REVIEW

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.

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
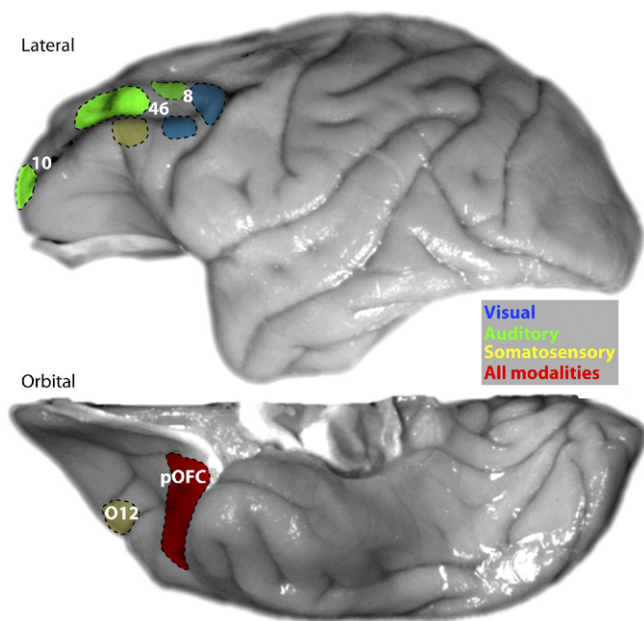
Figure 1. Primary targets of projections from sensory association cortices in lateral and orbital prefrontal cortices. The posterior orbitofrontal cortex is the most multisensory cortex because it receives input from cortices representing each of the sensory modalities. The diagram depicts the major 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
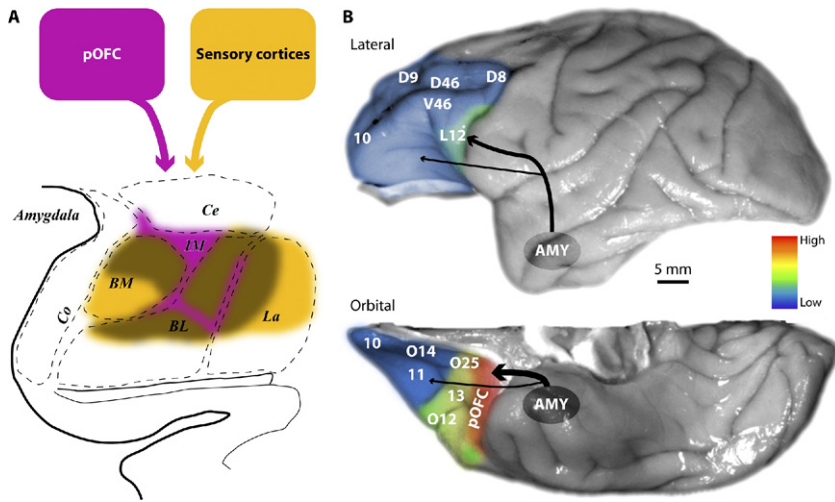
Figure 2. Connections between the prefrontal cortex and the amygdala. **(A)** Projections from posterior orbitofrontal cortex (pOFC) to the amygdala (magenta) target robustly the inhibitory intercalated masses in a unidirectional pathway. The pOFC also has bidirectional connections with the basal nuclei, where its connections overlap (brown) with sensory input (yellow) that reaches the amygdala from sensory association cortices. **(B)** Pseudo colored surface maps of the rhesus monkey brain show the strength of pathways from the amygdala that terminate in lateral (top) and orbital (bottom) prefrontal areas. The pOFC receives the strongest projections from the amygdala; the thickness of the arrows indicates pathway strength. AMY, amygdala; BL, basolateral nucleus; BM, basomedial nucleus; Ce, central nucleus; Co, cortical nuclei; IM, intercalated masses; La, lateral nucleus.

nuclei that are composed of much larger neurons. The IM nuclei are distinguished by their exclusive inhibitory nature and projections to the central amygdalar nucleus, the basal forebrain, and brainstem autonomic structures in several species (for a list of references see [33]). The central amygdalar nucleus is a major inhibitory output to subcortical autonomic structures (reviewed in [34]), which either increase or decrease autonomic drive through downstream projections to sympathetic or parasympathetic structures (35–38).

