Chapter 4

Sequential and parallel circuits for emotional processing in primate orbitofrontal cortex

Helen Barbas and Basilis Zikopoulos

4.1. Overview

The prefrontal cortex in primates guides behaviour by selecting information through a vast communication network with cortical and subcortical structures (Goldman-Rakic 1988; Fuster 1993; Barbas 1995a; Petrides 1996; Barbas 2000a). In addition to its long-held position as the central node for executive processing associated with lateral prefrontal areas, it is now clear that the orbitofrontal and medial sectors of the prefrontal cortex have rich connections with structures that process emotions (Barbas 1995a; Price *et al*. 1996; Barbas *et al*. 2002). The three distinct prefrontal sectors, namely the lateral, orbitofrontal and medial, are interconnected, and provide the basis for interaction of pathways underlying cognitive and emotional processes. The anatomic bond between these functionally distinct areas underscores the biologic significance of the synthesis of cognitive and emotional processes. Disruption of this linkage has profound effects on behaviour, as seen in several psychiatric and neurologic diseases affecting the orbitofrontal cortex (OFC).

This chapter focuses on the circuits that underlie the motivational component for the selection of relevant signals in behaviour. Decisions and actions are inextricably linked to the emotional significance of events, and the OFC has a key role in this process. This idea is supported by striking deficits in emotional behaviour and social interactions in both human and nonhuman primates after orbitofrontal damage (Damasio *et al*. 1994; Damasio 1994). Several features of the circuits of the OFC, particularly its connections with temporal structures, suggest that it is in an ideal position to convey signals associated with the emotional significance of events. Ultimately, the OFC communicates with lateral and caudal medial prefrontal cortices in synergistic functions in decision and action in behaviour. We address below the key features of circuits that likely underlie the role of the OFC in cognitive-emotional interactions.

4.2. Orbitofrontal cortex: location and definitions

The OFC encompasses a large area on the rostral basal surface of the brain (Fig. 4.1). In macaque monkeys it is found directly behind the eye socket, and assumes a concave

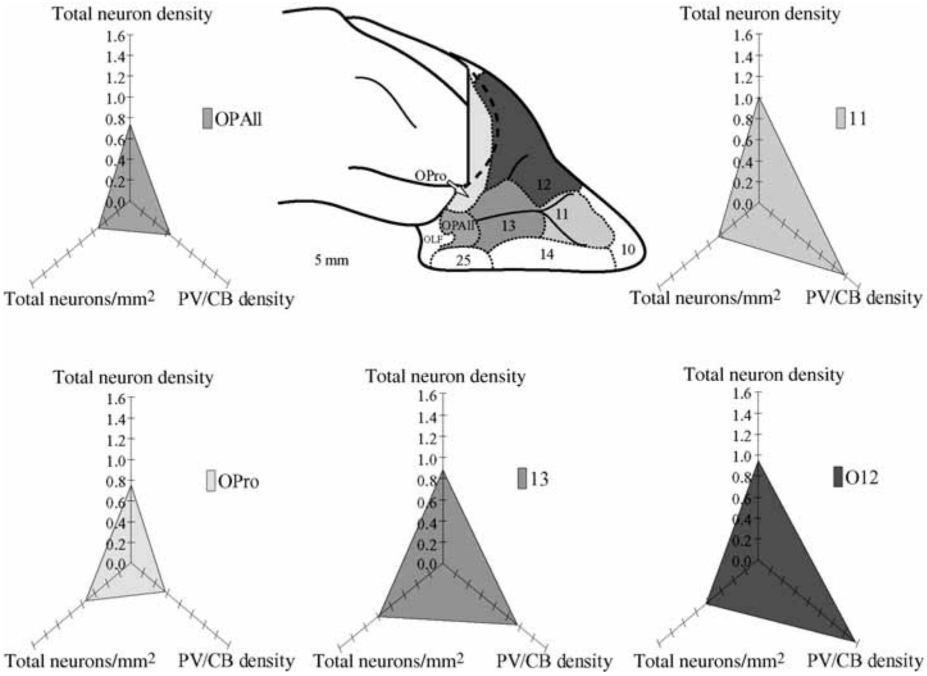

Fig. 4.1 Quantitative architectonic profiles of orbitofrontal cortices of the rhesus monkey. Areas are shown on the basal surface of the right hemisphere (top center). Fingerprints of the distinct orbitofrontal areas were constructed quantitatively on the basis of features that discriminate among areas, including density of neurons, total neurons/mm^2 and the ratio of parvalbumin (PV) to calbindin (CB) neurons. The temporal pole at top center was rendered transparent (thick dotted lines) to show the underlying orbitofrontal cortex. The map is according to Barbas and Pandya (1989). Abbreviations: OPro, orbital proisocortex (dysgranular cortex); OPAll, orbital periallocortex (agranular cortex).

shape around the orbit. The orbitofrontal cortex is bordered caudally by the olfactory areas and the anterior insula, and rostrally it extends to the frontal pole. The most anterior part encompasses area 10, the only prefrontal area to have orbital, medial and lateral components.

This chapter focuses primarily on the caudal part of the OFC, the part with the strongest and most specialized anatomic interactions with temporal lobe structures. References to the OFC here do not include the basal (orbital) part of area 10, whose structural features and connections differ from other orbitofrontal areas. In addition, the discussion does not include the cortex of the medial wall, namely areas 9, 14 and 10 rostrally, or areas 24, 32 and 25 in the anterior cingulate. The areas of the medial wall are not geographically part of the OFC and have a distinct set of connections. In the rhesus monkey, areas 14 and 25 extend over a short distance to the medial edge of the basal surface (Barbas and Pandya 1989). The connections of the orbital parts of areas 14 and 25 are similar to their medial counterparts, and are not included in the descriptions of the OFC.

Areas 14, 25, and 32 share some features with the OFC, but also differ from the OFC in several key connections. We suggest that medial and orbitofrontal cortices have distinct roles in emotional function and cognitive-emotional interactions, as discussed towards the end of this chapter.

The focus of this review is on those orbitofrontal cortices that are situated lateral to areas 14 and 25, as shown in Figure 4.1. The orbitofrontal region is composed of several types of cortices, including an agranular area, which has only three identifiable layers, dysgranular areas (which have four identifiable layers), and granular (eulaminate) areas, which have six distinct layers. Agranular and dysgranular type cortices are collectively called limbic. The distinction of eulaminate from limbic cortices has several implications for the organization of connections and ultimately the function of these structurally distinct cortices (Dombrowski *et al*. 2001). On the one hand, higher laminar complexity increases local processing power, but, on the other hand, limbic areas have widespread connections and may exercise a tonic influence on the neuraxis (Barbas 1995b). The significance of cortical type is underscored by evidence that the pattern of cortico-cortical connections can be predicted on the basis of the broad laminar features of the interconnected areas (Barbas 1986; Barbas and Rempel-Clower 1997; Barbas 2000b), as discussed under the section titled "The role of the OFC in emotional memory".

The rostral extent of the the OFC includes areas 11 and the orbital part of area 12, both of which are eulaminate areas, characterized by six layers, including a distinct granular layer 4. The most caudal extent of the OFC includes the agranular cortex, which lacks a granular layer 4, and has been named area OPAll (Barbas and Pandya 1989), or area OFap (Morecraft *et al*. 1992), which are coextensive. The agranular cortex has been subdivided into areas13a, Iam, Iapm by Carmichael and Price (1994). The agranular cortex is bordered laterally and rostrally by the dysgranular cortex, which has an incipient granular layer 4 [area OPro in (Barbas and Pandya 1989); OFdg in (Morecraft *et al*. 1992); Iai, Ial, Iapl in (Carmichael and Price 1994)]. An adjacent region, area 13, is also dysgranular in type (Barbas and Pandya 1989). Area 13 is incorporated into area OFdg in the map of (Morecraft *et al*. 1992, and is largely coextensive with areas 13b, 13m, 13l in the map of (Carmichael and Price 1994). References to architectonic areas in this chapter and in Figure 4.1 are according to the map of (Barbas and Pandya 1989), which was modified from the classic map of (Walker 1940).

There are both structural and connectional features to suggest that the posterior and anterior orbitofrontal cortices (areas OPAll, OPro and 13, O12, 11, respectively) are distinct areas. From a structural perspective, the identity of individual areas can be determined objectively by analyzing their architectonic features using unbiased quantitative methods (Dombrowski *et al*. 2001). As shown in Figure 4.1, area l 'fingerprints' based on highly informative cellular features can distinguish among architectonic areas in the orbitofrontal region. These features include neuronal density, the total number of neurons found under 1 mm^2 (which depends on the depth of the cortex), and the distribution of two classes of inhibitory neurons, identified by the expression of the calcium binding proteins parvalbumin (PV) and calbindin (CB). The quantitative architectonic profiles demonstrate the individuality of orbitofrontal areas, but also suggest similarities among areas. Fingerprints based on these features suggest that the posterior orbitofrontal areas OPAll and OPro have similar architectonic profiles, as do areas O12 and 11. Area 13 occupies an intermediate position between the caudally situated areas OPro and OPAll, on one hand, and the rostrally situated areas O12 and 11, on the other. Consistent with the architectonic findings, area 13 shares connectional features with its rostral and caudal neighbors. Moreover, although area 13 and area OPro are both dysgranular and have been considered to be one area (Morecraft *et al.* 1992), their quantitative architectonic profiles suggest that they are distinct.

We present evidence that connectional features distinguish the posterior (areas OPAll, OPro) from the anterior orbitofrontal cortices. The topography and pattern of connections of the posterior OFC suggest that they are earlier processing areas for emotional information than the anterior orbitofrontal areas. Throughout this chapter we focus on the most striking features of posterior OFC, as they pertain to emotions. Posterior orbitofrontal cortices are connected with anterior orbitofrontal areas, which, in turn, are connected with lateral prefrontal areas, in pathways that likely underlie the flow of information for the synthesis of cognitive and emotional processes.

4.3. **The posterior orbitofrontal cortex is a global environmental integrator**

Processing signals from the external environment

Analysis of the features of the environment is prerequisite to emotional processing. The OFC, in general, is distinguished for its multimodal circuitry, comparable in this respect to the perirhinal region in the temporal lobe (Van Hoesen *et al.* 1972; Van Hoesen 1975; Insausti *et al.* 1987; Suzuki and Amaral 1994), with which it has strong connectional and functional ties. The orbitofrontal cortices are enriched with projections from visual, auditory, somatosensory, and polymodal cortices (Morecraft *et al.* 1992; Barbas 1993; Carmichael and Price 1995b). While all orbitofrontal areas receive projections from several unimodal sensory association cortices, there are foci within the OFC that receive more robust projections from one modality over the others (e.g., Morecraft *et al.* 1992; Barbas 1993; Baylis *et al.* 1995; Carmichael and Price 1995b); [(Cavada *et al.* 2000; Barbas *et al.* 2002)]. However, it should be noted that neurophysiological studies show considerable overlap of sensory inputs within the OFC and many neurons respond to stimuli from several modalities (Kringelbach and Rolls 2004).

The posterior orbitofrontal areas (areas OPro, OPAll) have the most multimodal circuits. They are distinguished for their unique connections with olfactory cortices (Barbas 1993; Carmichael *et al.* 1994), in addition to connections with visual, auditory, somatosensory, and gustatory cortices (Takagi 1986), as shown in an example in Figure 4.2. The anterior orbitofrontal areas also receive input from visual, auditory, and somatosensory areas. In addition, area 12 and rostral area 13 receive projections from

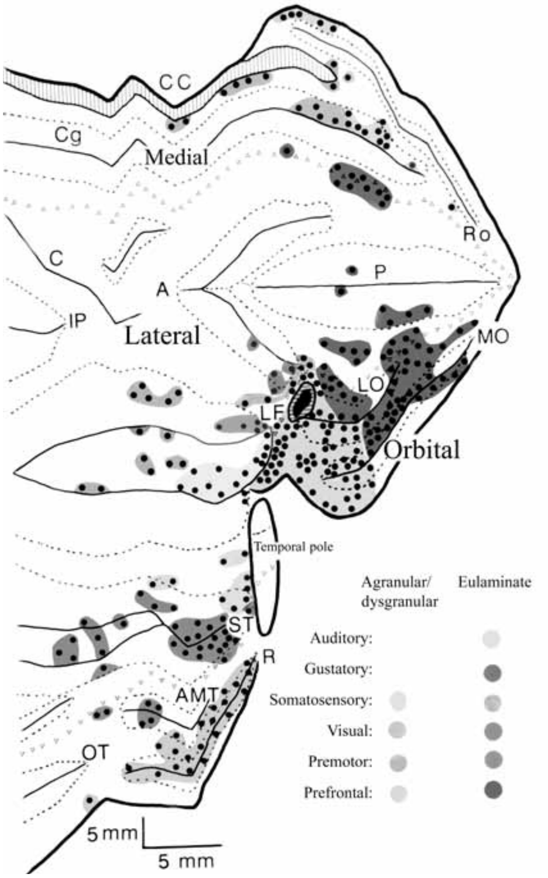

Fig. 4.2 Diverse cortical projections in orbitofrontal cortex. Unfolded two-dimensional map of the prefrontal cortex showing the origin of projection neurons (black dots) directed to orbitofrontal area OPro on the basal surface (black area, injection site; surround horizontal lines, halo of injection site). Projection neurons originate in visual association (overlay), gustatory (●), somatosensory (●), auditory (●), premotor (●) and prefrontal cortices (●). Area OPro receives some projections from the olfactory prepiriform cortex as well (not shown). Dark shades show eulaminate areas, light shades agranular/dysgranular (limbic) cortices. Triangles separate the medial (top) from the lateral (center) surfaces, and the lateral from the basal (bottom) surfaces. Vertical stripes (top) show the corpus callosum. A, arcuate sulcus; AMT, anterior middle temporal dimple; C, central sulcus; CC, corpus callosum; Cg, cingulate sulcus; IP, intraparietal sulcus; LF, lateral fissure; LO, lateral orbital sulcus; MO, medial orbital sulcus; OT, occipitotemporal sulcus; P, principal sulcus; R, rhinal sulcus; Ro, rostral sulcus; ST, superior temporal sulcus;

gustatory areas. However, the rostral orbitofrontal areas do not receive direct projections from olfactory areas (Morecraft *et al.* 1992; Barbas 1993; Carmichael *et al.* 1994).

The sensory input to all orbitofrontal cortices originates from late-processing sensory association areas (Barbas 1992; Barbas 1995a). The sole exception to this pattern is the

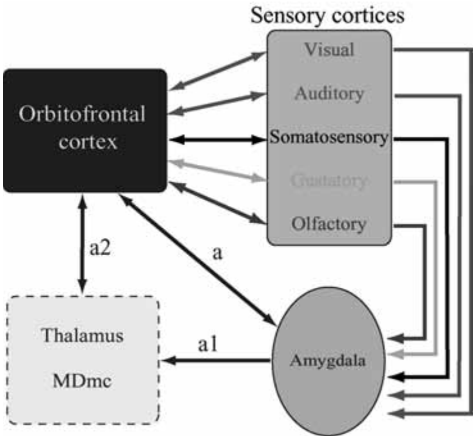

Fig. 4.3 Direct and indirect sensory input to orbitofrontal cortex. Projections from sensory association cortices reach orbitofrontal cortex as well as the amygdala, which has strong bidirectional connections with orbitofrontal cortex (a). The amygdala also projects to MDmc of the thalamus (a1), which has strong bidirectional connections with orbitofrontal cortex (a2). The connections of the amygdala with sensory areas are presumed to be bidirectional as well.

olfactory input to the posterior OFC, which emanates from the piriform cortex and the anterior olfactory nucleus (Barbas 1993) that are considered to be a part of the primary olfactory cortex (Price 1990). Unlike the large extent of cortical areas devoted to the visual, auditory and somatosensory modalities, the olfactory cortex is comparatively small in macaque monkeys.

Processing signals from the internal environment

The above discussion shows that through their connections with sensory association cortices, the OFC can sample the entire sensory periphery (Figure 4.3). In addition, input from the internal environment, related to drives and motives, is necessary for emotional processing. In this respect, all orbitofrontal areas receive particularly robust projections from cortical limbic areas in the medial temporal lobe and the cingulate cortex (Cavada *et al*. 2000; Barbas 2000a), which likely provide information about the internal environment. In addition, as discussed below, the OFC has a special relationship with the amygdala, and strong connections with the medial thalamic nuclei that belong to the limbic thalamus. To sum up, the OFC can be viewed as an integrator of the external and internal environments, a feature that may be necessary for signaling the emotional significance of events.

