Sensory Pathways and Emotional Context for Action in Primate Prefrontal Cortex

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Connections of the primate prefrontal cortex are associated with action. Within the lateral prefrontal cortex, there are preferential targets of projections from visual, auditory, and somatosensory cortices associated with directing attention to relevant stimuli and monitoring responses for specific tasks. Return pathways from lateral prefrontal areas to sensory association cortices suggest a role in selecting relevant stimuli and suppressing distracters to accomplish specific tasks. Projections from sensory association cortices to orbitofrontal cortex are more global than to lateral prefrontal areas, especially for posterior orbitofrontal cortex (pOFC), which is connected with sensory association cortices representing each sensory modality and with structures associated with the internal, or emotional, environment. A specialized projection from pOFC to the intercalated masses of the amygdala is poised to flexibly affect autonomic responses in emotional arousal or return to homeostasis. The amygdala projects to the magnocellular mediodorsal thalamic nucleus, which projects most robustly to pOFC among prefrontal cortices, suggesting sequential processing for emotions. The specialized connections of pOFC distinguish it as a separate orbitofrontal region that may function as the primary sensor of information for emotions. Lateral prefrontal areas 46 and 9 and the pOFC send widespread projections to the inhibitory thalamic reticular nucleus, suggesting a role in gating sensory and motivationally salient signals and suppressing distracters at an early stage of processing. Intrinsic connections link prefrontal areas, enabling synthesis of sensory information and emotional context for selective attention and action, in processes that are disrupted in psychiatric disorders, including attention-deficit/hyperactivity disorder.

Key Words: Amygdala, attention-deficit/hyperactivity disorder (ADHD), lateral prefrontal, mediodorsal nucleus, obsessive-compulsive disorder (OCD), orbitofrontal cortex, thalamic reticular nucleus

The prefrontal cortex in primates receives input from the entire sensory periphery through projections from sensory association cortices. But unlike sensory cortices, which process distinct aspects of the environment, the prefrontal cortex is an action-oriented region and processes sensory information selectively to accomplish specific tasks.

Here, we provide an overview of sensory pathways through the prefrontal cortex within a functional perspective. Sensory information is broadly defined to include pathways that link the prefrontal cortex with the external (sensory) environment and with the internal (emotional) environment. Purposive behavior requires selective attention to stimuli for specific tasks within a motivational context. This targeted review is not comprehensive, as further details of prefrontal connections have been reviewed elsewhere (e.g., [1,2]).

The major sensory-recipient sites of prefrontal cortex are found on the lateral and orbital surfaces. Discussion here focuses on the possible role of lateral prefrontal cortices in two aspects of goal-directed behavior. One pertains to selective attention to stimuli that are relevant for the task at hand, exemplified by connections with visual/visuomotor cortices. The other pertains to the equally important function of suppressing distracters, demonstrated by example of projections from lateral prefrontal areas to auditory association cortices. Connections of posterior orbitofrontal cortex (pOFC) with sensory cortices are intricately associated with pathways through the amygdala for action within an emotional context. This function is exemplified by a specialized projection from the pOFC to the amygdalar intercalated masses (IM), which has a key role in flexible regulation of emotional expression based on behavioral context. It is this flexibility that appears to be lost in disorders marked by anxiety, including phobias and obsessive-compulsive disorder. Dorsolateral prefrontal areas and pOFC also send widespread and specialized projections to the thalamic reticular nucleus, which filters information between thalamus and cortex and may help shift attention rapidly to relevant and motivationally significant stimuli for action. Focused attention is necessary to accomplish even simple tasks, a process that is disrupted in psychiatric disorders characterized by distractibility, such as attention-deficit/hyperactivity disorder (ADHD).

Medial prefrontal cortices, including the anterior cingulate cortex (ACC), have significant connections only with auditory association areas. The ACC is associated with attentional and emotional control, and its connections differ from other prefrontal areas and will be discussed only briefly for comparison.