The pOFC projects robustly to the IM nuclei, outlining their extent with exquisite specificity at the outskirts of the basal amygdalar nuclei (33). This circuitry places the pOFC in a strategic position to influence the internal processing of the amygdala and its output to central autonomic structures (33). Physiological and behavioral findings have suggested that cortical projections to IM are involved when rats learn to associate a stimulus with shock and exhibit fear, as well as in dampening autonomic output during extinction, when rats remember that the stimulus no longer signals shock (reviewed in [39]).

How do the inhibitory IM neurons mediate opposing effects depending on emotional circumstance? Circuit models in rats have suggested that topographic differences in the cortical innervation of IM neurons may help explain behavioral flexibility (39). By contrast, previous findings indicate that the inhibitory neurons in IM are diverse in morphology and neurochemistry (e.g., [40,41]), which may more parsimoniously explain the opposing functions. The IM system clearly has a key and flexible influence on the internal processing of the amygdala and may be the site of action of drugs such as cycloserine, now in clinical trials for the treatment of anxiety disorders (42).

The circuits through IM resemble the cortical-striatal-thalamic loop, which releases the ventral anterior and mediodorsal thalamic nuclei from pallidal inhibition, allowing initiation of movement. In the case of the excitatory input from pOFC to the inhibitory IM nuclei, the subsequent projection is to the inhibitory central amygdalar nucleus, which innervates autonomic hypothalamic structures. In this system, movement refers to autonomic activation, which can lead to opposite functional outcomes, depending on circumstance. One outcome involves downstream activation of sympathetic centers that innervate peripheral autonomic structures (e.g., the lungs and heart) in emotional arousal; the other involves return to autonomic homeostasis through innervation of parasympathetic structures. Restoring appropriate balance in these opposing functions is a major challenge for psychiatric disorders marked by anxiety.

Overlap of pOFC and Cortical Sensory Connections in Basal Amygdala

The pOFC is also connected with the basal nuclei of the amygdala through specialized bidirectional pathways in the posterior half of the amygdala, where pOFC input and output zones are partly segregated (33). Moreover, some amygdalar sites that are connected with pOFC are also connected with anterior temporal and insular sensory cortices (43) associated with emotional significance (44) (Figure 2A). This circuitry suggests that sensory information reaches the pOFC directly from the cortex and indirectly through the amygdala. If sensory association areas convey signals to the amygdala about the emotional significance of signals, they should be "feedforward" in type and originate in the upper cortical layers, as in projections from earlier to later processing sensory areas (45). We recently provided support for this hypothesis, because in sensory and polymodal cortices projection neurons directed to the amygdala were found mostly in the upper layers (43).

Projections from the Amygdala to pOFC

The pOFC receives the most robust amygdalar projections among prefrontal cortices, which originate most densely from the basal nuclei (46,47) (Figure 2B), and terminate preferentially in the upper layers of prefrontal cortex (48), suggesting a predominant "feedback" pattern. In the upper cortical layers, these robust amygdalar terminations are intermingled with calbindin inhibitory neurons, which have been implicated in reducing noise at the fringes of active columns in lateral prefrontal cortex during working memory tasks (49). We suggest that the robust input from the amygdala to the upper layers of prefrontal cortex may have a similar role, poised to eliminate distracters and help focus attention on emotionally salient events.

In addition, some projections from the amygdala reach the middle layers of pOFC and ACC, which sets these regions apart as recipient of projections that may be considered feedforward (47). However, most feedforward projections to pOFC arrive through another source, the thalamic MDmc nucleus, as elaborated below.