Specialized bidirectional connections linking orbitofrontal cortex with the amygdala may underlie emotional processing

One of the most distinctive features of the OFC is its anatomic and functional linkage with the amygdala, an anterior temporal structure with a key role in emotions (Nishijo *et al.* 1988; Davis 1992; Damasio 1994; LeDoux 1996). The anatomic connections of the OFC with the amygdala are robust and bidirectional (Nauta 1961; Pandya *et al.* 1973; Jacobson and Trojanowski 1975; Aggleton *et al.* 1980; Porrino *et al.* 1981; Van Hoesen 1981; Amaral and Price 1984; Barbas and De Olmos 1990; Morecraft *et al.* 1992; Carmichael and Price 1995a; Chiba *et al.* 2001). The projections from the OFC are organized along a rostrocaudal gradient. The strongest connections in this circuit involve the posterior sector of the OFC and the posterior half of the amygdala (Ghashghaei and Barbas 2002; Barbas and De Olmos 1990; Stefanacci and Amaral 2002). Moreover, the amygdala resembles the OFC in its wealth of circuits with sensory areas, as summarized in Figure 4.3. Like the OFC, the amygdala receives projections from the sensory association cortices representing each of the sensory modalities (Herzog and Van Hoesen 1976; Turner *et al.* 1980). Like the OFC, the cortical sensory projections to the amygdala originate preferentially in areas representing late-processing sensory cortices, which are specialized in processing the features of stimuli and their memory.

Direct and indirect sensory input to orbitofrontal cortex may be necessary for emotional processing

The above discussion suggests that sensory input reaches the OFC directly by projections from sensory association cortices, and indirectly through the amygdala, which receives projections from the same sensory association cortices, as depicted in the diagram in Figure 4.3. However, previous studies did not directly investigate whether the sectors of the amygdala that receive sensory information are the same sites that are connected with orbitofrontal cortices. A recent study addressed this issue in the same experiments, and provided direct evidence that pathways from anterior temporal visual and auditory association cortices, on one hand, and caudal orbitofrontal areas, on the other, occupy overlapping territories within the basal complex of the amygdala (Ghashghaei and Barbas 2002). This evidence suggests that a closely linked triadic network links the amygdala, orbitofrontal, and anterior temporal cortices. Moreover, this circuit implies that sensory input reaches orbitofrontal cortices directly through cortico-cortical pathways (Barbas 1993; Rempel-Clower and Barbas 2000), and indirectly through the amygdala (Barbas 1995a). This highly organized network may form the basis for processing the emotional significance of events within a behavioural context, forming reward associations in cognitive tasks that are inextricably linked with emotional associations (Malkova *et al.* 1997; Schoenbaum *et al.* 1999; Hikosaka and Watanabe 2000; Baxter *et al.* 2000; Wallis and Miller 2003). There is evidence that orbitofrontal areas have an important role in encoding in long term memory changes in reward contingencies that accompany changes in task demands (Tremblay and Schultz 2000). Neurons in the OFC and the amygdala respond to sensory stimuli when they are significant for behaviour, and cease to respond when the stimuli lose their motivational value (Lipton *et al.* 1999; Tremblay and Schultz 1999; Schoenbaum *et al.* 2000). This habituation of activity has also been shown in recent functional imaging studies of the human amygdala during repeated exposure to fearful and neutral faces, suggesting the regulation of neural activity in the brain regions involved in detecting novelty (Fischer *et al.* 2003). The mechanisms for this habituation are unclear, but it is possible that there is a reduction in the allocation of resources to the stimuli of decreasing salience.

The motivational value of the stimuli mentioned above is in many cases dependent on reward expectancy, which is based on information provided by associated reward-predicting stimuli. Numerous studies have shown that neurons in the OFC and the amygdala respond to reward-predicting cues and are also activated in relation to the expectation and detection of reward (Schoenbaum and Eichenbaum 1995; Schoenbaum *et al.* 1999; Tremblay and Schultz 2000; Schoenbaum *et al.* 2003; Saddoris *et al.* 2005); (Schultz *et al.* 2000; Rolls 2000; Baxter and Murray 2002).

Relationship of orbitofrontal cortex to striatal and brainstem reward centres

The striatum (including the nucleus accumbens) is another brain region that responds similarly to the OFC, but is additionally activated during the preparation, initiation and execution of movements, related to the expected reward (Schultz *et al.* 2000). As lesion studies have indicated, the nucleus accumbens (NAc) is critical for encoding and using information regarding the learned significance of cues predictive of reward or aversive outcome (Schoenbaum and Setlow 2003). Just like the OFC and the amygdala, the NAc is a site of convergence for numerous sources of motivational information, including the basolateral complex of the amygdala (BLA), the OFC, the medial prefrontal cortex and dopaminergic ventral tegmental area (VTA) neurons (Groenewegen *et al.* 1990; Lynd-Balta and Haber 1994; Haber *et al.* 1995; Phillips *et al.* 2003). Studies in the rat have shown that dopamine terminals from the VTA synapse on PFC pyramidal cells that project to the NAc. Moreover, in rats there seems to be a selective PFC synaptic input to GABA-containing mesoaccumbens and dopamine-containing mesocortical VTA neurons (Carr *et al.* 1999; Carr and Sesack 2000). A direct path from BLA sends glutamatergic afferents to the NAc that overlap anatomically and functionally with dopaminergic afferents in this nucleus. Indirectly, the central nucleus of the amygdala probably disinhibits dopaminergic neurons in the VTA, which project to the NAc (Phillips *et al.* 2003). Thus, it appears that information about the value of stimuli is conveyed from the amygdala to the NAc, where it can be potentiated or “gain-amplified” by dopamine (Cardinal *et al.* 2002). Although links between the PFC, the amygdala, the ventral striatum and the midbrain dopaminergic neurons exist in the primate brain (Fudge and Haber 2000; Ghashghaei and Barbas 2002), to date there are no detailed studies demonstrating overlaps and other possible interactions of those pathways. This is in contrast to the compelling literature analyzing such interactions in the rat brain and therefore, any cross-species comparisons should be made with caution.

Midbrain dopamine neurons, which respond to unpredicted primary rewards, also rapidly adapt to the information provided by reward-predicting stimuli (Schultz *et al.* 2000) and through interactions with the NAc, the amygdala and the OFC adjust the gain of reward-related responses participating in mechanisms that select the action associated

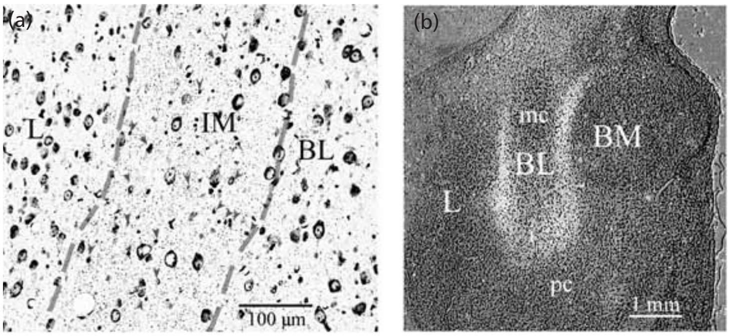

Fig. 4.4 Pattern of axonal terminations from posterior orbitofrontal cortex in the amygdala. (a) Brightfield photomicrograph showing the intercalated masses of the amygdala (IM) interposed between the nuclei of the amygdala, which are composed of small neurons and are GABAergic. (b) Darkfield photomicrograph of the section shown in A, showing axons from posterior orbitofrontal area OPro targeting heavily the intercalated masses of the amygdala (white grain), found between the lateral (L), basolateral (BL) and basomedial (BM; also known as accessory basal) nuclei of the amygdala.

Source: Adapted from Ghashghaei and Barbas 2002. "See Plate section in the color gallery."

with the largest reward (Kalivas and Nakamura 1999; Cardinal *et al*. 2002; Tobler *et al*. 2005). Therefore, the circuitry linking midbrain dopaminergic neurons, NAc, amygdala and OFC is clearly implicated in a variety of reward perception and adaptive behavioural responses. It seems that dopaminergic afferents signal changes in the availability or receipt of rewarding stimuli, the value of which is potentiated in the NAc, whereas the input from the amygdala enables necessary associations with the conditioned stimuli, and afferents from the OFC integrate the information from short-term memory into behavioural responses. Complex interactions between these structures play an important role in forming associations between specific sensory stimuli and biologically significant events that have emotional and motivational valence.

Distinction of input-output zones in the amygdala linking it with posterior orbitofrontal cortex

As discussed above, the connectional studies show that the posterior OFC is robustly connected with the caudal sector of the amygdala, and both the structures receive projections from sensory cortices representing each sensory modality. The most striking distinguishing feature of the connections of orbitofrontal areas with the amygdala is in their pattern. Axons from posterior orbitofrontal areas terminate around the borders of the magnocellular basolateral nucleus, forming a dense U-shaped pattern (Ghashghaei and Barbas 2002), as shown in Figure 4.4. Projection neurons in the amygdala directed to posterior orbitofrontal areas are positioned around the axonal terminations, occupying adjacent sites of the basal complex (Ghashghaei and Barbas 2002). This unique pattern of connectivity suggests a certain degree of segregation of input and output zones in the amygdala that link it with the posterior OFC. No other prefrontal areas show such remarkable degree of anatomic specialization in the amygdala.

The projections from the posterior OFC are particularly striking for preferentially targeting the outskirts of the basal complex of the amygdala, and terminating most densely not in the basal nuclei themselves, but in the narrow margins interposed between the nuclei of the basal complex (Fig. 4a). The margins include a dense array of small neurons, known as intercalated masses (IM), whose function was unknown in classic studies (De Olmos 1990). It is now evident that neurons in most IM nuclei in macaques are GABAergic (Pitkanen and Amaral 1994), as they are in several other species, and project to the central nucleus of the amygdala, the basal forebrain, and the brainstem (Moga and Gray 1985; Nitecka and Ben Ari 1987; Paré and Smith 1993a; Paré and Smith 1993b; Paré and Smith 1994; Pitkanen and Amaral 1994). The central nucleus, in turn, is enriched in inhibitory neurons, and is the main output of the amygdala to hypothalamic and brainstem autonomic structures (Jongen-Relo and Amaral 1998; Saha *et al*. 2000; Ghashghaei and Barbas 2002).

Implications of orbitofrontal circuits in behavior

Evidence on the GABAergic nature of IM neurons adds special significance to the pattern of projections from posterior the OFC to the amygdala. Thus, beyond the reciprocity of connections linking orbitofrontal areas with the basal nuclei of the amygdala, caudal orbitofrontal efferents target heavily and unidirectionally the intercalated masses, suggesting a direct influence on an internal system of the amygdala. The characteristic pattern of termination is evident only for axons originating in the posterior OFC. Neither rostral orbitofrontal, nor medial prefrontal areas show this pattern of connection with the amygdala. A previous study includes a figure that shows this pattern (van Hoesen 1981), without reference to the IM, as it predated recent studies on the significance of the IM in inhibitory control within the amygdala (Moga and Gray 1985; Paré and Smith 1993b; Paré and Smith 1994).

On the basis of the above evidence, we summarize the implications of the circuitry from the posterior OFC to the IM of the amygdala in Figure 4.5. This circuitry suggests that orbitofrontal projections have a net effect of suppressing activity in the central nucleus and down-regulating its inhibitory output to hypothalamic and brainstem autonomic centres. The orbitofrontal pathway to the IM thus appears to have a permissive effect on autonomic centres, allowing the activation of hypothalamic and brainstem autonomic centres as the circumstance demands. Activity in hypothalamic and brainstem autonomic centres can be enhanced by direct excitatory projections from orbitofrontal and medial prefrontal areas (Ongur *et al*. 1998; Rempel-Clower and Barbas 1998; Barbas *et al*. 2003). Pathways with disinhibitory or excitatory effects on the hypothalamus and brainstem may be recruited when the synergistic activity of the amygdala and the OFC signal an emotionally charged circumstance. This could arise when a potential danger lurks in the environment, such as a loud noise that may suggest a dangerous explosion.

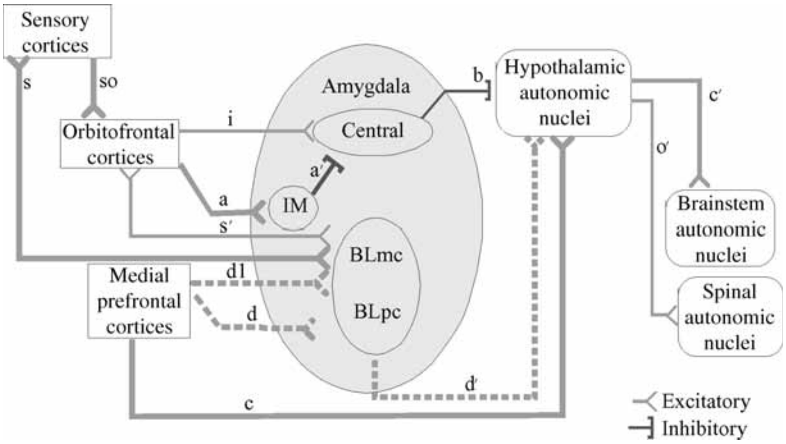

Fig. 4.5 Summary of pathways linking prefrontal cortex with structures associated with perception and expression of emotions. Line thickness represents the density of projections. The orbitofrontal cortex as sensor of the environment*:* The orbitofrontal cortex and the amygdala receive projections from every sensory modality through the cortex (pathways so, s), and are interconnected, providing pathways for direct (so), and indirect (s and s') sensory input to orbitofrontal cortex. The orbitofrontal cortex disinhibits hypothalamic autonomic centers: Orbitofrontal axons terminate heavily in the intercalated masses of the amygdala (IM, pathway a), which project to the central nucleus (a'), which projects to hypothalamic autonomic centers (pathway b). Activation of pathways (a, a') leads to disinhibition of hypothalamic autonomic centers, which innervate brainstem and spinal autonomic centers (pathways c', o'). Posterior medial prefrontal (anterior cingulate) areas as effectors for emotional expression: A direct pathway from medial prefrontal cortex innervates hypothalamic autonomic centers (c), forming asymmetric, and presumed excitatory synapses in the lateral and posterior hypothalamic areas (not shown); this pathway also innervates brainstem autonomic centers (not shown). An indirect pathway courses from medial prefrontal cortices to the parvicellular sector of the basolateral nucleus of the amygdala (BLpc, pathway d), which projects to hypothalamic autonomic centers (d'), and is presumed to be excitatory. Activation of the direct or indirect pathways ultimately activates brainstem and spinal autonomic nuclei (pathways c, c', o'), which directly innervate peripheral organs. Red, inhibitory pathways; green, excitatory pathways.

Source: From Barbas *et al.* 2003.

There is yet another pathway from the caudal OFC, which is lighter than the pathway to IM, and targets directly the central nucleus of the amygdala (Carmichael and Price 1995a; Ghashghaei and Barbas 2002). The activation of this pathway would have an effect opposite to that of the pathway to the IM by inhibiting autonomic centres. This pathway has the potential to suppress the hypothalamic autonomic activity, and may be recruited when further information arrives that the loud noise was from a bursting balloon and was harmless.

The above circuits suggest that a highly specialized set of connections links the OFC with the amygdala. This circuit partially segregates the input and output zones in the amygdala that link it with the posterior OFC. In addition, the circuit has specific effects on the internal systems of the amygdala. A robust pathway from the posterior OFC to the

IM is positioned to increase the autonomic drive, and a smaller direct pathway to the central nucleus of the amygdala is consistent with a dampening autonomic drive. No other area shows such a remarkable degree of specificity for processing signals related with emotionally charged events as the posterior OFC. Further, the posterior OFC shares with the sensory association cortices sites of interaction in the basal complex of the amygdala (Ghashghaei and Barbas 2002). On the basis of the highly specific circuits, we suggest that the caudal OFC is the earliest processing cortical area for emotional signals.

The proposed circuits have functional implications for information processing through the amygdala. The orbitofrontal to IM pathway may be akin to the pathway from the cortical areas to the basal ganglia (Alexander *et al.* 1986). In the cortico-striatal system, cortical axons target inhibitory neurons in the neostriatum, which innervate and inhibit neurons in the internal segment of the globus pallidus (GPi), which, in turn, synapse and inhibit the motor nuclei of the thalamus. These thalamic nuclei, such as the ventral anterior nucleus, have robust and bidirectional connections with the frontal cortex, including premotor and prefrontal cortices (McFarland and Haber 2002; Xiao and Barbas 2004). The mediodorsal nucleus, which is the principal thalamic relay for prefrontal cortices, also receives projections from GPi. The overall effect of the activation of the corticostriatal system is disinhibition downstream, at the level of the thalamus, allowing the activation of other circuits. In the corticostriatal system, the final effect is disinhibition of the motor nuclei of the thalamus and the mediodorsal nucleus, allowing the initiation of executive functions and motor activity through an activation of the reciprocal pathways with the frontal cortex, including prefrontal, premotor and motor areas.

By analogy with the corticostriatal system, in the orbitofrontal pathways to the IM nuclei of the amygdala, the final effect is the disinhibition of hypothalamic autonomic centres. The hypothalamus, in turn, is disinhibited, allowing its activation from other sources. Posterior orbitofrontal cortices as well as posterior medial prefrontal cortices in the anterior cingulate project robustly to hypothalamic autonomic centres (Rempel-Clower and Barbas 1998; Ongur *et al.* 1998). A pathway from medial area 32 forms excitatory synapses with hypothalamic neurons (Barbas *et al.* 2003), comparable to the highly efficient thalamocortical system (Ahmed *et al.* 1994). The hypothalamus, in turn, can activate brainstem and spinal autonomic centres (Barbas *et al.* 2003), the final efferent pathway to autonomic organs, such as the lungs and heart, whose activity increases during an emotional arousal.

