that it is often viewed as a defining characteristic of intracerebral lesions.\textsuperscript{156} Originally, this behavior was described in terms of a “drive disinhibition” syndrome because the response occurred in the context of perseverative go responses in go/no-go paradigms.\textsuperscript{132,157} However, the drive disinhibition hypothesis fails to explain why inferior convexity–lesioned animals respond perseveratively on two choice alternation tasks\textsuperscript{148,153,154} or why these animals engage in perseverative nonresponding following reversals of go and no-go stimuli.\textsuperscript{158,159} A simple inability to inhibit motor responses cannot explain these impairments. A consistent component of tasks on which inferior convexity–lesioned animals perseverate is the requirement that the animal alter its behavior away from a predominant or previously reinforced response style.\textsuperscript{156,160} In order to do this, an animal must recognize that the previously rewarded or predominant response is not generating the expected reward and then use this information to select a different response. The presence in the lateral OFC of cells responsive to the withholding of reward (or showing rapid reversal for reward and punishment) could provide a basis through which response failures get coded.\textsuperscript{117,118} The inferior convexity region also has cells that show activity correlated to both go and no-go responses.\textsuperscript{117,161} The region is thus in a position to act as an interface between error detection and response selection. Inferior convexity–lesioned animals who lack this interface would be unable to modulate their behavior appropriately in the face of changing reinforcement contingencies.

In contrast to the effects of medial OFC lesions, lesions of the lateral OFC do not impair extinction learning.\textsuperscript{151} The lateral OFC and medial OFC thus appear to play complementary and dissociable roles in situations in which rewards are withheld. The medial OFC appears necessary for normal extinction, whereas the lateral OFC is required for modulating behavior in situations in which more than one choice (including no response) is reinforced over time. Interestingly, error detection cells in the medial OFC show different neurophysiological features than do lateral OFC error detection cells.\textsuperscript{118} Medial OFC error detection cells frequently fail to respond except when reward is withheld. In contrast, the error detection cells in the lateral OFC alter their firing in response to both reward and nonreward.\textsuperscript{118} This difference between lateral and medial OFC cells may relate to differences in the ease of extinction and reversal in the olfactory and visual domains. Although reversal and extinction cells are observable in both the medial and the lateral OFC, the medial region is more involved in olfaction, and more olfactory-responsive cells extinguish rather than reverse their firing following a reversal in olfactory–gustatory reward reinforcement contingencies.\textsuperscript{137} In contrast, visually responsive cells, which are more prominent in the lateral OFC, more frequently reverse rather than extinguish their firing.

The OFC’s ability to reverse and extinguish firing to reinforcers, especially its ability to rapidly reverse firing to visual stimuli, critically distinguishes it from other areas involved in stimulus-reinforcer associations. For instance, the amygdala, which is clearly involved in forming stimulus-reinforcer associations, does not show equivalently rapid reversal abilities.\textsuperscript{162} Because of this, normal OFC processing becomes paramount in situations in which reinforcement changes occur too rapidly for the amygdala to alter its less fluid stimulus-reinforcer associations. The OFC’s involve-
ment in fluidly coding changes in stimulus-response
reinforcer contingencies appears to relate directly to
many of the deficits observed in humans with OFC le-
sions. Humans with OFC lesions show both reversal
and extinction deficits similar to those seen in nonhu-
man primates. Moreover, the degree of impairment
on these tasks is associated with the social and emo-
tional dysfunction that characterizes OFC-lesioned
patients.

Coding of Expectancies and
Relative Reward Value

As already noted, the OFC has cells that code when ex-
pected reinforcers are withheld. This indicates that the
OFC processes information about not only reinforcers
that are currently present but also expected (future) re-
inforcers. Single-cell studies have directly observed
cells in the OFC that fire in anticipation of appetitive
or aversive reinforcers. During instrumental
learning, these cells appear to modify their firing even
before the animal has learned to reliably perform the
reinforced behavior. Thus, the cells are not merely fir-
ing as a consequence of learned behavior. Rather, they
appear to provide information about reinforcers that
helps guide the learning of the behavior.

Schultz and colleagues have conducted some of
the most thorough investigations of expectancy represen-
tations in the OFC. They used a delayed go/no-go
task with monkeys and observed OFC cells that fire
during the period preceding a reward and terminate
soon after the receipt of the reward. These cells fire af-
after the animal has already performed the necessary
movement or nonmovement and thus do not reflect
what the animal did. Strikingly, these cells show pro-
longed activity if the reward is delayed and abbrevi-
ated activity if the reward arrives early. Thus, these cells
appear specifically linked to the anticipation of the re-
ward, with their onset occurring once the reward is re-
ceived.

To date, the neural bases of expectancies have re-
ceived little attention in the cognitive neuroscience lit-
erature. However, a recent PET study suggests that the
human OFC becomes active during breaches in ex-
pectancies. This converges with the primate litera-
ture indicating the presence of OFC cells that specifi-
cally fire when expected outcomes fail to materialize.
In many cases, the OFC’s processing of rewarding
stimuli does not consist of a simple representation of
the reinforcer. Instead, many reward-related cells in
the OFC appear to code for the relative reward value
of stimuli. Thus, the OFC not only participates in
determining whether a rewarding stimulus (or its as-
associated conditioned stimulus) is present but also
codes for the reinforcer’s relative reward value. Not
surprisingly, animals with OFC lesions are unable to
modify their behavior during reinforcer devaluations.