Thalamic Projections from MDmc to pOFC for Emotions and Memory

Among prefrontal cortices, MDmc targets most robustly the pOFC (50). The MDmc receives a strong projection from the amygdala, as well as cortical and subcortical structures related to learning, memory, and emotion (48,51). The robust MDmc pathway to pOFC, therefore, is an indirect route from the amygdala to pOFC
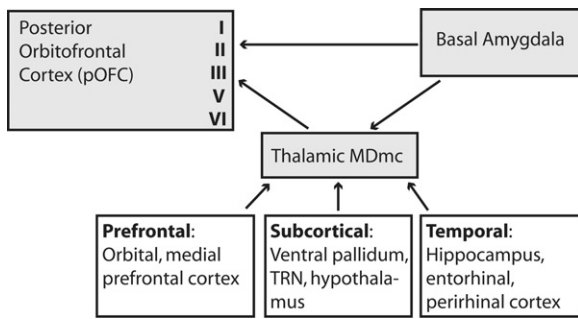
Figure 3. Sequential pathways for emotions. Schematic representation of direct projections from the amygdala to posterior orbitofrontal cortex, as well as indirect projections through the thalamic mediodorsal magnocellular (MDmc) nucleus, which is innervated by the amygdala. The terminations in the cortex show the predominance of direct amygdalar projections to the superficial layers and MDmc projections mostly to the middle cortical layers. The strong reciprocal projections from orbitofrontal cortex to MDmc and from posterior orbitofrontal cortex to the amygdala are not shown. TRN, thalamic reticular nucleus.

(Figure 3). Projections from MDmc target most heavily the middle layers of pOFC, in a feedforward pattern (52), and are largely complementary to the feedback pattern of direct amygdalar projections (47).

The sequential pathway from the amygdala to MDmc and then to pOFC may be a pathway for emotional processing, much like sensory information is sent from the periphery to sensory thalamic nuclei and on to the primary sensory cortices. The serial pathway from the amygdala through the thalamus provides a mechanism for integrating emotional and sensory information in orbitofrontal cortex (OFC), a process that is crucial for learning and memory. In fact, thalamic mediodorsal (MD) lesions result in anterograde amnesia in primates (53). An intact MDmc may be necessary for updating internal reward values, as monkeys with MDmc lesions continue responding to stimuli even after they have been satiated of the associated food reward (54). This pattern of response is similar to that seen following amygdala lesions in primates (55). Together, these findings show that the pathway from the amygdala through the thalamus to orbitofrontal cortex is necessary for maintaining flexible stimulus-reward associations.

It follows that this circuit, which plays a role in integrating emotional and sensory signals, has been implicated in the pathology of disorders such as obsessive-compulsive disorder (OCD) and autism spectrum disorder (56,57). Obsessive-compulsive disorder is characterized by the recurrence of intrusive thoughts and impulses, leading to repetitive compulsive behaviors (56). Recent models of OCD rely on overactivation of loops connecting error detection (related to the anterior cingulate cortex), anxiety (signaled by the amygdala), complex behaviors (gated by basal ganglia and encoded in prefrontal cortices), and reinforcement (signaled by OFC) (56). Several lines of evidence support the involvement of OFC in OCD symptomatology. Neuroimaging studies have identified structural abnormalities in OCD patients, including decreased volume of OFC and increased gray matter density in OFC and thalamus (58,59). Functional neuroimaging studies of OCD patients have demonstrated OFC activation during provocation of symptoms (60). The connections of OFC with the basal ganglia and thalamus have been targeted therapeutically with neurosurgical lesions and deep brain stimulation in pharmacologically resistant OCD (61).

Processing of signals with affective significance is important for normal function and can be critical for survival. Selective attention to threatening stimuli, for example, is prerequisite for fast decision

and action. What are the pathways for focusing on motivationally significant signals and ignoring distracters when decisions must be reached rapidly? An important link that may be critical for speedy responses is the special circuitry that both pOFC and MDmc have with a specialized thalamic nucleus, the reticular, as elaborated below.

Prefrontal Attentional Regulation of Sensory Signals through the Thalamic Reticular Nucleus

Like the specialized projection from pOFC to the amygdalar intercalated masses, some prefrontal areas, including pOFC, target in a unique way another exclusively inhibitory system, the thalamic reticular nucleus (TRN) (Figure 4), which forms a thin veil around the dorsal thalamus (62). It is reciprocally connected with all nuclei of the dorsal thalamus and is innervated by projections from the cortex but does not project to the cortex. Because of this circuitry, its strategic placement between thalamus and cortex, and inhibitory nature, the TRN is in a unique position to regulate thalamocortical communication, brain oscillations, and the sleep-wake cycle (63,64). The TRN also acts as a filter, sieving information between thalamus and cortex, allowing signals to pass to the cortex or blocking them by innervating and inhibiting thalamic projection neurons (65,66). When TRN neurons are activated by trains of cortical or thalamic inputs, they fire in bursts followed by a slow recovery before they can fire again, a property thought to limit the ability to shift attention frequently in a fast rhythm (67).