4.4. Conscious awareness of the significance of the environment may depend on the OFC

The above evidence suggests that the topography and pattern of the connections linking the amygdala with the OFC likely underlie the processing for emotional behaviour, but do not necessarily indicate that this interaction is critical for interpreting the emotional significance of events for action. A clue that the interaction between the amygdala and the OFC is necessary for a conscious appreciation of emotions emerged from disparate experimental approaches. For example, there is evidence that activity in the human amygdala can increase even when stimuli are presented tachistoscopically, below the level of conscious awareness (Whalen *et al*. 1998). A subcortical pathway between the right amygdale and the pulvinar and superior colliculus seems more active than pathways between the amygdala and the OFC in similar situations (Morris *et al*. 1999). Similarly, in rats, a short subcortical loop connecting the amygdala with the thalamus can support fear conditioning (Romanski and LeDoux 1992). The wiring of the amygdala appears to allow fast and fairly automatic processing for emotional attention and vigilance through its connections with limbic structures underlying the processing of the internal environment. In this sense the amygdala may act as a supraspinal reflex for the internal milieu, poised to direct attention to an event of significant emotional import.

The above evidence raises the question of the neural structure(s) that may account for awareness of the emotional significance of the environment, which is necessary for taking informed action. Classic studies indicate that the cortex is necessary for conscious perception of emotions (Kennard 1945). We suggest that the direct and indirect connections of orbitofrontal cortices with sensory cortices (discussed above) have a critical role in this function. Direct cortical sensory input may provide a global overview of the external environment, and the indirect sensory input through the amygdala may provide the emotional context necessary to interpret the significance of environmental events (Barbas 1995a). The connectional architecture between the caudal OFC and the amygdala allows several processes to occur. First, the partial segregation of input and output zones that link the amygdala with the posterior OFC may allow local processing within the amygdala, akin to the processing among linked layers within a cortical column. Second, the bidirectional connections between the OFC and neurons of the basal nuclei of the amygdala may allow prolongation of a signal between the OFC and the amygdala, as sensory information is assessed to determine whether autonomic structures must be recruited. This prolongation of activity may be comparable to the enhancement of feature-specific activity in sensory cortices, such as between the primary visual cortex and the lateral geniculate nucleus in nonhuman primates (Sillito *et al*. 1994). In this case, feedback cortical projections to the thalamus lead to the synchronization of "preferred" or "relevant" relay cell firing, effectively increasing the gain of the input for feature-linked events detected by the cortex. By analogy with the sensory cortex, the IM nuclei, the basal nuclei, and the central nucleus of the amygdala may be likened to different layers, allowing local control of neural computations. The entire complement of extrinsic and intrinsic connections of the amygdala enables monitoring, updating, and integrating sensory signals, so that an adequate judgment can be made regarding the emotional significance of events. This may be necessary in order to determine to what extent autonomic structures need to be recruited.

4.5. **The role of the OFC in emotional memory**

Connections with medial temporal cortices

Common experience tells us that people zero in on stimuli that are emotionally salient in the environment, be it a beautiful flower or a colorful bird while walking through a meadow, or a terrible accident while driving on a busy highway. Such motivationally relevant stimuli are more likely to be remembered among the barrage of "neutral" stimuli impinging upon our senses at any one time. In this respect, the posterior OFC has strong connections with several structures associated with long-term memory that may process emotionally salient information. Some of these connections involve the entorhinal (area 28) and perirhinal (areas 35, 36) cortices (van Hoesen *et al.* 1975; Morecraft *et al.*1992; Barbas 1993; Carmichael and Price 1995a). These medial temporal areas are interconnected, and the entorhinal cortex robustly innervates the *Hippocampus* (Witter *et al.* 1989; Leonard *et al.* 1995; Nakamura and Kubota 1995; Suzuki *et al.* 1997; Rosene and Van Hoesen 1987; Squire and Zola 1996). But what is the nature of the input transmitted from the posterior OFC to the entorhinal cortex? As discussed above, the OFC has widespread connections with sensory areas and with the amygdala, and is in a strategic position to process information about the emotional significance of stimuli, and to associate stimuli with reward (Rolls 1996; Watanabe 1998). Neurons in the OFC respond to stimuli that predict reward (Tremblay and Schultz 1999). This process requires memory for associations between specific stimuli, and that is based largely on the emotional significance of such experiences (Cahill and McGaugh 1998). In humans, the OFC has a specific role in distinguishing between mental representations of the current situation and irrelevant memories (Schnider and Ptak 1999; Schnider *et al.* 2000). The orbitofrontal cortex thus is in a strategic position to issue signals about emotional significance to the entorhinal cortex, which may be used to encode events into long-term memory.

Of special significance in this context is the pattern of connections, as axons from the OFC innervate the middle layers of the entorhinal cortex (Rempel-Clower and Barbas 2000). By analogy with sensory systems, this laminar pattern of projection is associated with "feedforward" or "bottom-up" communication, linking earlier processing areas with later processing areas. This pattern is contrasted with projections that terminate mostly in layer I, linking the later processing and earlier processing cortices. This evidence suggests that the orbitofrontal cortical input to the entorhinal cortex reflects feedforward rather than feedback projections.

We have previously linked the laminar pattern of connections to the structural relationship of the linked areas within the prefrontal cortex (Barbas and Rempel-Clower,1997), a model supported in the connections between prefrontal and temporal areas as well (Barbas 1986; Barbas *et al.* 1999; Rempel-Clower and Barbas 2000; Barbas *et al.* 2005b). The structural model for connections states that the pattern of connections is determined by the structural relationship of the connected areas. In this model, "forward" or bottom-up connections simply reflect connections proceeding from an area with either more layers or higher cell density than the cortex of destination. According to the rules of the structural model, projections from the dysgranular posterior OFC to the agranular entorhinal cortex are expected to be mostly "feedforward", which is substantiated by data (Rempel-Clower and Barbas 2000), and shown in Figure 4.6. By analogy with sensory systems, "forward" projections reflect "bottom-up" processing. It is thus possible that information gathered from sensory areas is processed in the OFC and sent as feedforward signals to the entorhinal cortex to encode an emotionally memorable event into long-term memory through projections to the *Hippocampus*. In turn, the

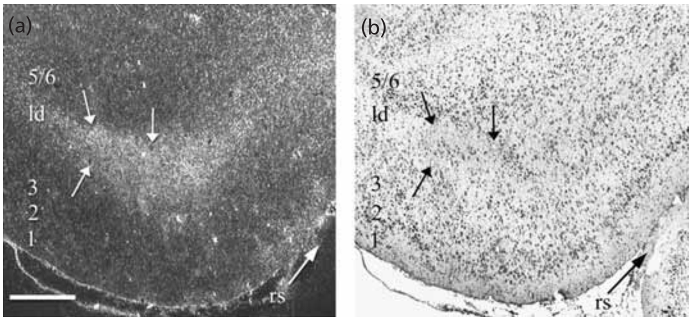

Fig. 4.6 *"Forward" pattern of termination from orbitofrontal cortex to entorhinal cortex*. (a) Pathways from orbitofrontal cortex terminate preferentially in the middle layers of the entorhinal cortex in the temporal lobe (white grain), the lamina dissecans (ld), shown under darkfield illumination. (b) Brightfield photomicrograph of the same section, showing the cell sparse lamina dissecans (ld). Numbers indicate cortical layers. rs, rhinal sulcus. Arrows show matching blood vessels. Scale bar, 500 μm.

Source: Adapted from Rempel-Clower and Barbas 2000.

Hippocampus sends direct projections to the posterior OFC (Rosene and Van Hoesen 1977; Barbas and Blatt 1995; Insausti and Munoz 2001). A recent study suggests that the *Hippocampus* is part of a flexible, rapid memory system that forms unique associations between the places where rewards are found in the environment (Rolls and Xiang 2005). Therefore, there seems to be a close interaction between the hippocampal learning system and the orbitofrontal cortical system involved in associating objects and rewards. Lesions of the OFC in rhesus monkeys and marmosets impair rapid object-reward learning (Pears *et al.* 2003; Izquierdo *et al.* 2004).

Common connections of the orbitofrontal cortex and the amygdala with the mediodorsal and anterior thalamic nuclei

In addition to having a panoramic view of the entire sensory environment, the OFC and the amygdala have another feature in common: the well-known projection to the magnocellular part of the thalamic mediodorsal (MDmc) nucleus (Aggleton *et al.* 1980; Aggleton and Mishkin 1984; Russchen *et al.* 1987). The significance of this common connection is based on the role of the MDmc nucleus in long-term memory and emotional memory. Specifically, the OFC is connected preferentially with the caudal part of the MD (Barbas *et al.* 1991; Dermon and Barbas 1994), whose damage in both human and nonhuman primates results in severe deficits in long-term memory (Victor *et al.* 1971; Isseroff *et al.* 1982; Zola-Morgan and Squire 1985). The interconnected network linking the amygdala, the MD and the OFC (Fig. 3) may underlie the processing of emotionally significant events into long-term memory.

There is yet another common thalamic pathway between the amygdala and the OFC, the anterior medial (AM) nucleus (Xiao and Barbas 2002b). The AM is part of the anterior thalamic limbic nuclei (Armstrong 1990), and links several orbitofrontal areas, as well as anterior cingulate areas with multiple systems underlying the processing of long-term memory and emotions (Xiao and Barbas 2002a; Xiao and Barbas 2002b). Like MDmc, the anterior thalamic nuclei are part of a circuit associated with long-term memory, through direct connections with the hippocampal formation, a circuit seen in several species, including rats, cats and monkeys (Meibach and Siegel 1977; Somogyi *et al.* 1978; DeVito 1980; Aggleton *et al.* 1986; Van Groen and Wyss 1990).

The implication of the anterior nuclei in long-term memory has emerged from behavioural studies(Aggleton and Brown 1999). There is evidence that monkeys with lesion of the anterior thalamus, including the AM nucleus and the MD, are impaired in object recognition and in associating objects with reward (Aggleton and Mishkin 1983). In humans, infarction of the AM nucleus results in deficits in episodic and recognition memory (Parkin *et al.* 1994; Ghika-Schmid and Bogousslavsky 2000; Nolan *et al.* 2001; Kishiyama *et al.* 2001; Gaffan and Gaffan 1991). In diseases affecting long-term memory, including Alzheimer's disease, and Korsakoff's syndrome, there are structural abnormalities or neuronal loss in the AM nucleus (Victor *et al.* 1971; Mair *et al.* 1979; Braak and Braak 1991; Kopelman 1995; Braak *et al.* 1996).

Beyond their role in long-term memory, the anterior thalamic nuclei are a focal point in the classic circuit for emotions, as proposed by Papez on the basis of clinical observations (Spiegel and Wycis 1962; Mark *et al.* 1963; Mark *et al.* 1970; Clarke *et al.* 1994; Young *et al.* 2000; Ghika-Schmid and Bogousslavsky 2000; George *et al.* 2001; Tasker and Kiss 1995). The association of the AM nucleus in emotional behaviour is also evident in other species. For example, in rats, lesion of the AM nucleus reduces auditory fear conditioning responses (Celerier *et al.* 2000).

The initial circuit proposed by Papez did not include the amygdala (Papez 1937). As discussed above, there is strong evidence that the amygdala is an important component in circuits underlying emotional processing. Recent evidence indicates that the amygdala projects to the AM thalamic nucleus as well (Xiao and Barbas 2002b). This circuit, therefore, extends the classic circuit for emotions, and further demonstrates a common link between the OFC and the amygdala, with the MD as well as the AM nucleus. The involvement of both of these thalamic nuclei in long-term memory and emotions suggests that they may have a special role in emotional memory.

The rich variety of the connections of orbitofrontal areas extends to their thalamic connections as well. In contrast to lateral prefrontal cortices, whose thalamic projections originate predominantly in the multiform and parvicellular sectors of the mediodorsal nucleus, orbitofrontal areas receive substantial projections from numerous “limbic” thalamic nuclei, including the midline and anterior, in addition to projections from MDmc (Barbas *et al.* 1991; Dermon and Barbas 1994). The intralaminar thalamic nuclei also provide a significant projection to posterior orbitofrontal and posterior medial areas, and to a lesser extent to rostral orbital areas, another feature that differentiates the posterior from the anterior orbitofrontal cortices (Dermon and Barbas 1994).

4.6. **Orbitofrontal-striato-thalamic circuits for emotional processing**

The prefrontal cortex is an action-oriented region, a feature generally associated with lateral prefrontal areas. But are all prefrontal areas, including the OFC, associated with action? The prefrontal cortex, in general, has a special relationship with the basal ganglia, because it not only projects to the neostriatal parts of the basal ganglia, like the rest of the cortex, but its thalamic interactions are modulated by signals from the internal segment of the globus pallidus (GPi). Among the thalamic nuclei that project to prefrontal cortex, the MD and ventral anterior (VA) receive the most prominent projections from GPi (Steriade *et al*. 1997). The VA nucleus is connected with prefrontal as well as premotor areas (Kievit and Kuypers 1977; Jacobson *et al*. 1978; Kunzle 1978; Baleydier and Mauguiere 1980; Ilinsky *et al*. 1985; Asanuma *et al*. 1985; Goldman-Rakic and Porrino 1985; Preuss and Goldman-Rakic 1987; Yeterian and Pandya 1988; Barbas *et al*. 1991; Chiba *et al*. 2001; Middleton and Strick 2002; McFarland and Haber 2002); (Cavada *et al*. 2000) in circuits classically implicated in motor functions (Goldman-Rakic 1987; Graybiel 2000; Haber and McFarland 2001; Anderson 2001). However, recent evidence suggests that circuits through the basal ganglia have a role beyond motor control, including cognition, reward evaluation, motivated behaviour, learning, and memory (Middleton and Strick 1994; Mitchell *et al*. 1999; Hikosaka *et al*. 1999; Schultz *et al*. 2000; Middleton and Strick 2000; Hollerman *et al*. 2000; Graybiel 2000; Sato and Hikosaka 2002; Toni *et al*. 2002) which may be traced to pathways through the prefrontal cortex.

The VA nucleus is connected with all prefrontal cortices. However, connections are particularly robust with only a few areas, including lateral areas 9 and 8, medial area 32, and the posterior OFC (Xiao and Barbas 2004). Among orbitofrontal areas, area OPro stands apart from all others in having very robust and bidirectional connections with the VA nucleus (Dermon and Barbas 1994; Xiao and Barbas 2004). The comparatively denser projections of specific prefrontal areas to the VA may be significant in view of the role of areas 8 and 9 in executive functions. Similarly, the robust connections of medial area 32 and the posterior OFC with the VA may be associated with a different set of actions in emotional expression.

The most striking feature of the connections of the posterior OFC with the VA nucleus lies in their pattern. Bidirectional connections in the VA nucleus that link it with area OPro are organized in distinct clusters, as shown in Figure 4.7. With the exception of area 8, only the caudal OFC shows a focused, modular pattern in these connections. These patchy connections in the VA may represent functional modules that can be selected for specific actions. Like the MD, the VA receives robust projections from GPi of the basal ganglia in circuits that likely support the central executive functions of the prefrontal cortex. Moreover, the strong connections linking medial and orbitofrontal cortices with the VA suggest a role of this pathway in translating motivational and emotional processing into action.

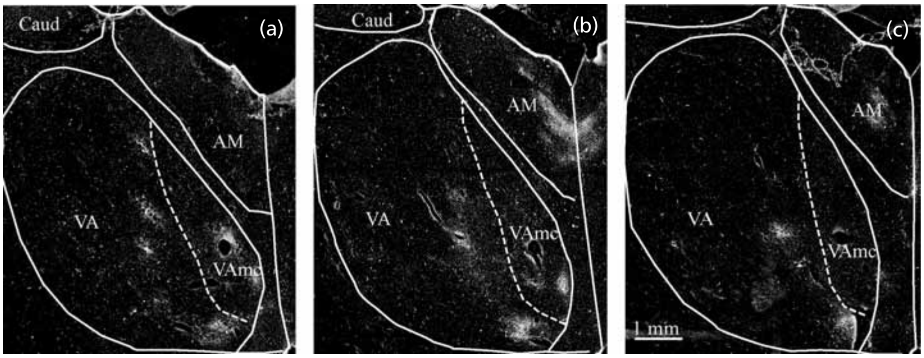

Fig. 4.7 *Modular connections of posterior orbitofrontal cortex with the ventral anterior (VA) nucleus of the thalamus*. (a–c) Darkfield photomicrographs from coronal sections from rostral (a) to caudal (c) VA nucleus showing anterograde label in VA (yellow grain) from axonal terminations originating in posterior orbitofrontal area OPro (not shown), labeled with HRP-WGA. AM, anterior medial thalamic nucleus. Caud, caudate nucleus; VA, principal VA nucleus; VAmc, VA magnocellular. Scale bar, 1 mm.

Source: Adapted from Xiao and Barbas 2004. "See Plate section in the color gallery."