Sensory Connections of Lateral Prefrontal Cortices for Behavior

Sensory projections to lateral prefrontal cortices originate from visual, auditory, and somatosensory association cortices (Figure 1). Although no prefrontal area is strictly unimodal in its connections, unimodal sensory cortices innervate preferentially specific lateral prefrontal loci. Projections from visual association cortices target most heavily the frontal eye fields (FEF) and the caudal extent of area 46 (3,4), which collectively are called periarcuate cortex. Visual input to periarcuate cortex is associated with orientation to visual stimuli for specific tasks. Neurons that respond to visual stimuli increase their activity when monkeys shift their gaze to a stimulus that is relevant for the task (5). In this respect, the FEF (area 8) and caudal area 46 are distinguished by strong bidirectional connections with the intraparietal visuomotor cortex (areas ventral lateral intraparietal, dorsal lateral intraparietal, and 7a) (3,4,6,7). These connections provide the pathways for activation of periarcuate cortices when primates search the environment and orient to behaviorally relevant visual stimuli (reviewed in [8]).

The role of periarcuate areas in visual search is manifested after its damage by the phenomenon of neglect in nonhuman primates

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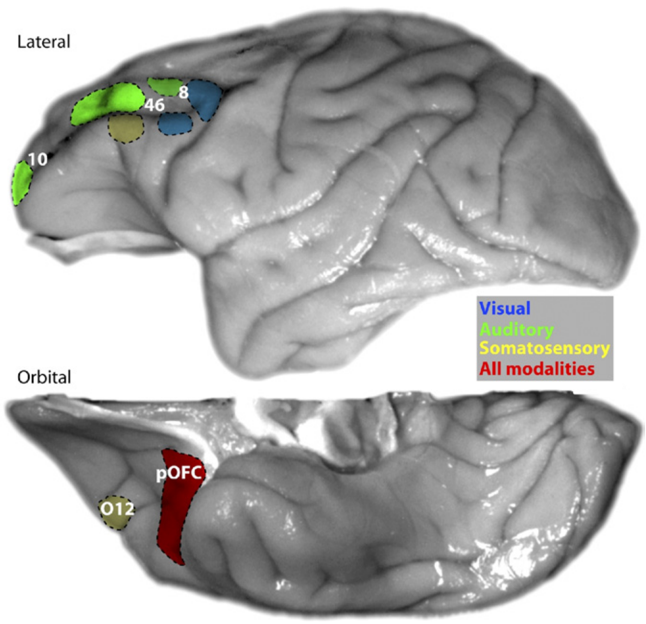

Figure 1. Primary targets of projections from sensory association cortices in lateral and orbital prefrontal cortices. The posterior orbitofrontal cortex is the most multisensory cortex because it receives input from cortices representing each of the sensory modalities. The diagram depicts the major sites of sensory inputs, not all sites. pOFC, posterior orbitofrontal cortex.

and humans, who show profound inattention to stimuli on the side opposite the lesion, whether stimuli are real or remembered representations of the environment (reviewed in [9]). Reciprocal projections from lateral prefrontal areas reach visual association areas as well (7,10,11), exercising top-down control of visual attention (see also Miller, this issue).

The specific connections of the visual-recipient prefrontal cortices in the FEF are matched by their projection to the superior colliculus and connections with the lateral (multiform) and intralaminar thalamic nuclei associated with eye movement (reviewed in [12]). Thalamic nuclei that project to FEF, including the multiform mediodorsal, suprageniculate, and limitans nuclei, receive projections from the superior colliculus and the lateral substantia nigra, all of which have a role in eye movement (reviewed in [12]).