EMOTIONAL AND SOCIAL BEHAVIOR

Effects of Lesions on Emotional
Behavior in Animals

OFC lesions produce robust alterations in emotional
behaviors in animals. In cats, prefrontal lesions that
impinge on the OFC produce a general lowering of
thresholds for emotional reactions, especially rage re-
actions. OFC lesions in vervet monkeys produce in-
creases in aggressive responses in certain settings,
but lesions in rhesus monkeys produce robust long-
term and stable decrements in aggressive responses
and increases in fearful withdrawal. In rhesus
monkeys, the posterior portion of Walker’s area 13 ap-
ppears to represent the critical lesion site for producing
these behavioral alterations. In both species, the ani-
imals show increased social withdrawal. This has most
closely been observed with vervet monkeys who show
dramatic decreases in social grooming and other affil-
iative behaviors as well as substantial declines in so-
cial rank. In summary, OFC lesions produce robust
changes in affiliative and other emotional behaviors in
animals. The specific changes differ depending on the
species and probably the size and location of the lesion
focus, but the lesions consistently reduce the ability to
function within a social environment.

Effects of Lesions on Affect in Humans

OFC lesions in humans produce alterations in a wide
range of affective behavior. Approximately half
of the patients with bilateral or right OFC lesions in
one study required psychiatric treatment. In con-
trast, unilateral left OFC lesions appear to produce less
dramatic psychiatric problems than do right lesions.
Patients with right OFC lesions appear particularly
susceptible to increases in negative emotions, report-
ing heightened incidences of depression, anger, irrita-
bility, and anxiety. OFC lesions also appear to lead to
increased overt hostility and verbal aggressiveness, al-
though subjects with these lesions sometimes show lit-
tle awareness of their increased aggressiveness.
In contrast to the increased negative emotionality associated with OFC lesions, euphoria, exuberance, and hyperactivity sometimes increase as a consequence of reduced OFC functioning.\textsuperscript{176,177,180} These intense affective responses may reach maniac-like levels. Alternatively, patients may show a global heightening of emotional responsivity to socially relevant stimuli. Intense (pseudobulbar-like) emotional expressions disconnected from relevant social stimuli also may occur in such individuals. For instance, Damasio and Anderson\textsuperscript{182} described a patient who would frequently laugh or cry in social situations despite the absence of humorous or sorrowful stimuli. When questioned while laughing or crying, the patient denied feeling particularly happy or sad. Paradoxically, a blunting of affect sometimes occurs following these lesions.

The Pseudopsychopathic Personality

The alterations in emotional responsivity that occur in humans with OFC lesions are frequently accompanied by a characteristic pattern of social disinhibition.\textsuperscript{1,173,182–184} OFC-lesioned patients often are described as coarse, tactless, and generally lacking in empathy and social restraints. Reports of excessive involvement in pleasure-seeking behaviors, especially sexual behaviors, are common with such individuals. This excessive involvement in pleasurable activities is compounded by an apparent reduction in sensitivity to negative risks. Reports of patients making risky business decisions with disastrous consequences, despite the advice of others, repeatedly appear in the literature. In addition, these patients show impulsive and antisocial behavior. However, despite an apparent disregard for social rules, they usually lack the intentional viciousness or organization of a true antisocial personality disorder.\textsuperscript{182} Blumer and Benson\textsuperscript{173} aptly referred to these lesion-induced personality traits as “pseudopsychopathic.”

The functional basis of the pseudopsychopathic personality is unclear. But several clear deficits emerge with regularity in OFC-lesioned patients that may explain some of these behaviors. First, patients with OFC lesions show a marked loss of empathy.\textsuperscript{185} Second, humans with OFC lesions show impairments in emotional facial and vocal identification.\textsuperscript{186} Thus, these patients not only lack empathy for others but also have substantial difficulties identifying the emotional experience that others are experiencing based on emotional cues. Saver and Damasio\textsuperscript{193} examined a “pseudopsychopathic” patient with ventromedial lesions on a series of probes of social reasoning. Compared with control subjects, this patient showed no deficits in moral or social reasoning, and the patient’s ability to consider response options and predict the consequences of these responses was normal.

The inability of OFC-lesioned patients to appropriately identify facial emotion converges with neuroimaging studies implicating the OFC in the learning and recognition of faces and the identification of facial expressions of emotion.\textsuperscript{187–193} These abilities appear critical to the maintenance of appropriate social functioning in a complex society. The emotional reactions of other people that occur in response to one’s own behavior often act as primary or secondary reinforcers and provide important information about when one needs to modify one’s behavior. It is not difficult to see how the lack of such abilities could lead to socially inappropriate behavior, especially in someone with diminished inhibitory control.

Saver and Damasio concluded that the patient’s disregard for social rules and his disastrous decision making could not be attributed to a lack of social knowledge or moral reasoning, inability to generate appropriate response options, or inability to consider the consequences or risks associated with responses or social configurations.