An important feature of the projections from prefrontal cortices to the VA nucleus is their origin in layer V as well as layer VI. This pattern is unusual, as the predominant origin of cortical projections to the thalamus is layer VI in all cortices (Gilbert and Kelly 1975; Robson and Hall 1975; Lund *et al*. 1976; Jones and Wise 1977); (Jones 1985; Steriade *et al*. 1997), with layer V contributing a much lower proportion of projections (~10–20%). In sharp contrast, about half of the projection neurons to the VA originate in layer V (Xiao and Barbas 2004). The significance of this laminar pattern of projection is based on evidence from sensory systems, indicating that corticothalamic projections from layer V differ markedly from projections originating in layer VI (Rouiller and Welker 2000). There is some evidence that axons from neurons in cortical sensory areas in layer VI terminate as small and diffuse terminals in the thalamus, targeting the distal dendrites of thalamic neurons in the nuclei that project focally to cortical layer IV (Rockland 1996; Rouiller and Welker 2000). On the other hand, projections from layer V terminate as large and clustered axonal terminals in the thalamus, targeting the dendrites of thalamocortical projection neurons, which terminate widely, especially in cortical layer I (Jones 1985; Steriade *et al*. 1997; Rouiller and Welker 2000; Haber and McFarland 2001; Jones 2002). Although the pattern of termination in the VA nucleus of prefrontal neurons originating from layer V versus layer VI is not known, there is evidence of substantial projections from the VA to layer I of the frontal cortex (McFarland and Haber 2002); (Castro-Alamancos and Connors 1997). The patchy distribution of connections in the VA from the posterior OFC (as seen in Fig. 4.7) is consistent with a high distribution of neurons in layer V of the OFC that project to the VA (Xiao and Barbas 2004). Axons from the VA to layer I of the prefrontal cortex (including the OFC) may initiate activity in the apical dendrites of layer V neurons (Castro-Alamancos and Connors

1997), spreading excitation across cortical areas and back to the thalamus, recruiting other cortical areas in behaviour. Being one of the few prefrontal areas with robust connections with the VA, the OFC, with a significant contribution of projections to the VA from layer V, may have a key role in recruiting other prefrontal areas in emotional situations.

The AM nucleus is another thalamic nucleus that is connected with the OFC and the basal ganglia in both rats and monkeys (Groenewegen 1988; Xiao and Barbas 2002b). In the rhesus monkey, projections to the AM nucleus originate from the medial part of GPi, and are restricted to its rostral sector (Xiao and Barbas 2002b). The medial tip of GPi appears to represent a distinct output channel linking the basal ganglia with the AM nucleus and with the limbic component of the prefrontal cortex. The GPi site occupied by projections to the AM nucleus appears to be distinct from circuits linking lateral prefrontal, premotor, and motor cortices through the VA and VL nuclei (Hoover and Strick 1993; Middleton and Strick 2002). The pathway from the GPi site to the AM nucleus adds another parallel loop to the classic striato-thalamic circuit. The latter describes basal ganglia feedback projections to their principal cortical targets, the premotor and prefrontal areas, coursing indirectly through the thalamic motor nuclei VA/VL, MD and intralaminar nuclei (Rosvold 1972; Alexander *et al*. 1986; Groenewegen *et al*. 1990; Hoover and Strick 1993; Joel and Weiner 1994; Strick *et al*. 1995; Middleton and Strick 2000; Haber and McFarland 2001; McFarland and Haber 2002). Of added significance in this respect is the association of the AM nucleus with the amygdala, as noted above. These findings extend the classic basal ganglia circuit and give additional support for a role of the basal ganglia in emotional functions through association with the nuclei with a demonstrated role in emotional processes.

4.7. **Transfer of information from orbitofrontal cortex to lateral prefrontal cortices for decision and action**

The orbitofrontal areas have connections with structures that have a role in the emotional significance of events, but lack a direct access to the key systems that would allow decision and action in behaviour. One of the limitations is the level of detail of the signals conveyed from sensory association cortices to orbitofrontal cortices. Orbitofrontal areas are distinguished for their connections with the cortices associated with each of the sensory modalities, but sensory projections originate from the late-processing sensory cortices. While this input may provide an overview of the sensory environment, it lacks the detail that may be necessary for discrimination. Take, for example, the situation where one must decide whether a Fig. in a path in the forest is a snake or a harmless limb from a tree. The sensory input from late-processing visual areas likely lacks a resolution for discrimination, and thus may not be adequate for decision. However, lateral prefrontal areas are connected with a large variety of visual areas, going as far back as V2 (Barbas and Mesulam 1981; Barbas 1988). Lateral area 8, for example, receives a rich variety of visual input, much like other visual association cortices (Barbas 1988; Schall *et al*. 1995).

The pattern of connections among prefrontal areas, on one hand, and that with sensory cortices, on the other, suggest that prefrontal areas have a complementary role in processing information for decision and action in behaviour. Posterior orbitofrontal cortices have strong connections with anterior orbitofrontal areas (Barbas and Pandya 1989; Carmichael and Price 1996), which, in turn, are robustly connected with lateral prefrontal areas, as shown in Figure 4.8. Information about the emotional significance of events thus may be transmitted sequentially from the posterior OFC to the anterior OFC, and then to lateral prefrontal areas. Lateral prefrontal cortices, which are connected with early-processing visual areas, may retrieve information that may form the basis for making a decision about the identity of an ambiguous object in the path in the forest. This information may then be transmitted from lateral prefrontal areas to orbitofrontal cortices, activating one of the two paths from the posterior OFC to the amygdala, as discussed above: a pathway to the IM that would allow mobilization of autonomic structures, if the object in the path is a snake, or a direct path to the central nucleus of the amygdala that would dampen autonomic activity and allow return to autonomic homeostasis, if the figure is a stick.

Importantly, the laminar pattern of connections specified by the rules of the structural model (Barbas and Rempel-Clower 1997) is consistent with the flow of information for decision and action in behaviour. As discussed above, the relative distribution of connections in cortical layers depends on the structural relationship of the linked areas. When an area with fewer layers or lower cell density projects to an area with more layers or higher cell density, projection neurons originate predominantly in the deep layers, and their axons terminate in the upper layers (layers I-IIIa), a pattern akin to "feedback" connections. In contrast, projections proceeding in the reverse direction originate in the upper layers (II-III), and their axons terminate in the middle to deep layers (deep layers III to VI), analogous to "feedforward" connections. When areas that are close in structure are linked, connections involve most layers. Importantly, when the entire complement of connections is considered within a cortical system (such as the entire prefrontal cortex), the laminar pattern of connections is graded in a pattern that is predictable by the graded differences in the laminar structure of cortical areas.

The structural model for connections can be used to demonstrate a plausible flow of information for emotional processing in the prefrontal cortical system that is predicted by rules relating connections to the cortical structure. Caudal orbitofrontal areas have fewer layers and lower overall density than rostral orbitofrontal areas (Dombrowski *et al*. 2001), though the differences in structure between these areas are not large. Consequently, the posterior OFC issues projections predominantly (though not exclusively) from its deep layers to the anterior OFC, targeting predominantly the superficial, but also substantially the deep layers of anterior orbitofrontal cortices. In turn, anterior orbitofrontal areas issue projections predominantly from their deep layers and target the upper layers (I-IIIa) of lateral prefrontal areas, including posterior area 46 (Fig. 9). The latter receives robust projections from early-processing visual areas, and may be in a position to extract information pertaining to the finer details of the

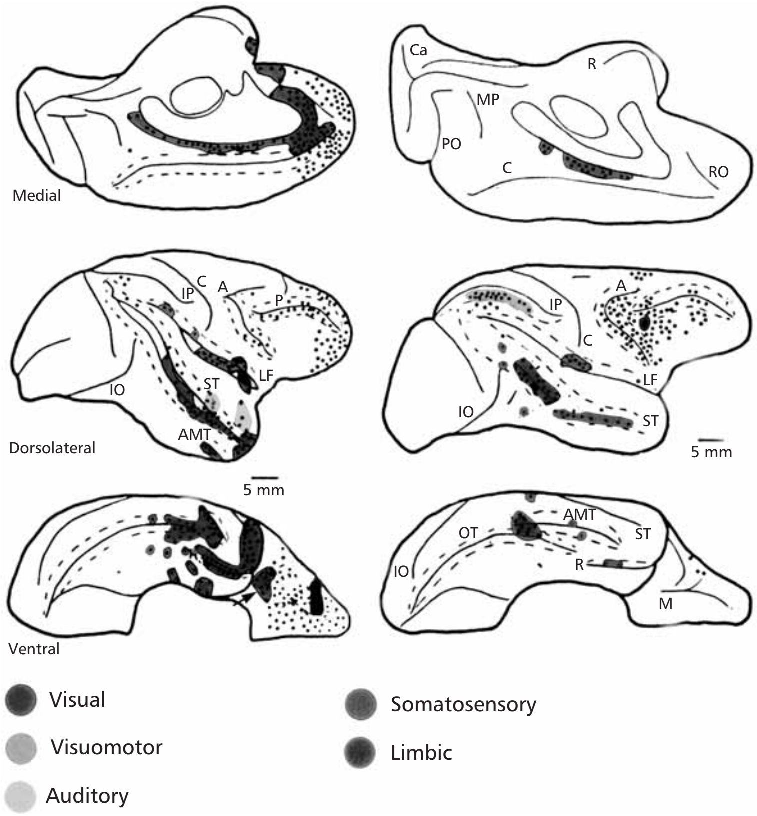

Fig. 4.8 *Sequential pathways for the flow of information in prefrontal cortices.* Comparison of the connections of an orbitofrontal area (left) and a lateral prefrontal area (right). (Left) Projection neurons (dots) directed to orbitofrontal area 11 (black area, bottom) originate from several sensory association cortices, as well as from posterior orbitofrontal cortex (arrow), a bidirectional pathway. In turn, area 11 is connected with lateral prefrontal cortices, such as area 46 in the principalis region (P). (Right) Projection neurons directed to the ventral part of lateral area 46 (black area, center) originate predominantly from visual (red overlay) and visuomotor (brown) cortices. Information about the external and internal environments reaching posterior orbitofrontal cortex could be conveyed to anterior orbitofrontal cortex and then to lateral prefrontal cortex through these pathways. See Plate section in the color gallery.

sensory environment, either directly, or through connections with adjacent area 8 (Barbas and Pandya 1989). Lateral prefrontal areas have more layers and a higher neuronal density than the orbitofrontal areas, and thus issue projections from their upper layers and target primarily the middle to deep layers of the OFC, including layer V, a pattern akin to "feedforward" connections. In turn, layer V is a major source of projections from prefrontal areas to the amygdala. The laminar relationships of these sequential connections provide a plausible path for the speedy transfer of information necessary for decision and action in behavior, as summarized in Figure 4.9.

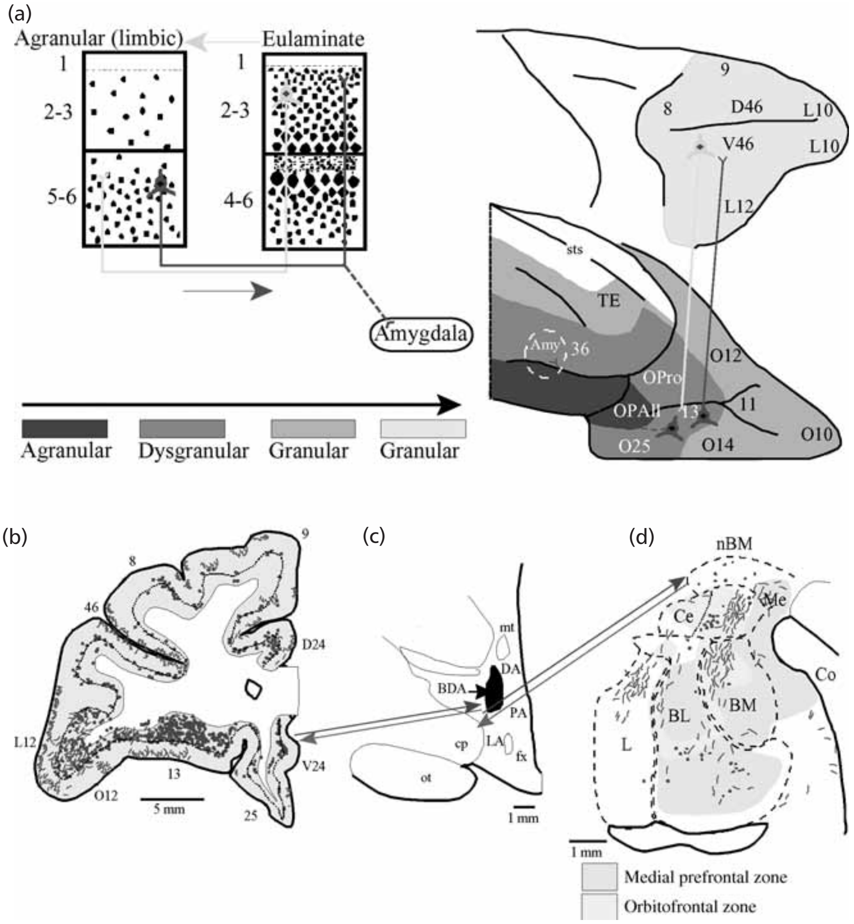

Fig. 4.9 *Laminar-specific pathways underlying the perception and expression of emotions.* (a) Eulaminate prefrontal areas (such as areas 46 and 8 on the lateral surface) receive detailed sensory input from early-processing sensory areas (not shown) and target the middle-deep layers of the agranular/dysgranular (limbic) prefrontal cortices (●), such as posterior orbitofrontal cortex. Neurons from the same layers, particularly layer 5, issue robust projections to the amygdala, and "feedback" projections to lateral eulaminate areas (●). The laminar pattern of connections is according to the rules of the structural model for connections (Barbas and Rempel-Clower 1997), and the pattern is consistent with the rapid transmission of sensory signals for emotional processing. (b) Medial and orbitofrontal cortices are bidirectionally connected with hypothalamic autonomic centers (c), which are also connected with the amygdala (d). These pathways form the basis for transmission of signals to hypothalamic autonomic centers which project to brainstem and spinal autonomic centers (not shown); the latter innervate peripheral organs for the expression of emotions, as shown in Figure 4.5.

The other factor that suggests a collaborative action of prefrontal areas in decision and action in behavior is their linkage with the motor systems that allow a motor response. Among prefrontal areas, posterior lateral area 8 and caudal area 46, the areas that have connections with early-processing sensory areas, also have the strongest connections with the neighboring premotor areas (Barbas 1992). Thus, information may flow from orbitofrontal to lateral prefrontal areas and to premotor areas for decision and action in behavior.

A more direct involvement of orbitofrontal areas in motor activity appears to lie within the realm of autonomic activation necessary for the expression of emotions. This is based on the direct connections of orbitofrontal as well as medial prefrontal cortices with hypothalamic and brainstem autonomic centres, as discussed above. In addition, the termination of axons from the posterior OFC to the IM of the amygdala has a permissive effect on this process, by disinhibiting the hypothalamus and allowing its activation from other sources, as discussed above. Finally, the interface of orbitofrontal cortices with the thalamic VA nucleus, associated with motor systems, and the AM nucleus, associated with emotions, may underlie pathways necessary for emotional expression, as noted above.

4.8. **Distinction of medial prefrontal from orbitofrontal areas in emotional processing**

The posterior OFC is considered to be part of the limbic component of the prefrontal cortex (Yakovlev 1948; Nauta 1979). Yakovlev's and Nauta's inclusion of the OFC as part of the limbic system followed the classic incorporation of caudal medial prefrontal areas in the anterior cingulate as the limbic system, as suggested by Broca (Broca 1878) and Papez (Papez 1937). The prefrontal cortex, therefore, has two distinct limbic components, characterized not only by their robust connections with other cortical and subcortical limbic structures, but also by their agranular or dysgranular architecture (Barbas 1997).

The two components of the prefrontal limbic system share some connectional features, but are also distinguished at the level of circuits and function in important ways (Barbas 1997). They are similar in their strong connections with other cortical and subcortical limbic structures, and in their widespread connections with the thalamus, and medial temporal memory-related cortices (Barbas *et al.* 1991; Dermon and Barbas 1994; Barbas *et al.* 1999).

The orbitofrontal and medial components of the prefrontal limbic system, however, also have important differences in their connections. One of their most distinguishing features is the extent of their connections with unimodal sensory association cortices. Unlike the posterior orbitofrontal areas, the medial prefrontal cortices lack direct connections with sensory association areas. The most notable exception is the strong and bidirectional connection of medial prefrontal cortices with auditory association areas (Barbas *et al.* 1999). Like the OFC, medial prefrontal areas are bidirectionally linked with the amygdala (Barbas and De Olmos 1990; Carmichael and Price 1995a), but their pattern differs markedly. The connections of the posterior OFC have partly segregated input and output zones in the amygdala, as discussed above. No such segregation is seen for the afferent and efferent connections of medial (cingulate) cortices, which are largely intermingled in the amygdala (Ghashghaei and Barbas 2002). Moreover, the axons from posterior medial prefrontal cortices occupy a wider territory than orbitofrontal axons in the amygdala, extending to the cortical and medial nuclei. The medially situated nuclei of the amygdala have different connections than the basal nuclei, and have a role in gustatory, olfactory and reproductive functions (Ghashghaei and Barbas 2002).