Cortical areas and their associated relay thalamic nuclei project onto the same parts of TRN, creating a crude topographic map of thalamus and cortex that divides TRN into sectors (68,69), an ante-
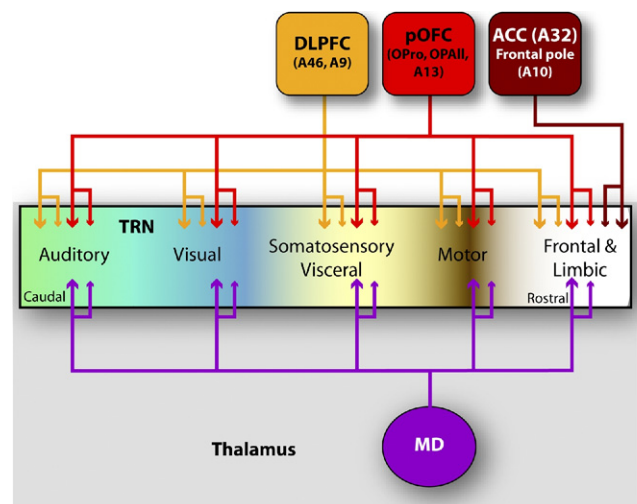

Figure 4. Prefrontal and mediodorsal thalamic projections to the thalamic reticular nucleus (TRN). Different TRN sectors are color-coded based on projections from cortical areas (frontal and limbic: white; motor: brown; somatosensory/visceral: yellow; visual: blue; auditory: green). Projections from all prefrontal cortices and the mediodorsal nucleus in the rhesus monkey are concentrated in the rostral (prefrontal) sector of TRN. However, mediodorsal nucleus, dorsolateral prefrontal (areas 46 and 9), and the posterior orbitofrontal cortex also extend projections to the central and posterior sectors of TRN, potentially influencing the flow of information from sensory and motor thalamic nuclei to the cortex. In addition, prefrontal areas uniquely innervate TRN neurons through a significant (about 10%) proportion of large and potentially more efficient terminals (indicated by the size of the arrowheads). ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; MD, mediodorsal nucleus; OPAll, orbital periallocortex; OPro, orbital proisocortex; pOFC, posterior orbitofrontal cortex.

rior frontal/limbic sector, a motor sector, a somatosensory/visceral sector, a visual sector, and an auditory sector, sequentially situated along the rostrocaudal extent of TRN (reviewed in [70]). Prefrontal projections to TRN target mostly its anterior part (71), where they extensively overlap with projections from the adjacent motor and premotor areas (Figure 4), consistent with the tight relationship of these cortices and the role of the prefrontal cortex in action. The rostral TRN sectors regulate most of the limbic thalamic nuclei, which have widespread cortical connections and are involved in motivation, arousal, and the state of alertness (62,64). The projections from frontopolar area 10 and ACC area 32, which has widespread cortical and subcortical connections (1), are constrained within the frontal TRN sector. Interestingly, this rostral-medial prefrontal corticothalamic network is believed to play a role in regulating the conscious state and motor preparation, and its disruption can cause generalized absence seizures, characterized by disrupted attention and unresponsiveness (72). The rostral TRN also receives input from the anterior hippocampus, which is strongly connected with ACC (reviewed in [1]) and the limbic thalamus, in pathways that are relevant for the spread of absence seizures (73). Stimulation of TRN and its pathways in a nonepileptic patient elicited neural activity akin in pattern to activity seen during absence seizures (74).

Interestingly, not all prefrontal cortices behave the same way in their projection to TRN. Lateral prefrontal areas 9 and 46 and the pOFC, as well as the MD thalamic nucleus, terminate in the anterior as well as the central and posterior parts of TRN, where they overlap with projections from sensory association areas (71) (Figure 4). This topography suggests that some lateral prefrontal areas, pOFC, and MD may be in a position to influence signals passing from sensory-related thalamic nuclei to the cortex and thereby affect attentional mechanisms. Areas 46 and 9 have a key role in working memory, and their widespread projections to TRN may allow selection of sensory signals and suppression of distracters at an early stage of processing. Disruption of these pathways may be involved in the distractibility and dysregulation of brain oscillations and sleep observed in schizophrenia (75–78).