Recent investigations using gambling simulations also have started to delineate the basis of the risk-taking behavior of these patients.\textsuperscript{194,195} PET data indicate that when persons without lesions make choices between high reward/high risk and low reward/low risk options, they activate portions of the right OFC and ventral frontal pole.\textsuperscript{196} Not surprisingly, patients with ventral frontal lesions perform poorly on gambling simulations. In particular, when given gambling tasks in which subjects have to balance future risks or punishment with immediate rewards or punishments, patients with ventromedial frontal (i.e., medial orbital gyrus, gyrus rectus, and subgenual cingulate) lesions show a relative insensitivity to the future consequences of behavior. These subjects do not appear to be simply hypersensitive to immediate reward or hyposensitive to immediate punishment. Rather, they appear to be largely uninfluenced by the potential for future reward or punishment compared with immediate reward or punishment. These studies suggest that the risky and often disastrous business decisions of OFC-lesioned individuals arise from a reduction of potential future consequences to influence decisions.
Autonomic Responses

Electrical stimulation of the OFC, particularly the posterior medial OFC, produces phasic changes in autonomic and endocrinological functions. Stimulation of this region produces both sympathetic and parasympathetic effects, including alterations in respiration, blood pressure, pupillary dilation, salivation, stomach tone, plasma cortisol levels, and inhibition of pyloric peristalsis. Lesions of the OFC in both human and nonhuman primates do not produce changes in the tonic regulation of visceral systems. Rather, they alter autonomic responses to stimuli that are behaviorally meaningful. For instance, humans with ventromedial prefrontal cortex lesions show significantly blunted autonomic responses to socially meaningful stimuli. They also show blunted responses to conditioned stimuli that have been associated with a startling loud sound, despite having normal responses to unconditioned stimuli. In humans, these deficits particularly arise from posterior but not anterior ventromedial lesions, which is consistent with the visceral-related afferents and efferents in the posterior medial region of the OFC. In some cases, lesions causing these effects may have encroached on area 25 in the subgenual cingulate, but this does not appear to have been the central focus in many of these cases. It is unclear whether these blunted autonomic responses reflect a cause, a consequence, or an integral part of the deficient (affective) decision making of these patients. Regardless of its specific role, abnormal autonomic functioning appears intimately tied to the emotional and social dysfunction in these patients.

Positron-Emission Tomography Studies of Emotions

PET studies that use anxiety-provoking paradigms frequently report alterations in regional cerebral blood flow (rCBF) within the OFC. Increases in rCBF in the left posterior OFC and medial OFC have been reported in psychiatrically healthy individuals anxious about an electric shock and infusion of cholecystokinin tetrapeptide (CCK), respectively. Furthermore, the amount of rCBF change in the left OFC appears to correlate with the level of induced anxiety. Pardo et al. observed significant rCBF increases in the inferior frontal gyrus, extending into the lateral OFC, in control subjects undergoing self-induced recall or imagining of dysphoric events.

Posterior lateral OFC activations also have been observed during script-induced anger. In an important series of PET studies, Rauch and colleagues and Shin and colleagues exposed patients with anxiety disorders to anxiety-provoking stimuli. Patients with social phobia, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder all had increased activity within posterior portions of the OFC compared with those who had neutral exposures. Other studies also have reported increased OFC activity in patients with anxiety disorders undergoing anxiety inductions. Of particular note, patients with OCD exposed to stimuli that provoke obsessions show increased OFC blood flow. Some data also suggest that psychiatrically healthy subjects exposed to auditory stimuli that provoke obsessive ruminations show increased OFC activity.

In contrast to the increased OFC activity observed in many anxiety-induction studies, Fredrikson and colleagues reported decreased OFC activity in two separate groups of patients with simple phobia undergoing exposure to a videotape presentation of phobic visual stimuli as compared with neutral stimuli. The Fredrikson studies differ from the other anxiety-induction studies in that all of the other studies, subjects were not viewing a fear-inducing object at the time of the scans but instead were contemplating or anticipating an aversive event or object that was either not present or not visible at the time of imaging.

Taken together, these studies suggest that OFC activity increases when subjects contemplate or imagine phobic or traumatic stimuli, whereas OFC activity decreases when subjects actually view phobic stimuli. This hypothesis received its most direct testing in a PET study by Shin et al., who contrasted visual imagery of combat-related pictures with viewing of combat-related pictures in patients with posttraumatic stress disorder and healthy control subjects. Although no significant differences were observed in OFC activity between the two conditions in the patients with posttraumatic stress disorder, greater left OFC activity occurred when healthy subjects performed visual imagery of the combat scenes than when they perceived them. We hope that future studies will clarify this issue.

PET studies also implicate the OFC in processes related to drug craving and/or the effects of drugs. In one study, human subjects with a history of cocaine craving showed increased regional brain metabolism in the OFC during the first week of cocaine withdrawal, and this activity correlated significantly with the level of craving for cocaine. Cocaine abusers exposed to
MNEMONIC AND HIGHER COGNITIVE FUNCTIONS

Memory in Nonhuman Primates With Orbitofrontal Cortex Lesions

The connections of the medial OFC gyrus rectus region with the hippocampus, entorhinal cortex, and thalamus suggest a role for medial OFC regions in processes related to mnemonic functions. OFC lesions that encompass areas 13 and 14 produce significant impairments on a visual delayed nonmatching-to-sample task (an object recognition task sensitive to hippocampal damage).222 The extent of this impairment increases significantly with delay, indicating that the deficit arises from mnemonic dysfunction rather than other task demands. Electrophysiological data also support the hypothesis that the OFC participates in some aspect of mnemonic coding. The cortex surrounding the medial and middle orbital sulci contains cells that alter their firing patterns during the delay periods of visual delayed matching-to-sample tasks.118 Some of these delay-period changes appear to occur only if the response made after the delay is correct.