Medial prefrontal cortices have stronger projections to hypothalamic autonomic centres, the spinal cord (Rempel-Clower and Barbas 1998) and brainstem autonomic centres (Ongur *et al*. 1998) than the OFC has. Several of the medially situated nuclei of the amygdala, which are connected with medial prefrontal cortices (but not orbitofrontal areas), project to the hypothalamus (Petrovich *et al*. 2001). These circuits suggest that the medial prefrontal cortex has multiple ways to access autonomic centres, and ultimately the emotional motor system. One pathway courses directly from medial prefrontal areas in the anterior cingulate to hypothalamic and brainstem autonomic centres (Rempel-Clower and Barbas 1998; Ongur *et al*. 1998; Freedman *et al*. 2000), and indirectly through the amygdala (Ghashghaei and Barbas 2002). The direct pathway from cingulate area 32 targets preferentially excitatory neurons in the hypothalamus, forming asymmetric, and presumed excitatory synapses mostly on spines in the hypothalamus (Barbas *et al*. 2003), which are enriched on dendrites of excitatory neurons (Peters *et al*. 1991). An indirect pathway involves a more diffuse projection from medial prefrontal cortices to the basolateral nucleus of the amygdala, which is known to project to hypothalamic and brainstem autonomic centres. There is evidence that the latter pathway has a role in the process of learning the significance of motivationally relevant cues (Petrovich *et al*. 2002). Another pathway from caudal medial prefrontal areas innervates, preferentially, the extended amygdala, a striatal-related structure in the basal forebrain, which is also involved in autonomic function (Ghashghaei and Barbas 2001). These varied pathways from medial prefrontal cortices may allow direct cortical control of autonomic functions in response to complex emotional situations.

Orbitofrontal areas as sensors, and medial areas as effectors of emotions

The connectional distinctions suggest that posterior orbitofrontal and posterior medial prefrontal cortices have complementary roles in emotional processing. Based on connectional features, posterior orbitofrontal areas may be viewed as the primary ‘sensory’ areas for emotional processing, as recipient of information from cortices associated with each and every sensory modality, as well as the internal environment. Orbitofrontal areas may specialize in integrating the external and internal environments. The rich sensory input to the OFC may make it possible to determine the emotional value of events and their conscious appreciation.

In contrast, medial prefrontal areas receive only limited information from sensory cortices, emanating preferentially from auditory association cortices. It is not clear what this strong connection of medial prefrontal areas with auditory association cortices signifies, though it may be related to the role of anterior cingulate areas in emotional communication (Vogt and Barbas 1988; Barbas *et al*. 2002). On the other hand, medial prefrontal cortices have rich, direct and indirect, and highly efficient networks with central autonomic pathways extending as far as spinal autonomic centres (Barbas *et al*. 2003). On the basis of these connectional features, medial prefrontal areas may be the chief effectors for autonomic response, appropriately named the emotional motor system (Holstege 1991; Alheid and Heimer 1996; Holstege *et al*. 1996). The dichotomy within the prefrontal emotional system is reminiscent of the distinction of separate streams for processing features and spatial information in the sensory systems (Ungerleider and Mishkin 1982), or distal and axial body representations in the motor-premotor system (Barbas and Pandya 1987). The strong and bidirectional connections linking the posterior OFC with posterior medial prefrontal cortices may facilitate a continuously updated dialogue between these functionally distinct cortices in behavior. Based on the structural similarity of orbitofrontal and anterior cingulate areas, the laminar pattern of their connections is generally columnar, each affecting the input as well as the output layers of the other. The strong linkage between the OFC and anterior cingulate areas also extends to their callosal connections (Barbas *et al*. 2005a).

4.9. **Implications for psychiatric diseases**

The OFC has been implicated in a number of psychiatric disorders, including depression, anxiety, phobias and obsessive-compulsive disorder (Zald and Kim 1996; Simpson *et al*. 2001; Mayberg 2003). Data from unmedicated subjects with depression show that regional cerebral blood flow and glucose metabolism are increased in the amygdala, the OFC and the medial thalamus. Structures implicated in modulating and mediating emotional and stress responses are pathologically activated during major depressive episodes, whereas regions implicated in attention and sensory processing are deactivated (Davidson 2002).

The OFC may have a critical role in monitoring the environment with direct effect on one of two pathways with opposite effects on autonomic activation: The pathway from the OFC to the IM would increase the gain of autonomic centres in emotionally charged circumstances. Or, the pathway from the OFC to the central nucleus of the amygdala would inhibit the hypothalamus and return to autonomic homeostasis. Changes in opposite directions in the activity of these circuits may be at the root of the dramatically different clinical symptomatologies in psychiatric diseases. Disorders characterized by abnormal fear, such as panic disorder, anxiety, phobias and obsessive-compulsive disorder (Zald and Kim 1996; Simpson *et al*. 2001; Mayberg 2003), may have over activity in the OFC in common, and in particular in the pathway from the caudal OFC to the IM. In contrast, the under activity of the OFC appears to underlie sociopathic personality disorder, characterized by dampening of autonomic responses in emotional situations (Bechara *et al*. 1996). These contrasting deficits demonstrate at the clinical level the primary role of the posterior OFC in the flow of information for emotions.

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References

Aggleton, J. P. and Brown, M. W. (1999) Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav Brain Sci* **22**:425–444.

Aggleton, J. P, Burton, M. J., and Passingham, R.E. (1980) Cortical and subcortical afferents to the amygdala of the rhesus monkey (*Macaca mulatta*). *Brain Res* **190**:347–368.

Aggleton, J. P., Desimone, R., and Mishkin M (1986) The origin, course, and termination of the hippocampothalamic projections in the macaque. *J Comp Neurol* **243**:409–421.

Aggleton, J. P. and Mishkin, M. (1983) Memory impairments following restricted medial thalamic lesions in monkeys. *Exp Brain Res* **52**:199–209.

Aggleton, J. P. and Mishkin, M. (1984) Projections of the amygdala to the thalamus in the cynomolgus monkey. *J Comp Neurol* **222**:56–68.

Ahmed, B., Anderson, J. C., Douglas, R. J., Martin, K. A., and Nelson, J. C. (1994) Polyneuronal innervation of spiny stellate neurons in cat visual cortex. *J Comp Neurol* **341**:39–49.

Alexander, G. E., Delong, M. R., and Strick, P. L. (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann Rev Neurosci* **9**:357–381.

Alheid, G. F. and Heimer, L. (1996) Theories of basal forebrain organization and the "emotional motor system". *Prog Brain Res* **107**:461–484.

Amaral, D. G. and Price, J. L. (1984) Amygdalo-cortical projections in the monkey *(Macaca fascicularis)*. *J Comp Neurol* **230**:465–496.

Anderson, M. E. (2001) Pallidal and cortical detriments of thalamic activity. In: *Basal ganglia and thalamus in health and movement disorders.* Kultas-Ilinsky, K. and Ilinsky, I.A., (eds), pp. 93–104. New York: Kluwer Academic/Plenum Publishers.

Armstrong, E. (1990) Limbic thalamus: anterior and mediodorsal nuclei. In: *The Human Nervous System* (Paxinos, G., ed.), pp. 469–481. New York: Academic Press, Inc.

Asanuma, C., Andersen, R. A., and Cowan, W. M. (1985) The thalamic relations of the caudal inferior parietal lobule and the lateral prefrontal cortex in monkeys: Divergent cortical projections from cell clusters in the medial pulvinar nucleus. *J Comp Neurol* **241**:357–381.

Baleydier, C. and Mauguiere, F. (1980) The duality of the cingulate gyrus in monkey. Neuroanatomical study and functional hypothesis. *Brain* **103**:525–554.

Barbas, H. (1986) Pattern in the laminar origin of cortico-cortical connections. *J Comp Neurol* **252**:415–422.

Barbas, H. (1988) Anatomic organization of basoventral and mediodorsal visual recipient prefrontal regions in the rhesus monkey. *J Comp Neurol* **276**:313–342.

Barbas, H. (1992) Architecture and cortical connections of the prefrontal cortex in the rhesus monkey. *Adv Neurol* **57**:91–115.

Barbas, H. (1993) Organization of cortical afferent input to orbitofrontal areas in the rhesus monkey. *Neuroscience* **56**:841–864.

Barbas, H. (1995a) Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. *Neurosci Biobehav Rev* **19**:499–510.

Barbas, H. (1995b) Pattern in the cortical distribution of prefrontally directed neurons with divergent axons in the rhesus monkey. *Cereb Cortex* **5**:158–165.

Barbas, H. (1997) Two prefrontal limbic systems: Their common and unique features. In: *The Association cortex: Structure and function* (Sakata, H., Mikami, A., and Fuster, J.M., eds), pp. 99–115. Amsterdam: Harwood Academic Publ.

Barbas, H. (2000a) Complementary role of prefrontal cortical regions in cognition, memory and emotion in primates. *Adv Neurol* **84**:87–110.

Barbas, H. (2000b) Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. *Brain Res Bull* **52**:319–330.

Barbas, H. and Blatt, G. J. (1995) Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. *Hippocampus* **5**:511–533.

Barbas, H. and de Olmos J (1990) Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. *J Comp Neurol* **301**:1–23.

Barbas, H., Ghashghaei, H., Dombrowski, S. M., and Rempel-Clower, N. L. (1999) Medial prefrontal cortices are unified by common connections with superior temporal cortices and distinguished by input from memory-related areas in the rhesus monkey. *J Comp Neurol* **410**:343–367.

Barbas, H., Ghashghaei, H., Rempel-Clower, N., and Xiao, D. (2002) Anatomic basis of functional specialization in prefrontal cortices in primates. In: *Handbook of Neuropsychology* (Grafman J., (ed)), pp. 1–27. Amsterdam: Elsevier *Science* B.V.

Barbas, H., Henion, T. H., and Dermon, C. R. (1991) Diverse thalamic projections to the prefrontal cortex in the rhesus monkey. *J Comp Neurol* **313**:65–94.

Barbas, H., Hilgetag, C. C., Saha, S., Dermon, C. R., and Suski, J. L. (2005a) Parallel organization of contralateral and ipsilateral prefrontal cortical projections in the rhesus monkey. *BMC Neurosci* **6**:32.

Barbas, H., Medalla, M., Alade, O., Suski, J., Zikopoulos, B., and Lera, P. (2005b) Relationship of prefrontal connections to inhibitory systems in superior temporal areas in the rhesus monkey. *Cereb Cortex* **15**:1356–1370.

Barbas, H., Mesulam, M. M. (1981) Organization of afferent input to subdivisions of area 8 in the rhesus monkey. *J Comp Neurol* **200**:407–431.

Barbas, H. and Pandya, D. N. (1987) Architecture and frontal cortical connections of the premotor cortex (area 6) in the rhesus monkey. *J Comp Neurol* **256**:211–218.

Barbas, H. and Pandya, D. N. (1989) Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *J Comp Neurol* **286**:353–375.

Barbas, H. and Rempel-Clower, N. (1997) Cortical structure predicts the pattern of cortico-cortical connections. *Cereb Cortex* **7**:635–646.

Barbas, H., Saha, S., Rempel-Clower, N., and Ghashghaei, T. (2003) Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. *BMC Neurosci* **4**:25.

Baxter, M. G. and Murray, E. A. (2002) The amygdala and reward. *Nat Rev Neurosci* **3**:563–573.

Baxter, M. G., Parker, A., Lindner, C. C., Izquierdo, A. D., and Murray, E. A. (2000) Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *J Neurosci* **20**:4311–4319.

Baylis, L. L., Rolls, E. T., and Baylis, G. C. (1995) Afferent connections of the caudolateral orbitofrontal cortex taste area of the primate. *Neuroscience* **64**:801–812.

Bechara, A., Tranel, D., Damasio, H., and Damasio, A. R. (1996) Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cereb Cortex* **6**:215–225.

Braak, H., and Braak, E. (1991) Alzheimer's disease affects limbic nuclei of the thalamus. *Acta Neuropathol (Berl)* **81**:261–268.

Braak, H., Braak, E., Yilmazer, D., de Vos, R. A., Jansen, E. N., and Bohl J (1996) Pattern of brain destruction in Parkinson's and Alzheimer's diseases. *J Neural Transm* **103**:455–490.

Broca, P. (1878) Anatomie compareι des enconvolutions cιrιbrales: Le grand lobe limbique et la scissure limbique dans la serie des mammifθres. *Rev Anthropol* **1**:385–498.

Cahill, L. and McGaugh J. L. (1998) Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci* **21**:294–299.

Cardinal, R. N., Parkinson, J. A., Hall, J., and Everitt, B. J. (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience and Biobehavioural Reviews* **26**:321–352.

Carmichael, S. T., Clugnet, M.-C., and Price, J. L. (1994) Central olfactory connections in the macaque monkey. *J Comp Neurol* **346**:403–434.

Carmichael, S. T. and Price, J. L. (1994) Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *J Comp Neurol* **346**:366–402.

Carmichael, S. T. and Price, J. L. (1995a) Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol* **363**:615–641.

Carmichael, S. T. and Price, J. L. (1995b) Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. *J Comp Neurol* **363**:642–664.

Carmichael, S. T. and Price, J. L. (1996) Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *J Comp Neurol* **371**:179–207.

Carr, D. B., O'Donnell, P., Card, J. P., and Sesack, S. R. (1999) Dopamine terminals in the rat prefrontal cortex synapse on pyramidal cells that project to the nucleus accumbens. *J Neurosci* **19**:11049–11060.

Carr, D. B. and Sesack, S. R. (2000) Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. *J Neurosci* **20**:3864–3873.

Castro-Alamancos, M. A. and Connors, B. W. (1997) Thalamocortical synapses. *Prog Neurobiol* **51**:581–606.

Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R. J., and Reinoso-Suarez, F. (2000) The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cereb Cortex* **10**:220–242.

Celerier, A., Ognard, R., Decorte, L., and Beracochea, D. (2000) Deficits of spatial and non-spatial memory and of auditory fear conditioning following anterior thalamic lesions in mice: comparison with chronic alcohol consumption. *Eur J Neurosci* **12**:2575–2584.

Chiba, T., Kayahara, T., and Nakano, K. (2001) Efferent projections of infralimbic and prelimbic areas of the medial prefrontal cortex in the Japanese monkey, *Macaca fuscata. Brain Res* **888**:83–101.

Clarke, S., Assal, G., Bogousslavsky, J., Regli, F., Townsend, D. W., Leenders, K. L., and Blecic S (1994) Pure amnesia after unilateral left polar thalamic infarct: topographic and sequential neuropsychological and metabolic (PET) correlations. *J Neurol Neurosurg Psychiat* **57**:27–34.

Damasio, A. R. (1994) *Descarte's Error: Emotion, Reason, and the Human Brain*. New York: G. P. Putnam's Sons.

Damasio, H., Grabowski, T., Frank, R., Galaburda, A. M., and Damasio A. R (1994) The return of Phineas Gage: clues about the brain from the skull of a famous patient. *Science* **264**:1102–1105.

Davidson, R. J. (2002) Anxiety and affective style: role of prefrontal cortex and amygdala. *Biol Psychiatry* **51**:68–80.

Davis, M. (1992) The role of the amygdala in fear and anxiety. *Ann Rev Neurosci* **15**:353–375.

de Olmos, J. (1990) Amygdaloid nuclear gray complex. In: *The Human Nervous System* (Paxinos, G., ed.), pp. 583–710. San Diego: Acedemic Press, Inc.

Dermon, C. R. and Barbas, H. (1994) Contralateral thalamic projections predominantly reach transitional cortices in the rhesus monkey. *J Comp Neurol* **344**:508–531.

DeVito, J. L. (1980) Subcortical projections to the hippocampal formation in squirrel monkey (*Saimira sciureus*). *Brain Res Bull* **5**:285–289.

Dombrowski, S. M., Hilgetag, C. C., and Barbas, H. (2001) Quantitative architecture distinguishes prefrontal cortical systems in the rhesus monkey. *Cereb Cortex* **11**:975–988.

Fischer, H., Wright, C. I., Whalen, P. J., McInerney, S. C., Shin, L. M., and Rauch, S. L. (2003) Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. *Brain Res Bull* **59**:387–392.

Freedman, L. J., Insel, T. R., and Smith, Y. (2000) Subcortical projections of area 25 (subgenual cortex) of the macaque monkey. *J Comp Neurol* **421**:172–188.

Fudge, J. L. and Haber, S. N. (2000) The central nucleus of the amygdala projection to dopamine subpopulations in primates. *Neuroscience* **97**:479–494.

Fuster, J. M. (1993) Frontal lobes. *Curr Opin Neurobiol* **3**:160–165.

Gaffan, D. and Gaffan, E. A. (1991) Amnesia in man following transection of the fornix. A review. *Brain* **114**:2611–2618.

George, M. S., Anton, R. F., Bloomer, C., Teneback, C., Drobes, D. J., Lorberbaum, J. P., Nahas, Z., and Vincent, D. J. (2001) Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. *Arch Gen Psychiatry* **58**:345–352.