The pOFC, which also has widespread terminations on TRN, receives diverse input from every sensory modality and structures monitoring the internal milieu and has strong connections with the amygdala and MDmc, as reviewed above. These circuits play an important role in evaluating the significance of stimuli, allowing cognitive flexibility to guide behavior (31,79 – 82). The pOFC–TRN network thus is ideally suited to direct attention toward emotionally relevant stimuli at an early stage of processing. Rapid responses are crucial for survival in the face of danger (83). Disruption of this circuit could lead to behavioral inflexibility and inability to appropriately shift from one thought or behavior to another, as seen in OCD and autism (56,84 – 87). Obsessive-compulsive disorder has been associated with abnormal activation in orbitofrontal cortex related to behavioral flexibility, as assessed by reversal learning tasks or task-switching exercises (88,89). Interestingly, physiologic and pharmacologic studies in animals and functional studies in humans suggest that the circuit linking orbitofrontal cortex with TRN and the thalamus is necessary for regulation of thalamocortical synchronization and integration, and its stimulation significantly decreases depression, obsession, and compulsion symptoms (90,91).

A final distinguishing feature of prefrontal projections to TRN is the presence of a significant proportion of large terminals (~10% of the total population), unlike projections from sensory or motor cortices, which are composed entirely of small terminals (71). Large terminals (boutons) have more mitochondria, larger synapses, and more synaptic vesicles, suggesting increased likelihood of neurotransmitter release upon stimulation and increased probability of

eliciting a postsynaptic action potential and signal propagation (23,92,93). Through these anatomical and functional specializations, the prefrontal cortex may magnify transmission of salient signals and at the same time suppress distracters. This circuitry suggests a previously unsuspected top-down attentional modulation by prefrontal cortex at an early stage of sensory processing through the thalamus.

Disorders that affect lateral prefrontal areas, such as ADHD (26), may consequently affect a pathway from areas 46 and 9 directed to excitatory and inhibitory neurons in auditory and other sensory association cortices, as well as to TRN. This evidence suggests that in ADHD there may be disruption by dual mechanisms in the process of directing attention to behaviorally relevant stimuli and ignoring distracters.

Synthesis of Information for Action

We have mentioned only in passing the connections of medial prefrontal areas, including those in ACC, that have an important but different role than the orbitofrontal. The ACC, in particular, receives sparse projections from sensory cortices outside the auditory, differing markedly in this respect from the orbitofrontal. The ACC has a critical role in allocating attentional resources (reviewed in [94,95]) and has the most widespread intrinsic and specialized connections (96) with prefrontal cortices (97). The ACC has stronger connections with motor effector systems than the orbitofrontal, including robust projections to central autonomic structures, output systems to autonomic structures in the amygdala (33), and brainstem vocalization structures associated with emotional communication (reviewed in [1,98,99]). Based on the above connections, the ACC may be considered the cortical motor effector for emotions.

In contrast, the pOFC is privy to a panoramic representation of the external and internal environments that is unparalleled in the cortex, as are its specialized and rich connections with the amygdala. The pOFC is thus poised to integrate rapidly the external sensory and the internal or emotional environment. Central to this discussion is the idea that highly processed information from the entire external and internal environment projects to the amygdala and then to MDmc, which projects most prominently to pOFC. This circuitry suggests that the pOFC is the primary sensory area for emotions, analogous to the primary sensory cortices. The entire spectrum of connections of pOFC is linked to the flexible establishment of emotional associations, in pathways that are disrupted in psychiatric diseases marked by anxiety. Compared with the enriched input to pOFC, projections from sensory association areas are more constrained and specialized in lateral prefrontal areas, projections from the amygdala are sparse, and connections with the thalamus are with other parts of MD, the parvicellular and multiform divisions. Projections from sensory association areas to lateral prefrontal areas have a role in directing the head, eyes, or limbs toward relevant stimuli for the task at hand. Ultimately, decision and action are embedded in a motivational context. The intricate interaction of sensory and emotional processes is manifested in the pathways that link lateral, orbitofrontal, and medial prefrontal cortices, which are recruited selectively and flexibly, depending on the circumstances. This delicate synthesis of information is disrupted and dissociated in several psychiatric diseases marked by anxiety, lack of flexibility, and distractibility.

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