Lesions elsewhere in the OFC of nonhuman primates frequently produce deficits on other memory tasks, but these deficits often reflect task-related problems that are not specific to mnemonic functions. For instance, ablations that include area 11 or 12 interfere with performance on tasks that require the retention of information about object or stimulus characteristics (such as color or pattern features) over brief delays.153,154,226 However, several features call into question whether these deficits relate to the mnemonic components of these tasks. Many of the lesioned animals show a high rate of perseverative responding. In one experiment, the animals showed impairment even when there was no delay,139 and in another experiment, increasing the delay time failed to increase the error rate.222 Taken together, these factors suggest that the performance deficit is not related to the mnemonic aspects of the tasks. More clearly mnemonic-related deficits result from inferior convexity lesions. Reversible lesions of the prefrontal cortex that impinge on ventral area 46 and area 121 produce delay-sensitive deficits on nonspatial memory tasks.227 However, the separate contributions of area 121 and ventral area 46 remain unclear. More evidence implicates ventral area 46 in these functions than area 121.46 Nevertheless, because of the close connections between area 121 and ventral area 46 and the similarity in many of the efferent connections of these structures, 121's contribution to visual working memory remains unresolved.

Learning in Nonhuman Primates

In most tasks that are impaired by OFC lesions in nonhuman primates, the lesions disproportionately impair the acquisition component of the task. For instance, the deficit in acquiring the delayed nonmatching-to-sample task that arises from combined lesions of areas 13 and 14 is greater than that observed following medial temporal lobe (combined hippocampal-amygdala-entorhinal) lesions.225,228 However, once the behavior is acquired, the impairment is less severe than that caused by medial temporal lobe lesions. A similar pattern characterizes the OFC's involvement in visual discrimination learning. Lesions of the OFC frequently impair the learning of object or pattern discriminations.139,152,229-231 This deficit arises following large lesions to the OFC or inferior convexity, although selective medial OFC and inferior convexity lesions sometimes do not produce this deficit. To investigate the source of this visual discrimination deficit, Voytko152 examined the ability of animals to perform already-learned discriminations under OFC cooling and found no deficit, despite the inability of these animals to learn new discrimination during OFC cooling. This suggests that the deficit arising from OFC lesions relates to the acquisition component of the task rather than reflecting an inability to perceptually discriminate objects or patterns. The learning deficits associated with the OFC lesions reflect a multimodal problem. Lesions of the inferior convexity produce impairments in learning auditory discriminations without impairing auditory sensory thresholds.148 Inferior convexity lesions even impair performance of tactile discrimination tasks, which clearly does not arise from a basic perceptual deficit.232

The OFC performs several functions that could potentially interfere with task acquisition. First, the ability to establish new stimulus-reinforcer associations is critical to learning discrimination, unless other strategies such as verbalization are available. Both visual and auditory discrimination tasks require the establishment of stimulus-reinforcer associations. A second component of learning these tasks involves altering responses based on changing contingencies.
a new task often requires that prepotent stimulus-response bonds be suppressed or extinguished based on the new reinforcement contingency. The fact that OFC cells respond to alterations in reinforcement contingencies faster than do cells in other regions may allow the OFC to rapidly influence learning and un-learning. Finally, the presence of error detection cells may allow the OFC to help correct wrong or previously rewarded responses. In the absence of such reward- and error-related information, lesioned animals rely on prepotent and often perseverative response styles.

**Memory in Humans With Orbitofrontal Cortex Lesions**

Lesions of the OFC in humans produce no consistent deficits on traditional neuropsychological tests of memory.\(^{182,183,233,234}\) However, memory impairments do arise on some less traditional mnemonic tasks. Prefrontal lesions involving an orbital focus have been reported to impair delayed-response and delayed-alternation tasks, even in the absence of impairment on the Wechsler Memory Scale.\(^{235}\) These deficits were not observed following prefrontal cortex lesions that excluded the OFC. Consistent with this finding, robust bilateral OFC activity (measured with PET) has been reported during the acquisition of a delayed-response alternation task.\(^{236}\) The greatest focus of activation on this task involved the anterior and lateral portions of the right OFC (Brodmann’s areas 11 and 47). Several PET studies have reported OFC activations during the recall of different types of verbal information.\(^{237–239}\) These activations have appeared in multiple areas of the OFC, with the right anterior extreme of the OFC (Brodmann’s area 10) showing the greatest consistency across studies.

In a series of studies comparing OFC-leukotomized schizophrenic patients with nonleukotomized schizophrenic patients, Stuss and colleagues\(^{234,240,241}\) found that leukotomized patients performed significantly worse than nonleukotomized patients when asked to recall consonant trigrams after an intervening interference task. All other memory tasks and attentional tasks were performed at an equivalent level to that attained by the nonleukotomized patients. These data suggest that the OFC plays a role in guiding memory during tasks with divided attentional demands. However, the generalizability of this result to nonschizophrenic individuals is questionable. Studies of nonpsychotic patients with ventromedial frontal lesions have not found a similar interference effect.\(^{184}\) In summary, although several studies suggest a role for the OFC in some aspect of mnemonic functions, the specific role remains poorly defined.