Ghashghaei, H. T. and Barbas, H. (2001) Neural interaction between the basal forebrain and functionally distinct prefrontal cortices in the rhesus monkey. *Neuroscience* **103**:593–614.

Ghashghaei, H. T. and Barbas, H. (2002) Pathways for emotions: Interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience* **115**:1261–1279.

Ghika-Schmid, F. and Bogousslavsky, J. (2000) The acute behavioral syndrome of anterior thalamic infarction: a prospective study of 12 cases. *Ann Neurol* **48**:220–227.

Gilbert, C. D. and Kelly, J. P. (1975) The projections of cells in different layers of the cat's visual cortex. *J Comp Neurol* **163**:81–105.

Goldman-Rakic, P. S. (1987) Motor control function of the prefrontal cortex. *Ciba Found Symp* **132**:187–200.

Goldman-Rakic, P. S. (1988) Topography of cognition: Parallel distributed networks in primate association cortex. *Ann Rev Neurosci* **11**:137–156.

Goldman-Rakic, P. S. and Porrino, L. J. (1985) The primate mediodorsal (MD) nucleus and its projection to the frontal lobe. *J Comp Neurol* **242**:535–560.

Graybiel, A. M. (2000) The basal ganglia. *Curr Biol* **10**:R509–R511.

Groenewegen, H. J. (1988) Organization of the afferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography. *Neuroscience* **24**:379–431.

Groenewegen, H. J., Berendse, H. W., Wolters, J. G., and Lohman, A. H. (1990) The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: evidence for a parallel organization. *Prog Brain Res* **85**:95–116.

Haber, S. and McFarland, N. R. (2001) The place of the thalamus in frontal cortical-basal ganglia circuits. *Neuroscientist* **7**:315–324.

Haber, S. N., Kunishio, K., Mizobuchi, M., and Lynd-Balta, E. (1995) The orbital and medial prefrontal circuit through the primate basal ganglia. *J Neurosci* **15**:4851–4867.

Herzog, A. G. and van Hoesen, G. W. (1976) Temporal neocortical afferent connections to the amygdala in the rhesus monkey. *Brain Res* **115**:57–69.

Hikosaka, K. and Watanabe, M. (2000) Delay activity of orbital and lateral prefrontal neurons of the monkey varying with different rewards. *Cereb Cortex* **10**:263–271.

Hikosaka, O., Nakahara, H., Rand, M. K., Sakai, K., Lu, X., Nakamura, K., Miyachi, S., and Doya, K. (1999) Parallel neural networks for learning sequential procedures. *Trends Neurosci* **22**:464–471.

Hollerman, J.R., Tremblay, L., and Schultz, W. (2000) Involvement of basal ganglia and orbitofrontal cortex in goal-directed behaviour. In: *Progress in Brain Research* (Uylings, H.B.M., van Eden, C.G., de Bruin, J.P.C., Feenstra, M.G.P., and Pennartz, C.M.A., eds), pp. 193–215. Paris: Elsevier Science.

Holstege, G. (1991) Descending motor pathways and the spinal motor system: limbic and non-limbic components. *Prog Brain Res* **87**:307–421.

Holstege, G., Bandler, R., and Saper, C. B. (1996) The emotional motor system. *Prog Brain Res* **107**:3–6.

Hoover, J. E. and Strick, P. L. (1993) Multiple output channels in the basal ganglia. *Science* **259**:819–821.

Ilinsky, I. A., Jouandet, M. L., and Goldman-Rakic, P. S. (1985) Organization of the nigrothalamocortical system in the rhesus monkey. *J Comp Neurol* **236**:315–330.

Insausti, R., Amaral, D. G., and Cowan, W. M. (1987) The entorhinal cortex of the monkey: II. Cortical afferents. *J Comp Neurol* **264**:356–395.

Insausti, R. and Munoz, M. (2001) Cortical projections of the non-entorhinal hippocampal formation in the cynomolgus monkey (Macaca fascicularis). *Eur J Neurosci* **14**:435–451.

Isseroff, A., Rosvold, H. E., Galkin, T. W., and Goldman-Rakic, P. S. (1982) Spatial memory impairments following damage to the mediodorsal nucleus of the thalamus in rhesus monkeys. *Brain Res* **232**:97–113.

Izquierdo, A., Suda, R. K., and Murray, E. A. (2004) Bilateral orbital prefrontal cortex lesions in rhesus monkeys disrupt choices guided by both reward value and reward contingency. *J Neurosci* **24**:7540–7548.

Jacobson, S., Butters, N., and Tovsky, N. J. (1978) Afferent and efferent subcortical projections of behaviourally defined sectors of prefrontal granular cortex. *Brain Res* **159**:279–296.

Jacobson, S. and Trojanowski, J. Q. (1975) Amygdaloid projections to prefrontal granular cortex in rhesus monkey demonstrated with horseradish peroxidase. *Brain Res* **100**:132–139.

Joel, D. and Weiner, I. (1994) The organization of the basal ganglia-thalamocortical circuits: open interconnected rather than closed segregated. *Neuroscience* **63**(2):363–379.

Jones, E. G. (1985) *The Thalamus*. New York (NY): Plenum Press.

Jones, E. G. (2002) Thalamic organization and function after Cajal. *Prog Brain Res* **136**:333–357.

Jones, E. G. and Wise, S. P. (1977) Size, laminar and columnar distribution of efferent cells in the sensory-motor cortex of monkeys. *J Comp Neurol* **175**:391–438.

Jongen-Relo, A. L. and Amaral, D. G. (1998) Evidence for a GABAergic projection from the central nucleus of the amygdala to the brainstem of the macaque monkey: a combined retrograde tracing and in situ hybridization study. *Eur J Neurosci* **10**:2924–2933.

Kalivas, P. W. and Nakamura, M. (1999) Neural systems for behavioural activation and reward. *Curr Opin Neurobiol* **9**:223–227.

Kennard, M. A. (1945) Focal autonomic representation in the cortex and its relation to sham rage. *J Neuropathol Exp Neurol* **4**:295–304.

Kievit, J. and Kuypers, H. G. J. M. (1977) Organization of the thalamocortical connexions to the frontal lobe in the rhesus monkey. *Exp Brain Res* **29**:299–322.

Kishiyama, M. M., Kroll, N. E. A., Yonelinas, A. P., Lazzara, M. M., Jones, E. G., and Jagust, W. J. The effects of bilateral thalamic lesions on recollection- and familiarity-based recognition memory jedgements: a case study. *Neuroscience Abstracts* 27, 530.9. 2001.

Ref Type: Abstract

Kopelman, M. D. (1995) The Korsakoff syndrome. *Br J Psychiatry* **166**:154–173.

Kringelbach, M. L. and Rolls, E. T. (2004) The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog Neurobiol* **72**:341–372.

Kunzle, H. (1978) An autoradiographic analysis of the efferent connections from premotor and adjacent prefrontal regions (Areas 6 and 9) in *Macaca fascicularis. Brain Behav Evol* **15**:185–234.

LeDoux, J. (1996) *The emotional brain*. New York: Simon & Schuster.

Leonard, B. W., Amaral, D. G., Squire, L. R., and Zola-Morgan, S. (1995) Transient memory impairment in monkeys with bilateral lesions of the entorhinal cortex. *J Neurosci* **15**:5637–5659.

Lipton, P. A., Alvarez, P., and Eichenbaum, H. (1999) Crossmodal associative memory representations in rodent orbitofrontal cortex. *Neuron* **2**:349–359.

Lund, J. S., Lund, R. D., Hendrickson, A. E., Hunt, A. B., and Fuchs, A. F. (1976) The origin of efferent pathways from the primary visual cortex, area 17, of the macaque monkey as shown by retrograde transport of horseradish peroxidase. *J Comp Neurol* **164**:287–304.

Lynd-Balta, E. and Haber, S. N. (1994) The organization of midbrain projections to the ventral striatum in the primate. *Neuroscience* 1–15.

Mair, W. G. P., Warrington, E. K., and Weiskrantz, L. (1979) Memory disorder in Korsakoff's psychosis a neuropathological and neuropsychological investigation of two cases. *Brain* **102**:749–783.

Malkova, L., Gaffan, D., and Murray, E. A. (1997) Excitotoxic lesions of the amygdala fail to produce impairment in visual learning for auditory secondary reinforcement but interfere with reinforcer devaluation effects in rhesus monkeys. *J Neurosci* **17**:6011–6020.

Mark, V. H., Barry, H., McLardy, T., and Ervin, F. R. (1970) The destruction of both anterior thalamic nuclei in a patient with intractable agitated depression. *J Nerv Ment Dis* **150**:266–272.

Mark, V. H., Ervin, F. R., and Yakovlev, P. I. (1963) Stereotactic Thalamotomy III. The verification of anatomical lesion sites in the human thalamus. *Arch Neurol* **8**:528–538.

Mayberg, H. S. (2003) Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br Med Bull* **65**:193–207.

McFarland, N. R. and Haber, S. N. (2002) Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. *J Neurosci* **22**:8117–8132.

Meibach, R. C. and Siegel, A. (1977) Thalamic projections of the hippocampal formation: evidence for an alternate pathway involving the internal capsule. *Brain Res* **134**:1–12.

Middleton, F. A. and Strick, P. L. (1994) Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science* **266**:458–461.

Middleton F. A, Strick, P. L. (2000) Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res Brain Res* Rev **31**:236–250.

Middleton, F. A., and Strick, P. L. (2002) Basal-ganglia 'projections' to the prefrontal cortex of the primate. *Cereb Cortex* **12**:926–935.

Mitchell, I. J., Cooper, A. J., and Griffiths, M. R. (1999) The selective vulnerability of striatopallidal neurons. *Prog Neurobiol* **59**:691–719.

Moga, M. M. and Gray, T. S. (1985) Peptidergic efferents from the intercalated nuclei of the amygdala to the parabrachial nucleus in the rat. *Neurosci Lett* **61**:13–18.

Morecraft, R. J., Geula, C., and Mesulam, M.-M. (1992) Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. *J Comp Neurol* **323**:341–358.

Morris, J. S., Ohman, A., and Dolan, R. J. (1999) A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc Natl Acad Sci USA* **4**:1680–1685.

Nakamura, K. and Kubota, K. (1995) Mnemonic firing of neurons in the monkey temporal pole during a visual recognition memory task. *J Neurophysiol* **74**:162–178.

Nauta, W. J. H. (1961) Fibre degeneration following lesions of the amygdaloid complex in the monkey. *J Anat* **95**:515–531.

Nauta, W. J. H. (1979) Expanding borders of the limbic system concept. In: *Functional Neurosurgery* (Rasmussen, T. and Marino, R., eds), pp. 7–23. New York: Raven Press.

Nishijo, H., Ono, T., and Nishino, H. (1988) Single neuron responses in amygdala of alert monkey during complex sensory stimulation with affective significance. *J Neurosci* **8**:3570–3583.

Nitecka, L. and Ben Ari, Y. (1987) Distribution of GABA-like immunoreactivity in the rat amygdaloid complex. *J Comp Neurol* **266**:45–55.

Nolan, E. C., Yonelinas, A. P., Hopfinger, J. B., Kroll, N. E. A., Baynes, K., Buonocore, M. H., Jagust, W. J., and Jones, E. G. Functional brain activation during associative and item recognition in a patient with thalamic infarct. *Neuroscience Abstract* 27, 530.10. 2001.

Ref Type: Abstract

Ongur, D., An, X., and Price, J. L. (1998) Prefrontal cortical projections to the hypothalamus in macaque monkeys. *J Comp Neurol* **401**:480–505.

Pandya, D. N., van Hoesen, G. W., and Domesick, V. B. (1973) A cingulo-amygdaloid projection in the rhesus monkey. *Brain Res* **61**:369–373.

Papez, J. W. (1937) A proposed mechanism of emotion. *AMA Arch Neurol Psychiat* **38**:725–743.

Pare, D. and Smith, Y. (1993a) Distribution of GABA immunoreactivity in the amygdaloid complex of the cat. *Neuroscience* **57**:1061–1076.

Pare, D. and Smith, Y. (1993b) The intercalated cell masses project to the central and medial nuclei of the amygdala in cats. *Neuroscience* **57**:1077–1090.

Pare. D. and Smith, Y. (1994) GABAergic projection from the intercalated cell masses of the amygdala to the basal forebrain in cats. *J Comp Neurol* **344**:33–49.

Parkin, A. J., Rees, J. E., Hunkin, N. M., and Rose, P. E. (1994) Impairment of memory following discrete thalamic infarction. *Neuropsychologia* **32**:39–51.

Pears, A., Parkinson, J. A., Hopewell, L., Everitt, B. J., and Roberts, A. C. (2003) Lesions of the orbitofrontal but not medial prefrontal cortex disrupt conditioned reinforcement in primates. *J Neurosci* **23**:11189–11201.

Peters, A., Palay, S. L., and Webster, H. D. (1991) *The fine structure of the nervous system. Neurons and their supporting cells*. New York: Oxford University Press.

Petrides, M. (1996) Lateral frontal cortical contribution to memory. Seminars in the *Neurosciences* **8**:57–63.

Petrovich, G. D., Canteras, N. S., and Swanson, L. W. (2001) Combinatorial amygdalar inputs to hippocampal domains and hypothalamic behaviour systems. *Brain Res Brain Res Rev* **38**:247–289.

Petrovich, G. D., Setlow, B., Holland, P. C., and Gallagher, M. (2002) Amygdalo-hypothalamic circuit allows learned cues to override satiety and promote eating. *J Neurosci* **22**:8748–8753.

Phillips, A. G., Ahn, S., and Howland, J. G. (2003) Amygdalar control of the mesocorticolimbic dopamine system: parallel pathways to motivated behaviour. *Neuroscience and Biobehavioural Reviews* **27**:543–554.

Pitkanen, A. and Amaral, D. G. (1994) The distribution of GABAergic cells, fibers, and terminals in the monkey amygdaloid complex: an immunohistochemical and in situ hybridization study. *J Neurosci* **14**:2200–2224.

Porrino, L. J., Crane, A. M., and Goldman-Rakic, P. S. (1981) Direct and indirect pathways from the amygdala to the frontal lobe in rhesus monkeys. *J Comp Neurol* **198**:121–136.

Preuss, T. M. and Goldman-Rakic, P. S. (1987) Crossed corticothalamic and thalamocortical connections of macaque prefrontal cortex. *J Comp Neurol* **257**:269–281.

Price, J. L. (1990) Olfactory system. In: *The Human Nervous System* (Paxinos, G., ed.), pp 979–998. San Diego: Academic Press.

Price, J. L., Carmichael, S. T., and Drevets, W. C. (1996) Networks related to the orbital and medial prefrontal cortex; a substrate for emotional behaviour? *Prog Brain Res* **107**:523–536.

Rempel-Clower, N. L. and Barbas, H. (1998) Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. *J Comp Neurol* **398**:393–419.

Rempel-Clower, N. L. and Barbas, H. (2000) The laminar pattern of connections between prefrontal and anterior temporal cortices in the rhesus monkey is related to cortical structure and function. *Cereb Cortex* **10**:851–865.

Robson, J. A. and Hall, W. C. (1975) Connections of layer VI in striate cortex of the grey squirrel (Sciurus carolinensis). *Brain Res* **93**:133–139.

Rockland, K. S. (1996) Two types of corticopulvinar terminations: round (type 2) and elongate (type1). *J Comp Neurol* **368**:57–87.

Rolls, E. T. (1996) The orbitofrontal cortex. *Philos Trans R Soc Lond B Biol Sci* **351**:1433–143.

Rolls, E. T. (2000) The orbitofrontal cortex and reward. *Cereb Cortex* **10**:284–294.

Rolls, E. T. and Xiang, J. Z. (2005) Reward-spatial view representations and learning in the primate Hippocampus. *J Neurosci* **25**:6167–6174.

Romanski, L. M. and LeDoux, J. E. (1992) Equipotentiality of thalamo-amygdala and thalamo-cortico-amygdala circuits in auditory fear conditioning. *J Neurosci* **12**:4501–4509.

Rosene, D. L. and van Hoesen, G. W. (1977) Hippocampal efferents reach widespread areas of cerebral cortex and amygdala in the rhesus monkey. *Science* **198**:315–317.

Rosene, D. L. and van Hoesen, G. W. (1987) *The hippocampal formation of the primate brain. A review of some comparative aspects of cytoarchitecture and connections*. In: Cerebral Cortex, Vol. 6 (Jones, E.G. and Peters, A., eds), pp. 345–455. New York: Plenum Publishing Corporation.

Rosvold, H. E. (1972) The frontal lobe system: cortical-subcortical interrelationships. *Acta Neurobiol Exp (Warsz)* **32**:439–460.

Rouiller, E. M. and Welker, E. (2000) A comparative analysis of the morphology of corticothalamic projections in mammals. *Brain Res Bull* **53**:727–741.

Russchen, F. T., Amaral, D. G., and Price, J. L. (1987) The afferent input to the magnocellular division of the mediodorsal thalamic nucleus in the monkey, *Macaca fascicularis. J Comp Neurol* **256**:175–210.