Projections from auditory and somatosensory association cortices also have preferential targets in lateral prefrontal cortex. Projections from auditory cortices innervate most robustly frontopolar area 10, the middle extent of dorsal area 46, and the anterior tip of the upper arcuate sulcus (area 8) (3,4). Within area 8, the auditory-recipient site coincides with a region whose stimulation elicits large saccades (13) and also receives projections from visual cortices, suggesting a role in orienting to peripheral visual and auditory stimuli with coordinated eye and head movements (4). Projections from somatosensory association cortices terminate most heavily in the middle extent of ventral area 46 and the adjacent area 12 (3,14).

As in the periarcuate region, sensory input to area 46 is associated with purposive behavior, and specifically, working memory tasks, including keeping track of self-generated responses in tasks with multiple components (reviewed in [15–17]). Area 10, which has the most robust connections with auditory association cortices among prefrontal cortices (3,18,19), is engaged when one must juggle more than one task within working memory (reviewed in [20–22]).

Selective attention implies that irrelevant signals are suppressed. How does the prefrontal cortex achieve this important function? Using prefrontal auditory connections as a model system, we have found that pathways from lateral prefrontal areas to auditory association cortices target not only excitatory neurons but also inhibitory neurons (19,23), which may help suppress activity associated with irrelevant stimuli. The significance of this circuit is based on evidence that patients with damage to lateral prefrontal cortex make more errors than control subjects when irrelevant auditory stimuli are introduced in auditory discrimination tasks, and their performance is correlated with decreased neural activity in dorsolateral prefrontal cortex and a concomitant increase in auditory cortices (reviewed in [24]). Similar findings are seen in aged humans with cognitive decline of prefrontal origin (25), who say that they cannot follow conversations in noisy environments. This evidence exemplifies the key role of pathways from prefrontal cortices in inhibitory control, whose compromise may contribute to the deficits observed in ADHD that affects lateral prefrontal cortices (26).

The above overview suggests a certain degree of topographic organization within the prefrontal cortex. However, prefrontal areas also receive projections from polymodal temporal association cortices. Moreover, neighboring prefrontal cortices are interconnected (27), allowing exchange of information, as in sensory cortices (28). This evidence suggests a bias, rather than exclusive processing of unimodal sensory information in prefrontal cortices.

Connections of Orbitofrontal Cortices and Emotional Processing

Projections from sensory association cortices to orbitofrontal cortex are more global than to lateral prefrontal cortex by virtue of their topography from anterior high-order sensory association cortices that represent each and every sensory modality (29,30) (Figure 1). Further, more than any other prefrontal region, the orbitofrontal cortex is connected with a host of cortical and subcortical limbic structures (reviewed in [31,32]). Multimodal input from the external (sensory) and internal (emotional) environments is directed most robustly to a posterior strip of orbitofrontal cortex, situated anterior to the temporal lobe and medial to the anterior insula (for discussion of the varied terminology of this region see [31]). The pOFC includes areas orbital periallocortex and orbital proisocortex and the posterior part of area 13 in the map of Barbas and Pandya (27). The pOFC is distinct from anterior orbitofrontal areas (anterior part of area 13, area 11, and orbital area 12), which also receive input from several sensory modalities, though not all. Connections with olfactory areas, for example, are restricted to pOFC.

The connections of pOFC place it in an ideal position to integrate the external and internal environments. The pOFC also has the most specialized connections with the amygdala and the most robust connections with the magnocellular sector of the mediodorsal (MDmc) nucleus of the thalamus. These connections set pOFC apart from other prefrontal areas, including rostral orbitofrontal areas, and suggest that it is a primary sensor of information for emotions, as elaborated below.

Specialized pOFC Projection to the Inhibitory Amygdalar IM

A specialized projection from pOFC innervates the amygdalar IM (Figure 2A) through a pathway that is not reciprocated. Tacked within narrow corridors between the main nuclei of the amygdala, the intercalated masses are composed of small neurons that are nearly inconspicuous and have frequently been overlooked in maps of the amygdala. The small size and squeezed topography of the IM nuclei belie their key role in the internal processing of the amygdala and influence on the more expansive neighboring basal