**Higher Cognitive Functions in Humans**

In general, OFC lesions in humans produce only minimal effects on IQ.\(^{184,234,241}\) These patients perform most neuropsychological functions, including language, visuospatial, attention, and executive functions, at normal levels. However, data from leukotomized schizophrenic patients suggest that some more subtle deficits may exist in OFC-lesioned patients. Leukotomized patients show difficulty making some conceptual shifts.\(^{241}\) Nevertheless, these patients usually show little perseveration on the Wisconsin Card Sorting Test, and when problems do develop on the Wisconsin Card Sorting Test, they tend to relate to failures to maintain set rather than perseveration.\(^{241}\) This is consistent with the heightened distractibility that occurs sometimes in such patients. In summary, patients with OFC lesions frequently have relatively normal neuropsychological abilities, and to the extent that neuropsychological deficits arise from these lesions, they appear far subtler than those arising from either the dorsolateral prefrontal or more posterior lesions. The subtlety of these deficits contrasts with the deficits in empathy, recognizing the emotions of others, and affiliative behavior, as well as the disastrous real-life decision making that characterizes these patients.

**THE ORBITOFRONTAL CORTEX IN NEUROPSYCHIATRIC ILLNESS**

In most cases, the link between OFC functioning and specific forms of psychopathology remains speculative. However, the OFC’s involvement in a wide range of functions related to emotional processing suggests a likely role for the OFC in a variety of neuropsychiatric conditions. Many of the functions observed by the OFC directly relate to abnormal psychological processes that characterize neuropsychiatric illness. For instance, the OFC’s involvement in modulating the motivational value of appetitive reinforcers implicates it in processes directly pertinent to substance abuse and other addictive behaviors.

In considering the OFC’s potential role in substance abuse, it is important to recall that the OFC sends direct projections to the ventral striatum, including the
nucleus accumbens. A wealth of evidence implicates the nucleus accumbens in the substrates of brain reward, especially those related to habit-forming drugs.\textsuperscript{119,242} Dopaminergic modulation of this region critically mediates initiation of a range of incentive-motivated behavior for naturally occurring rewards (e.g., sex, food).\textsuperscript{104,243} The OFC’s direct input into the ventral striatum allows it to modulate and provide current reward-related information to this pivotal brain-reward structure. Phylogenetically, the OFC is a more recently developed structure than the ventral striatum, and, as such, it appears to critically modulate the more primitive functions of the ventral striatum. The OFC processes reward-related activity with far greater flexibility than does the ventral striatum. For instance, satiety does not appear to reduce self-stimulation in the nucleus accumbens in the manner that it does in the OFC.\textsuperscript{133} The coding of satiety essentially involves a reduction in the motivational value of stimuli with prolonged exposure. Failure or weakness of this process leads to prolonged exposure to reinforcers and the continued high evaluation of their reinforcement value. In the case of habit-forming drugs, such prolonged exposure increases the vulnerability to the physiological effects of reinforcers such as tolerance and withdrawal. Thus, a failure of the OFC coding of satiety may lead to prolonged desire and exposure to drugs as well as increasing the risk of developing symptoms of dependency. Another potential source of OFC involvement in substance abuse relates to its high level of stimulus specificity in recognizing cues associated with reinforcers. Recognition of such associations triggers approach and other incentive-motivated behaviors aimed at obtaining the primary reinforcer. Studies of cocaine abusers highlight the importance of this role, indicating OFC activation during exposure to drug-related cues and suggesting a possible involvement of the OFC in craving.\textsuperscript{223,224}

The OFC’s role in gustatory reward and satiety suggests similar links to binge-eating behavior. As already noted, OFC lesions sometimes produce a failure to satiate in both human and nonhuman primates.\textsuperscript{126–131} Alternatively, the recognition of the associates of specific foods could influence the incentive craving for these foods. Although studies of reward-related functions in the OFC usually focus on intracerebral self-stimulation and gustatory reward, the OFC’s reward-related processes likely reflect a general process in modulating reward-related behaviors. This suggests that the OFC’s coding of satiety and reinforcer associations may play an active role in other impulse-control and compulsive behaviors in which individuals fail to stop behaviors once started or experience impulses when exposed to cues related to these rewarding actions.

On the surface, reducing the reinforcer value of stimuli based on satiety and recognizing reinforcer associates may appear to reflect contradictory processes. However, these both reflect variations of a general role in modulating behavior based on a comparison of potential reinforcers in the environment and the current needs of the organism. The rapid coding and integration of changes in external stimuli, internal states, and stimulus-reinforcer contingencies are necessary for the flexible adaptation of behavior in rapidly changing environments. In these situations, the OFC appears to perform essential operations. The OFC’s involvement in coding and modulating the motivational value of stimuli also suggests a potential role in affective disorders, in which the sensitivity to reward is either elevated (mania) or depressed (major depression). Whether primary or secondary to lesions, these affective episodes may be conceptualized in terms of abnormal coding of the motivational value of potential appetitive reinforcers. The frequency of depressive episodes and the occurrence of maniclike episodes following OFC lesions underscore the importance of the OFC in regulating these processes.\textsuperscript{174–178,180} Indeed, decreased orbital rCBF has been observed in manic patients.\textsuperscript{244}