Saddoris, M. P., Gallagher, M., and Schoenbaum, G. (2005) Rapid associative encoding in basolateral amygdala depends on connections with orbitofrontal cortex. *Neuron* **46**:321–331.

Saha, S., Batten, T. F., and Henderson, Z. (2000) A GABAergic projection from the central nucleus of the amygdala to the nucleus of the solitary tract: a combined anterograde tracing and electron microscopic immunohistochemical study. *Neuroscience* **99**:613–626.

Sato, M. and Hikosaka, O. (2002) Role of primate substantia nigra pars reticulata in reward-oriented saccadic eye movement. *J Neurosci* **22**:2363–2373.

Schall, J. D., Morel, A., King, D. J., and Bullier, J. (1995) Topography of visual cortex connections with frontal eye field in macaque: Convergence and segregation of processing streams. *J Neurosci* **15**:4464–4487.

Schnider, A. and Ptak, R. (1999) Spontaneous confabulators fail to suppress currently irrelevant memory traces. *Nat Neurosci* **2**:677–681.

Schnider, A., Treyer, V., and Buck, A. (2000) Selection of currently relevant memories by the human posterior medial orbitofrontal cortex. *J Neurosci* **20**:5880–5884.

Schoenbaum, G., Chiba, A. A., and Gallagher, M. (1999) Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning. *J Neurosci* **19**:1876–1884.

Schoenbaum, G., Chiba, A. A., and Gallagher, M. (2000) Changes in functional connectivity in orbitofrontal cortex and basolateral amygdala during learning and reversal training. *J Neurosci* **20**:5179–5189.

Schoenbaum, G. and Eichenbaum, H. (1995) Information coding in the rodent prefrontal cortex. I. Single-neuron activity in orbitofrontal cortex compared with that in pyriform cortex. *J Neurophysiol* **74**(2):733–750.

Schoenbaum, G. and Setlow, B. (2003) Lesions of nucleus Accumbens disrupt learning about aversive outcomes. *J Neurosci* **23**:9833–9841.

Schoenbaum, G., Setlow, B., Saddoris, M. P., and Gallagher, M. (2003) Encoding Predicted Outcome and Acquired Value in Orbitofrontal Cortex during Cue Sampling Depends upon Input from Basolateral Amygdala. *Neuron* **39**:855–867.

Schultz, W., Tremblay, L., and Hollerman, J. R. (2000) Reward processing in primate orbitofrontal cortex and basal ganglia. *Cereb Cortex* **10**:272–284.

Sillito, A. M., Jones, H. E., Gerstein, G. L., and West, D. C. (1994) Feature-linked synchronization of thalamic relay cell firing induced by feedback from the visual cortex. *Nature* **369**:479–482.

Simpson, J. R., Snyder, A. Z., Gusnard, D. A., and Raichle, M. E. (2001) Emotion-induced changes in human medial prefrontal cortex: I. During cognitive task performance. *Proc Natl Acad Sci USA* **98**:683–687.

Somogyi, G., Hajdu, F., Tombol, T., and Madarasz, M. (1978) Limbic projections to the cat thalamus. A horseradish peroxidase study. *Acta Anat (Basel)* **102**:68–73.

Spiegel, E. A. and Wycis, H. T. (1962) Clinical and physiological applications: thalamotomy. In: *Monographs in biology and medicine Vol. 2: Stereoencephalotomy* (Spiegel, E.A., ed.), pp. 132–135. New York: Grune and Stratton.

Squire, L. R. and Zola, S. M. (1996) Structure and function of declarative and nondeclarative memory systems. *Proc Natl Acad Sci USA* **93**:13515–13522.

Stefanacci, L. and Amaral, D. G. (2002) Some observations on cortical inputs to the macaque monkey amygdala: an anterograde tracing study. *J Comp Neurol* **451**:301–323.

Steriade, M., Jones, E. G., and McCormick, D. A. (1997) *Thalamus—Organization and function*. Oxford: Elsevier *Science*.

Strick, P. L., Dum, R. P., and Picard, N. (1995) Macro-organization of the Circuits Connecting the Basal Ganglia with the Cortical Motor Areas. In: *Models of Information Processing in the Basal Ganglia* (Houk, J. C., Davis, J. L., and Beiser, D. G., eds), pp 117–130. Cambridge, MA: The MIT Press.

Suzuki, W. A. and Amaral, D. G. (1994) Perirhinal and parahippocampal cortices of the macaque monkey: Cortical afferents. *J Comp Neurol* **350**:497–533.

Suzuki, W. A. Miller, E. K., and Desimone, R. (1997) Object and place memory in the macaque entorhinal cortex. *J Neurophysiol* **78**:1062–1081.

Takagi, S. F. (1986) Studies on the olfactory nervous system of the old world monkey. *Prog Neurobiol* **27**:195–250.

Tasker, R. R. and Kiss, Z. H. (1995) The role of the thalamus in functional neurosurgery. *Neurosurg Clin N Am* **6**:73–104.

Tobler, P. N., Fiorillo, C. D., and Schultz, W. (2005) Adaptive coding of reward value by dopamine neurons. *Science* **307**:1642–1645.

Toni, I., Rowe J., Stephan K. E., and Passingham, R. E. (2002) Changes of cortico-striatal effective connectivity during visuomotor learning. *Cereb Cortex* **12**:1040–1047.

Tremblay, E. and Schultz, W. (2000) Reward-related neuronal activity during go/no-go task performance in primate orbitofrontal cortex. *J Neurophysiol* **83**:1864–1876.

Tremblay, L. and Schultz, W. (1999) Relative reward preference in primate orbitofrontal cortex. *Nature* **398**:704–708.

Turner, B. H., Mishkin, M., and Knapp, M. (1980) Organization of the amygdalopetal projections from modality- specific cortical association areas in the monkey. *J Comp Neurol* **191**:515–543.

Ungerleider, L. G. and Mishkin, M. (1982) *Two cortical visual systems*. In: Ingle, D.J., Goodale, M.A., and Mansfield, R.J.W. (eds) *Analysis of VisualXXBehaviour*, MIT Press, Cambridge, MA 549–586.

van Groen, T. and Wyss, J. M. (1990) The connections of presubiculum and parasubiculum in the rat. *Brain Res* **518**:227–243.

van Hoesen, G. W. (1975) Some connections of the entorhinal (area 28) and perirhinal (area 35) cortices of the rhesus monkey. I. Temporal lobe afferents. *Brain Res* **95**:1–24.

van Hoesen, G. W. (1981) The differential distribution, diversity and sprouting of cortical projections to the amygdala of the rhesus monkey. In: *The Amygdaloid complex* (Ben-Ari, Y., ed.), pp 77–90. Amsterdam: Elsevier/North Holland Biomedical Press.

van Hoesen, G. W., Pandya, D. N., and Butters, N. (1972) Cortical afferents to the entorhinal cortex of the rhesus monkey. *Science* **175**:1471–1473.

van Hoesen, G. W., Pandya, D. N., and Butters, N. (1975) Some connections of the entorhinal (area 28) and perirhinal (area 35) cortices of the rhesus monkey. II. Frontal lobe afferents. *Brain Res* **95**:25–38.

Victor, M., Adams, R. D., and Collins, G. H. (1971) *The Wernicke-Korsakoff Syndrome*. Philadelphia: F.A. Davis Company.

Vogt, B. A. and Barbas, H. (1988) *Structure and connections of the cingulate vocalization region in the rhesus monkey*. In: The Physiological control of mammalian vocalization (Newman JD, ed.), pp. 203–225. New York: Plenum Publ. Corp.

Walker, A. E. (1940) A cytoarchitectural study of the prefrontal area of the macaque monkey. *J Comp Neurol* **73**:59–86.

Wallis, J. D. and Miller, E. K. (2003) Neuronal activity in primate dorsolateral and orbital prefrontal cortex during performance of a reward preference task. *Eur J Neurosci* **18**:2069–2081.

Watanabe, M. (1998) Cognitive and motivational operations in primate prefrontal neurons. *Rev Neurosci* **9**:225–241.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., and Jenike, M. A. (1998) Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci* **18**:411–418.

Witter, M. P., van Hoesen, G. W., and Amaral, D. G. (1989) Topographical organization of the entorhinal projection to the dentate gyrus of the monkey. *J Neurosci* **9**:216–228.

Xiao, D. and Barbas, H. (2002a) Pathways for emotions and memory I. input and output zones linking the anterior thalamic nuclei with prefontal cortices in the rhesus monkey. *Thalamus and Related Systems* **2**:21–32.

Xiao, D. and Barbas, H. (2002b) Pathways for emotions and memory II. afferent input to the anterior thalamic nuclei from prefrontal, temporal, hypothalamic areas and the basal ganglia in the rhesus monkey. *Thalamus and Related Systems* **2**:33–48.

Xiao, D. and Barbas, H. (2004) Circuits through prefrontal cortex, basal ganglia, and ventral anterior nucleus map pathways beyond motor control. *Thalamus & Related Systems* **2**:325–343.

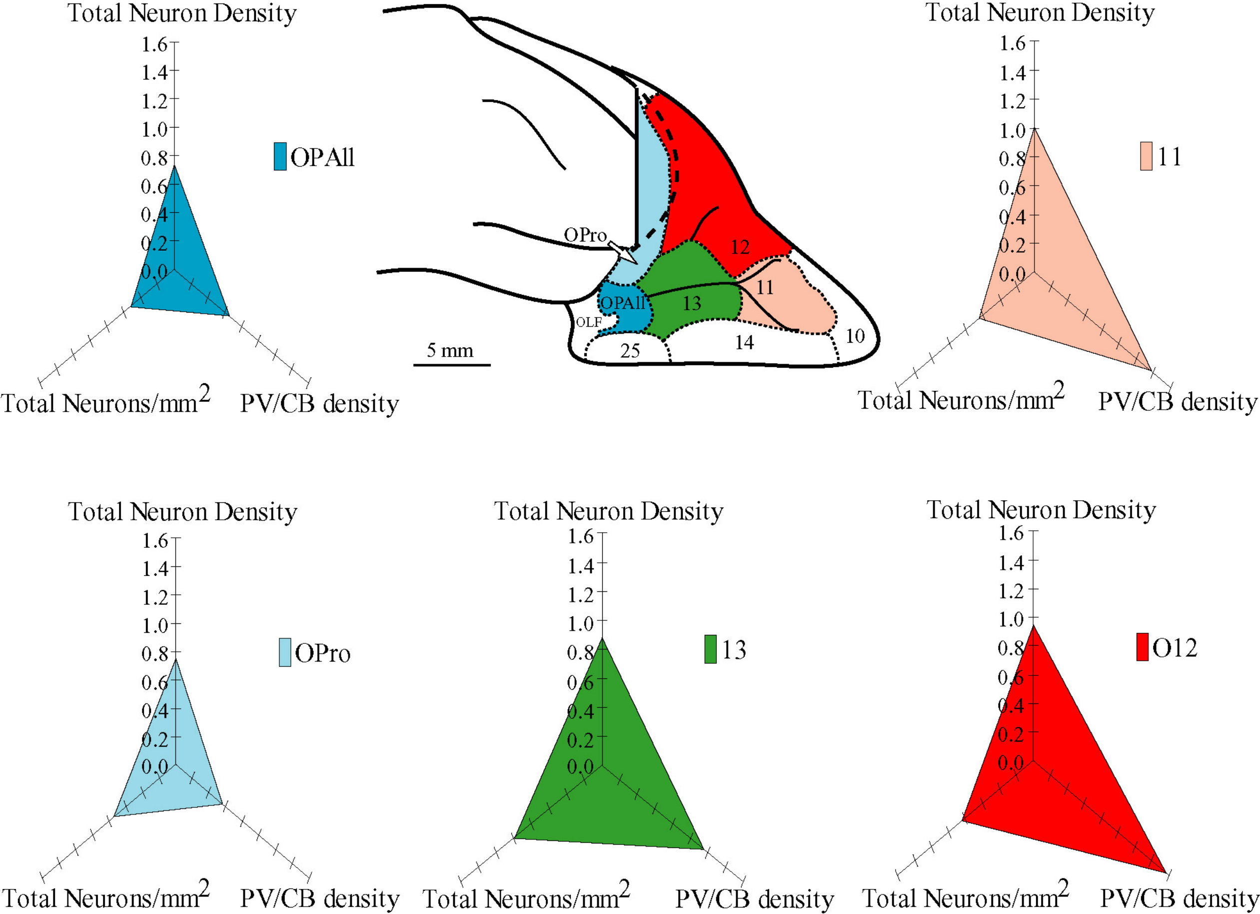
Yakovlev, P. I. (1948) Motility, behaviour and the brain: Stereodynamic organization and neurocoordinates of behaviour. *J Nerv Ment Dis* **107**:313–335.

Yeterian, E. H. and Pandya, D. N. (1988) Corticothalamic connections of paralimbic regions in the rhesus monkey. *J Comp Neurol* **269**:130–146.

Young, K. A., Manaye, K. F., Liang, C., Hicks, P. B., and German, D. C. (2000) Reduced number of mediodorsal and anterior thalamic neurons in schizophrenia. *Biol Psychiatry* **47**:944–953.

Zald, D. H. and Kim, S. W. (1996) Anatomy and function of the orbital frontal cortex, I: anatomy, neurocircuitry; and obsessive-compulsive disorder. *J Neuropsychiatry Clin Neurosci* **8**:125–138.