Of course, OFC functions may be disrupted, or biased by far more subtle processes. Specifically, emerging data suggests that alterations in serotonergic functioning may powerfully modulate the OFC’s processing of affective information. Powerful alterations in serotonergic functioning may modulate the OFC’s processing of affective information. For instance, depressive relapses caused by tryptophan depletions are specifically associated with reductions in OFC metabolism.\textsuperscript{245} OFC involvement in processes related to empathy and recognition of affect provides another area through which OFC dysfunction might relate to psychopathology. In particular, disorders such as psychopathy (antisocial personality disorder), in which individuals show a lack of empathy, excessive aggression, and a reduced sensitivity to risks, show direct parallels to the effects of OFC lesions in humans. The effects of OFC lesions in nonhuman primates also provide parallels to the emotional and affiliative dysfunction seen in Asperger’s disorder or even in the schizophrenic spectrum.
The OFC also processes aversive stimuli. Of particular interest, OFC cells can associate previously neutral stimuli with aversive stimuli.\textsuperscript{28,47} This involvement in recognizing aversive stimuli provides a strong theoretical link to the anxiety disorders. Learning the associates of aversive stimuli and recognizing conditioned and unconditioned stimuli with aversive properties lie at the core of behavioral conceptualizations of anxiety disorders. Many investigators have emphasized the amygdala's role in these processes.\textsuperscript{75,80} The differential roles of the OFC and amygdala are unclear. The OFC has not received as close scrutiny as the amygdala in this regard. This partly reflects the fact that rodents do not provide a good model for studying OFC functions, whereas more substantial similarities exist between the amygdala in the rodent and the primate. However, lesions of the ventral portions of the medial prefrontal cortex in rodents (which shows similarities to the medial OFC in primates) do not affect the acquisition of aversive conditioning.\textsuperscript{143} They do, however, disrupt the extinction of aversive conditioning. Thus, at least in rodents, the critical role of the OFC appears to be in altering already-established aversive reinforcement contingencies. This corresponds to studies in nonhuman primates, which indicate that the OFC has greater flexibility and speed than the amygdala in processing changes in aversive reinforcement contingencies. For instance, when a visual stimulus that was previously rewarded starts being punished, OFC cells rapidly alter their firing.\textsuperscript{137} A similarly rapid process of learning appears in OFC cells when a previously punished response becomes rewarded. To our knowledge, alterations in responses of similar speed and flexibility have never been reported in studies examining the amygdala. Furthermore, the OFC shows greater stimulus specificity in its coding of aversive stimuli, possibly allowing detection of more subtle discrimination of specific stimulus-reinforcer contingencies. PET stimulation studies in patients with anxiety disorders and healthy control subjects further suggest the importance of activity in the OFC for anxiety disorders.\textsuperscript{207-209,212-215} Of all the anxiety disorders, OCD shows the most robust and replicated link to OFC functioning. Therefore, in the remainder of this chapter, we focus on the potential role of the OFC in the expression of obsessive-compulsive symptoms.

**Obsessive-Compulsive Disorder**

PET studies frequently report OFC hypermetabolism in OCD patients at rest.\textsuperscript{246-249} OCD patients also show robust increases in OFC activity immediately after or during exposure to triggering stimuli.\textsuperscript{213,217,250} Furthermore, successful pharmacological treatment of OCD with selective serotonin reuptake inhibitors is associated with significant reductions in OFC metabolism.\textsuperscript{251,252} Both pharmacological and behavioral treatments of OCD alter the pattern of correlations between OFC, basal ganglia, and thalamic metabolism, consistent with previous evidence implicating the OFC–basal ganglia loops in OCD.\textsuperscript{252-257}

The specific role that the OFC plays in OCD remains speculative. However, several possibilities arise based on the normal functions subserved by the OFC. We examine these possibilities in the following paragraphs. The focus on the OFC is not intended to imply that other areas such as the cingulate do not participate in OCD but to stimulate research on the specific contributions of the OFC to obsessive-compulsive symptoms.

The OFC’s role in processing information about aversive stimuli and their associates provides a useful starting point. For instance, OFC hyperactivity might be theorized to relate to a hypervigilance or hypersensitivity to detecting conditioned and unconditioned aversive stimuli. Similarly, OFC hyperactivity might simply reflect heightened anxiety or anxiety sensitivity. However, these possibilities fail to capture the unique properties of OFC processing. To clarify the OFC’s role, it is useful to return to what distinguishes OFC processing from amygdala processing. The distinguishing characteristics relate to the OFC’s high degree of flexibility and stimulus specificity in coding reinforcement-related information. Patients with OCD are frequently inflexible in how they code the affective value of stimuli over time. For instance, many individuals without OCD experience discomfort associated with a desire to wash after touching a dirty bathroom stall. However, this discomfort and desire decrease rapidly following washing. In contrast, OCD patients do not appropriately modify their coding of the affective value of the situation following washing but continue to experience discomfort or desire. In essence, these patients show an inflexibility in modulating their coding of stimulus-reinforcer contingencies once they have been activated by exposure to a triggering stimulus. Thus, it may be speculated that dysfunction of the normal flexible coding of the OFC could result in the perseverative affective coding that occurs in OCD.

Behavioral researchers have often noted that the performance of compulsions is reinforced in that context they are performed.  That is, OCD patients tend to wash their hands after touching a dirty bathroom stall, despite the fact that washing does not reduce the experiential discomfort associated with the stall itself. This behavior may be driven by an increase in OFC activity immediately after or during exposure to the stall. In turn, this increase in OFC activity may be driven by the OFC’s processing of the stall as an aversive situation. The cognitive misattribution of the stall as aversive, as opposed to neutral or rewarding, may be due to the OFC’s increased activity, which in turn may drive the wash response. This process may be analogous to the OFC’s role in the acquisition of conditioned aversive stimuli. OFC hyperactivity may be involved in the acquisition of conditioned aversive stimuli by altering already-established aversive reinforcement contingencies. Thus, OFC hyperactivity may play a role in the acquisition of conditioned aversive stimuli, as well as the acquisition of OCD-related compulsions.
pulsions almost always lead to a temporary reduction in anxiety or distress.\textsuperscript{258,259} Relief from anxiety represents a negative reinforcement. As such, the OFC may act to motivate operant responses (compulsive behaviors) to receive this type of reinforcement in the same manner as its acts for gustatory reward and intracerebral self-stimulation. Thus, although motivated by different types of reinforcers, similar processes and neural substrata may mediate the urge to perform compulsions and other addictive behaviors.

Sensory-specific satiety forms the basis of one of the OFC’s most unique contributions to the brain-reward system. It may be hypothesized that a similar process of satiety acts during avoidance responding. Such a process would help limit continued avoidance responding when the aversive reinforcer is no longer pertinent. It is this very process that often seems to be lacking in OCD patients, who in essence fail to reach a point at which they feel “satiated” in their safety. The failure to reach this “satiety” for safety would directly explain why OCD patients with washing compulsions continue to feel compelled to wash long after a person without OCD would consider such behavior unnecessary. Although the OFC’s mediation of such a process remains purely theoretical, it is consistent with its role in handling appetitive reinforcers.

Another distinguishing feature of the OFC is its apparent ability to engage internal representations of the current reinforcement value of stimuli that are not actually present at the current time. Many of the studies reporting increased OFC activity in humans involved paradigms in which subjects were not actually exposed to an aversive stimulus during the scan period itself. Rather, the subjects were asked to think about or contemplate a recently presented stimulus or told that they would receive a stimulus that they did not actually receive during the scan period. Several additional lines of evidence support the contention that the OFC generates or accesses internal representations of aversive events. First, cells that are engaged by unconditioned reinforcers (gustatory stimuli) are similarly engaged by the olfactory and visual associates of the reinforcer, and the extent of the engagement depends not on the reinforcer being present but on the motivational value of the reinforcer. Second, OFC activity increases when subjects specifically attempt to imagine or recall emotional events. Third, OFC lesions decrease the influence of future consequences of behavior. Fourth, some OFC cells show activity that appears to represent the expectancy of a reward in behavioral paradigms. Furthermore, the presence of error detection cells in the OFC implies the presence of an expectancy for reward. Such expectancies must exist for cells to fire specifically when a reward that would normally have occurred is withheld. If the OFC processes information about aversive expectancies, hyperactivity in this region could therefore lead to the excessive representations of future aversive events or stimuli.

Internal representations or expectancies of future aversive events or consequences of behavior dominate the clinical picture of OCD. Internal representations (repetitive thoughts and images) of dreaded events, such as getting ill, hurting someone, or causing some calamity, frequently lie at the core of the obsessive-compulsive symptom picture. Therefore, OFC hyperactivity may reflect or cause overengagement of aversive expectancies. Furthermore, because of the OFC’s involvement in stimulus-reinforcer associations, these internal representations of aversive events may become associated with neutral stimuli that happen to be present at the same time as the internal representation. In other words, the OFC could potentially provide a substrate for the behavioral conditioning of external stimuli with internally generated reinforcer representations.

Goldman-Rakic\textsuperscript{271} suggested that the OFC is involved in maintaining internal representations of the reinforcement value of stimuli in working memory. Although speculative, the presence of OFC cells that maintain their firing during delay tasks supports this possibility. Viewed from this working memory perspective, the inability of OCD patients to inhibit intrusive thoughts and images could reflect a hyperactive working memory process in which internally generated representations (expectancies) are maintained indefinitely in a state of moment-to-moment awareness. In the extreme case, this information might become locked “on-line,” despite repeated attempts to eliminate the representation. In such cases, the individual may repeatedly perform behaviors aimed at reducing the anxiety associated with the representation. However, because the representation continues to be maintained on-line, the individual feels compelled to repeat the behaviors to avert the dreaded event.

Another potential source of obsessive-compulsive behaviors arises from the activity of error detection cells in the OFC. OCD patients frequently perceive that they performed previous responses inadequately. If the error coding of OFC cells were hypersensitive, such that responses consistently were coded as errors, individuals might repeatedly experience their responses as inadequate. In extreme cases, this could
lead to repetitive attempts to perform acts “just right.” To date, our understanding of such error detection cells is limited to animal paradigms, but with the increased temporal resolution of functional magnetic resonance imaging, it might be possible to design paradigms for studying the neural substrates of error detection in healthy control subjects.