Zola-Morgan, S. and Squire, L. R. (1985) Amnesia in monkeys after lesions of the mediodorsal nucleus of the thalamus. *Ann Neurol* **17**:558–564.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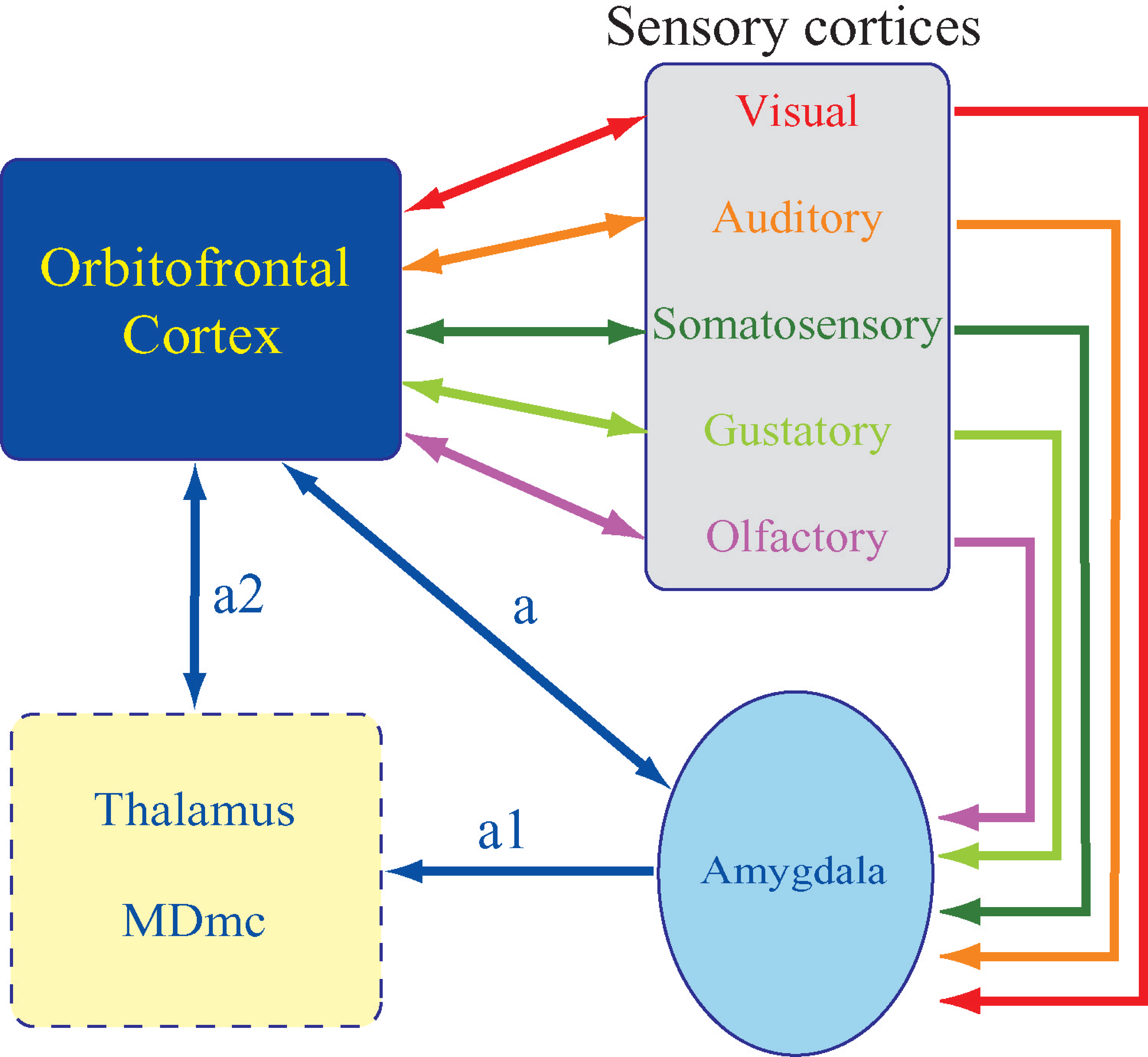
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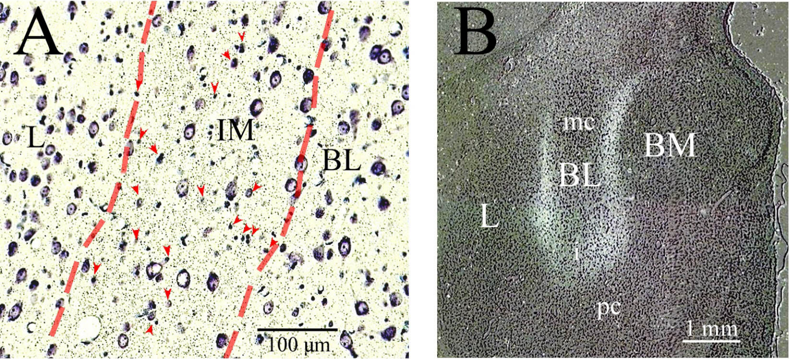
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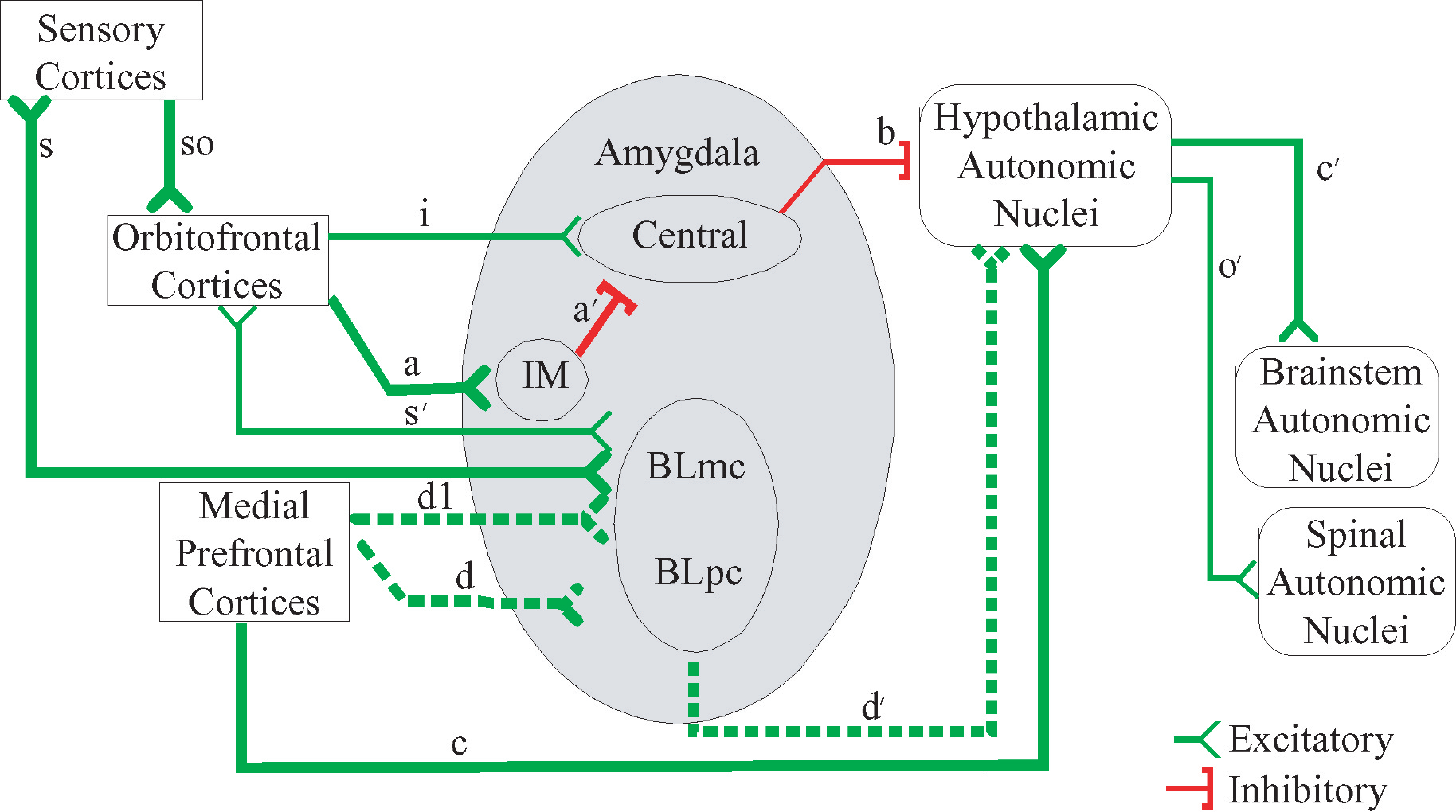
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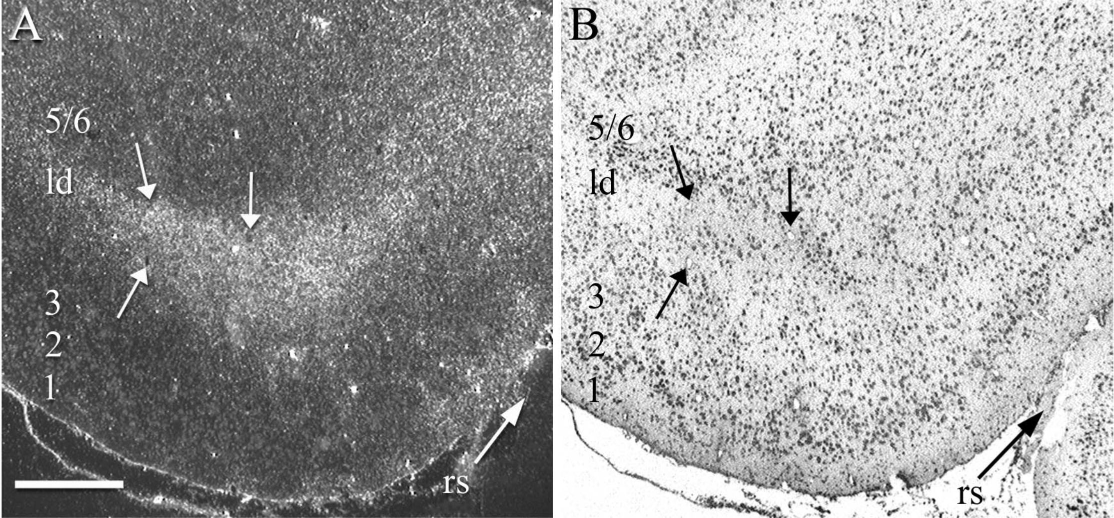
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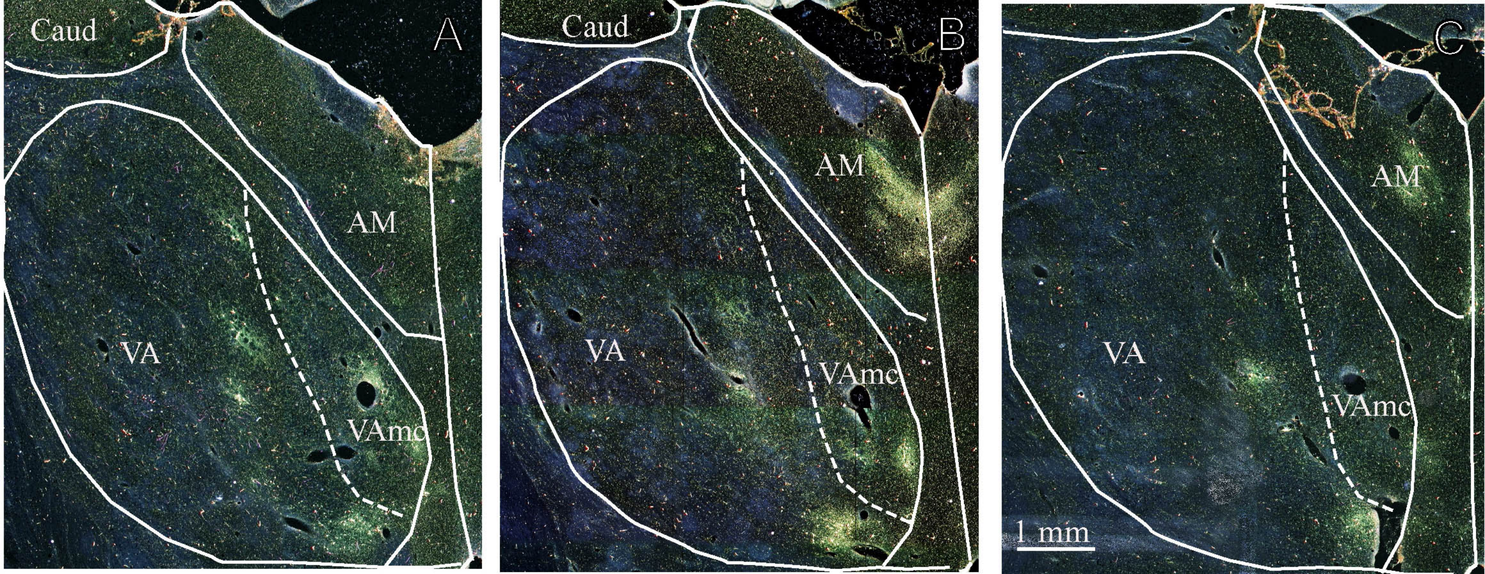
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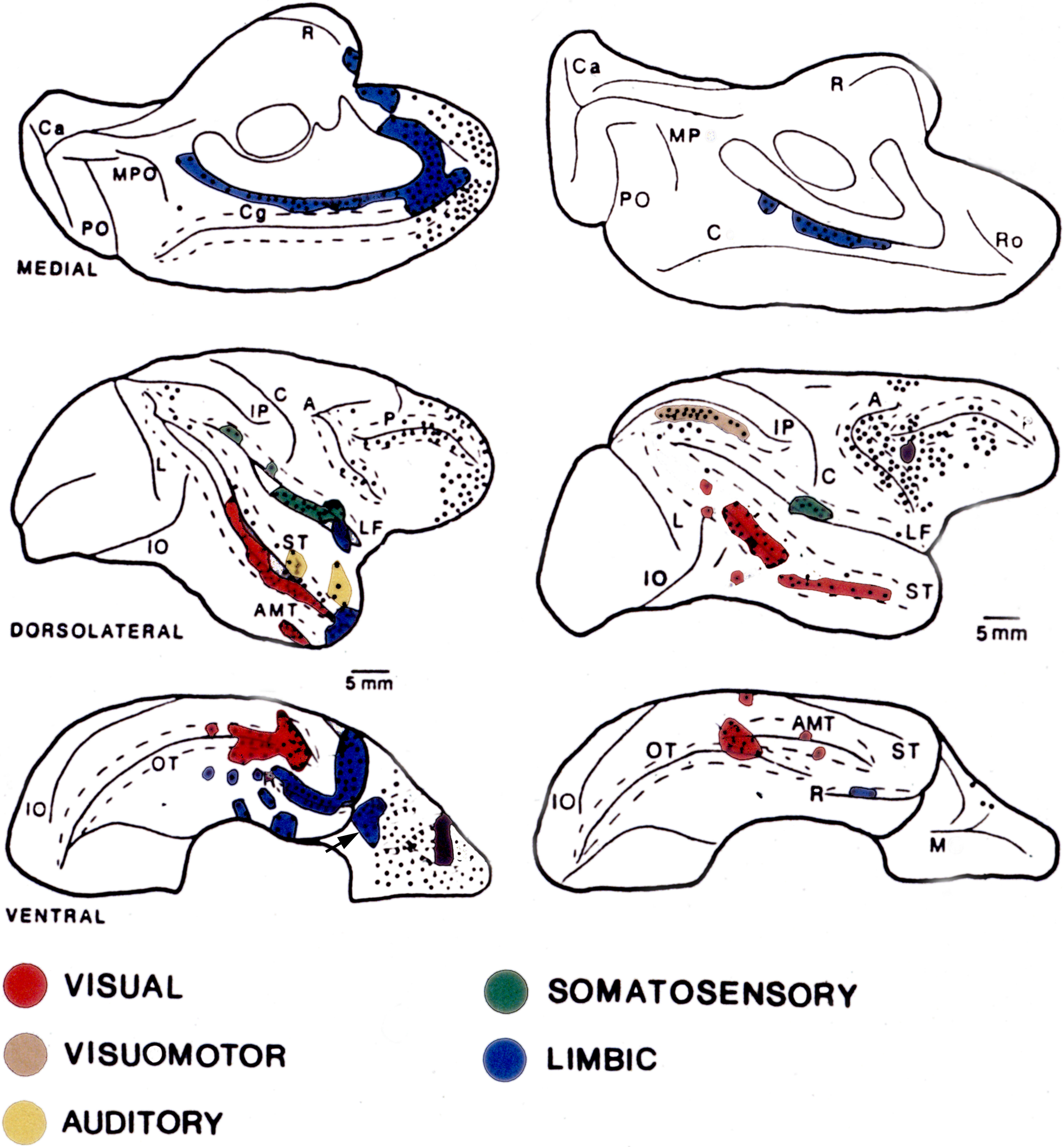
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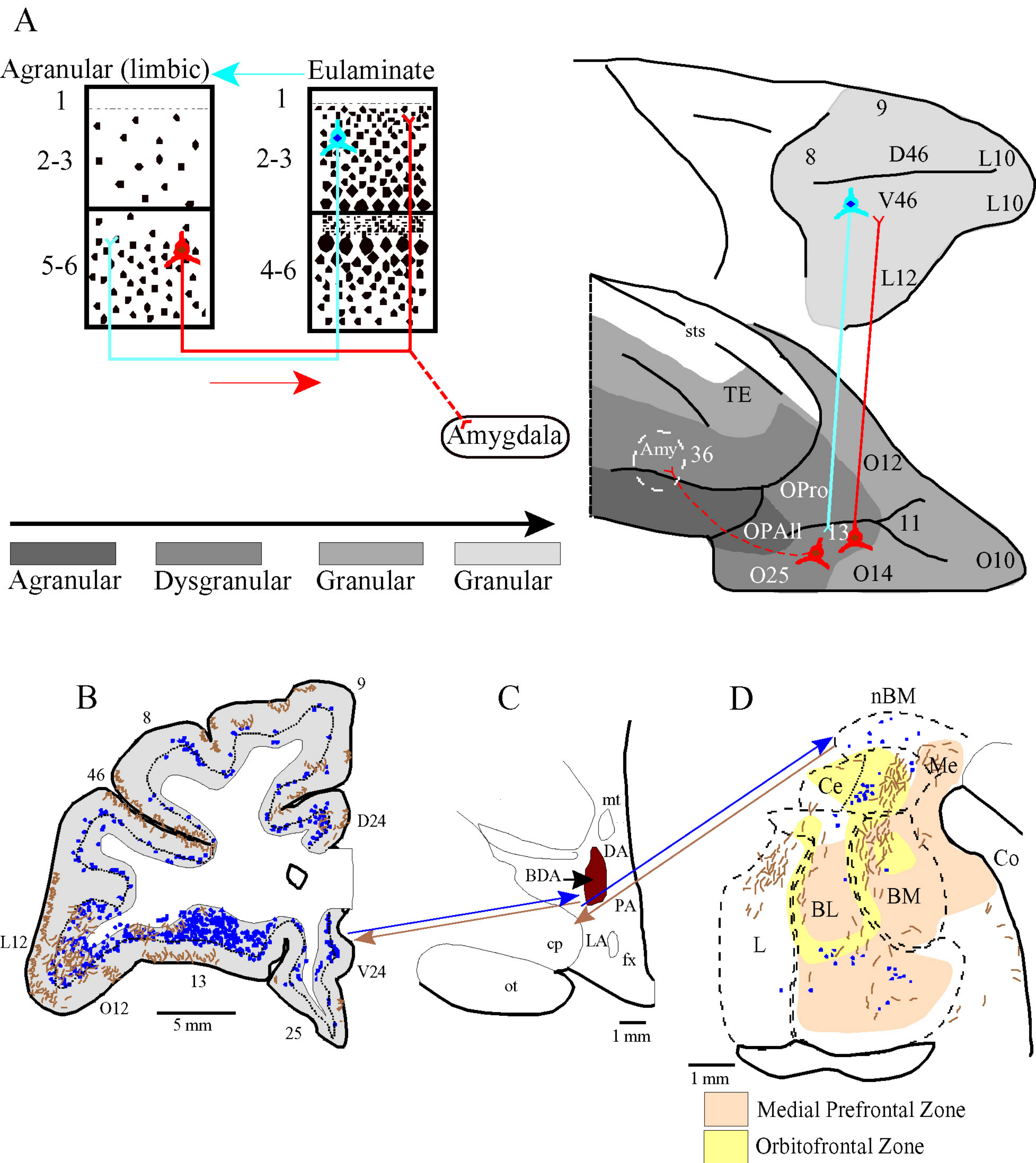
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