Finally, OFC hyperactivity may relate to the very processes that appear so deficient in the pseudopsychopathic condition. For instance, whereas the pseudopsychopathic individual participates in risky behavior despite knowledge of the risks, OCD patients appear excessively concerned with such risks. The pseudopsychopathic individual shows a lack of concern and an irresponsibility toward others, but OCD patients often show excessive concern with how their actions will affect others. Similarly, feelings of guilt, shame, anxiety, and concern for social norms, which seem so lacking in pseudopsychopathic persons, appear accentuated in OCD patients.

The source of OFC hyperactivity in OCD remains unclear. Given the responsivity of OCD to serotonin reuptake inhibitors, and the abnormal serotonergic functioning observed in some neuroendocrine challenge studies, the possibility that a specific serotonergic abnormality leads to OFC hyperactivity must be considered. Consistent with this possibility, cerebrospinal fluid levels of the serotonin metabolite 5-hydroxyindoleacetic acid negatively correlate with OFC metabolic levels in nonhuman primates.

An important source of OFC regulation arises within the OFC–basal ganglia loops. Heightened caudate nucleus metabolism has been observed in OCD patients at rest, and these levels decline following successful behavioral and pharmacological therapy. Moreover, these declines are associated with a reduction in the effective connectivity (correlation of metabolism) between the caudate and OFC. These changes in OFC–basal ganglia–thalamic correlations have led to the hypothesis that abnormal functioning within the basal ganglia loops represents the core pathological process in OCD. Based on the neurochemical properties of the connections within the OFC–basal ganglia loops, three hypotheses have been proposed.

First, hyperactivity within the caudate is proposed to lead to a disinhibition of the MDmc. The thalamus acts as a gate or filter, which if disinhibited releases information to its efferent targets. Disinhibition thus would allow information that is normally gated in the MDmc to be passed through to the OFC. This adventitiously released information would be experienced as intrusive because of its inappropriate release into moment-to-moment awareness. Because intrusive information reaching the OFC likely reflects information related to aversive reinforcers or expectancies (i.e., the normal information processed in these loops), these stimuli would not be experienced as neutral because of the aversive nature of information processed in this circuit. Of course, appetitive reinforcer information also might be adventitiously released, but such information might not be experienced as ego-dystonic or intrusive.

A second effect of overactivity within these loops arises from the reciprocal connections between the OFC and the MDmc. Both projections use the excitatory neurotransmitter glutamate as their primary neurotransmitter. Because of this, a disinhibition of the thalamus could lead to the establishment of a positive feedback loop. Once activated, information transmitted between the two regions would be trapped in a perseverative feedback loop. In this manner, stimulus-reinforcer information, and other information related to OFC/MDmc processing, would get trapped on-line by feedback in the OFC/MDmc axis. Once such a feedback loop is established, even performance of activities such as compulsions aimed at responding to this information would likely fail to halt the feedback. Finally, disinhibition at core points within the OFC–basal ganglia circuit might lead to a feedback loop involving the entire OFC–striatal–pallidal–MDmc loop. Such feedback again would lead to perseveration of the normal processing within these connected structures.

Given the projections from the OFC to the caudate nucleus, OFC hyperactivity may cause caudate hyperactivity rather than the reverse. The specific functions of the portions of the caudate that receive OFC projections are not well known. Investigators sometimes label this as part of the “cognitive” striatum, but beyond indicating that this part of the striatum does not directly affect motor execution, this label has limited utility. In primates, cells in the OFC-recipient regions of the caudate show responses that suggest that they are directly influenced by OFC processing. Specifically, cells in this area respond to gustatory reward, and in at least one case, a caudate cell was reported to reduce its responsivity following satiety. Other portions of the caudate show activity in relation to routinized, habit-based behaviors, especially those involving sequentially chained actions. This has most clearly been demonstrated in terms of rat grooming behavior. Whether OFC-recipient portions of the caudate participate in routinized or sequential processes
remains to be determined. If this were the case, however, it might help to explain the sequential nature of many compulsive behaviors, including compulsions related to activities such as counting.

The ability of pharmacological treatment to normalize OFC metabolism raises the possibility that OFC hyperactivity reflects a state, as opposed to a trait, marker of OCD. Most discussions of the pathophysiology of OCD (including the preceding paragraphs) conceptualize the pathophysiology as causing obsessive-compulsive symptoms. However, the causal direction of the OFC hyperactivity in OCD is unknown. Cottraux et al. reported that both non-OCD and OCD subjects showed increases in OFC rCBF when presented with sentences containing obsessional content. Because OFC activation occurred in both patients and control subjects, it could reflect a “normal” process activated by obsessive rumination. Andreasen and colleagues recently argued that “resting” activity in the OFC reflects a process of silent mentation. If correct, this could suggest that the increased resting OFC metabolism in OCD simply reflects a greater engagement of obsessive ruminations in OCD patients than in control subjects without OCD.

CONCLUSIONS

In conclusion, the OFC forms a critical convergence zone between sensory and limbic regions. As such, it forms a pivotal substrate through which exteroceptive and interoceptive stimuli influence motivated behavior. Clearly, we have a long way to go in understanding how this region influences neuropsychiatric illness. However, our knowledge of the neurocircuitry and function of this region has increased dramatically in recent years. Future research aimed at unraveling the specific functions of the different OFC regions will likely produce a far greater understanding of the physiological basis of a broad spectrum of neuropsychiatric illness.

REFERENCES