

## REVIEW

# Flow of information for emotions through temporal and orbitofrontal pathways

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## Abstract

The posterior orbitofrontal cortex, anterior temporal sensory association areas and the amygdala have a key role in emotional processing and are robustly interconnected. By analogy with the pattern of connections in early processing sensory areas, anterior temporal sensory and polymodal association cortices send primarily feedforward projections to posterior orbitofrontal cortex and to the amygdala originating in the supragranular layers, in pathways that may provide signals about the external environment. The amygdala innervates all layers of the posterior orbitofrontal cortex, including the middle, or feedforward, target layers, in a pathway that may convey information about emotional context. The posterior orbitofrontal cortex targets dual systems in the amygdala which have opposite effects on central autonomic structures. Both pathways originate in posterior orbitofrontal cortex, but one targets heavily the inhibitory intercalated masses, whose activation can ultimately disinhibit central autonomic structures during emotional arousal. The other pathway innervates the central nucleus of the amygdala, and can lead to downstream inhibition of central autonomic structures, resulting in autonomic homeostasis. The choice of pathway may depend on emotional context, and probably involves other prefrontal areas, including lateral prefrontal areas, which have executive functions. Lateral prefrontal cortices issue feedforward projections that target layer 5 of orbitofrontal cortex, which is the chief output layer to the amygdala. These laminar-specific pathways suggest sequential and collaborative interactions in evaluating the sensory and emotional aspects of the environment for decision and action in complex behaviour.

**Key words** amygdala; cognition; emotions; laminar connections; prefrontal cortex; primates; temporal cortex.

## Introduction

The prefrontal cortex in primates receives information from most of the cerebral cortex and from subcortical structures, but at any one time it processes only what is relevant for the task at hand (reviewed in Dagenbach & Carr, 1994; Posner & DiGirolamo, 1998), whether it is a working memory task, associative learning or sequential aspects of behaviour, all of which have been associated with prefrontal function (reviewed in Goldman-Rakic, 1988; Fuster, 1995; Petrides, 1996; Passingham et al. 2000; Passingham & Sakai, 2004). Choosing relevant information is a complex process, and must be conducted within an emotional context that helps focus attention on specific aspects of the sensory environment. In a routine drive on the way home from work, for example, we sample the

environment nearly automatically, avoiding other cars and responding to road and traffic directives. But if there is an accident ahead, the surroundings suddenly acquire a new meaning and attention is fixed on the scene ahead.

This short review focuses on pathways that may mediate the process of selective attention for emotional events. It specifically addresses the question of whether the patterns of connections between prefrontal cortex and other structures can provide information about the sequence of transmission of information for emotions. How is information from multiple signals about the external environment organized, and how is this information integrated with information about emotional context at the level of pathways? This review does not include a comprehensive account of the connections of all structures that may be associated with emotions, but focuses on pathways that link three structures that appear to have a key role in this process: anterior temporal sensory cortices, the amygdala and the orbitofrontal cortex. The anterior temporal sensory association cortices are connected with both orbitofrontal cortex and the amygdala, and probably provide information on the sensory attributes of the environment. The

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amygdala is situated in the anterior part of the temporal lobe and has a key role in emotions (Nishijo et al. 1988; Davis, 1992; Damasio, 1994; LeDoux, 1996), as does the orbitofrontal cortex (reviewed in Barbas, 2000; Cavada et al. 2000). The anterior temporal cortices, the posterior orbitofrontal cortex and the amygdala are robustly inter-linked in triad pathways that may help integrate information on the sensory features and the emotional significance of events, as elaborated upon below.

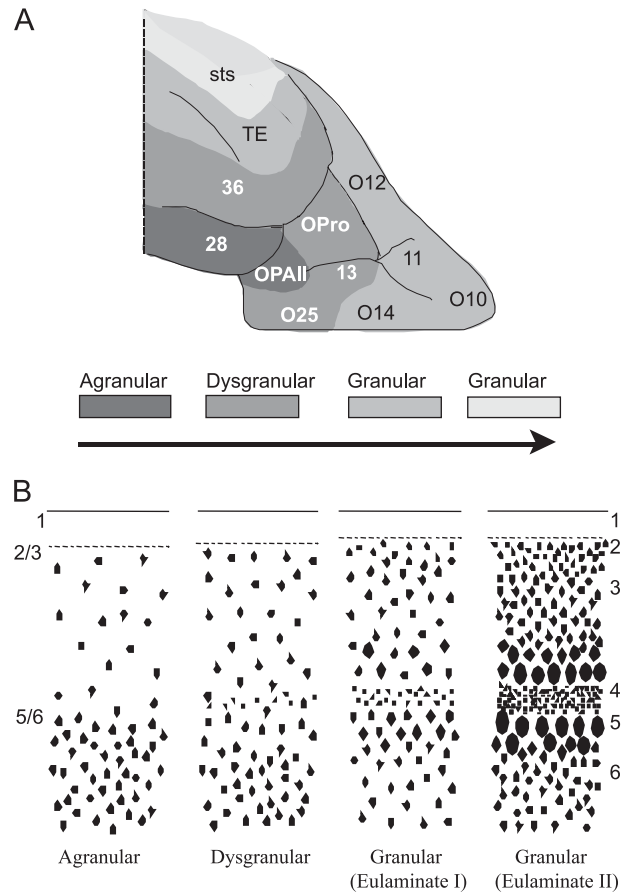
### Architecture of orbitofrontal cortex

Before discussing the principal connections of the orbitofrontal cortex it is necessary to review briefly its overall architecture, because it underlies both the topography and laminar patterns of connections (reviewed in Barbas et al. 2002). The orbitofrontal cortex is a large and heterogeneous region, extending from the basal part of the frontal pole anteriorly, to the olfactory areas posteriorly, as shown in Fig. 1. At its most anterior extent, the basal frontal pole includes the orbital part of area 10, which is adjoined posteriorly by area 11, which is bordered on the medial side by orbital area 14 and laterally by orbital area 12. Area 13 is situated behind area 11, occupying a central position on the basal surface. Behind areas 12 and 13 there is another cortical area, the orbital proisocortex [area OPro in Barbas & Pandya (1989), area OFdg in Morecraft et al. (1992); lai, lal in Carmichael & Price (1994)]. On the medial side of area 13, area 25 constitutes a caudal extension of area 14. The most caudal extent of orbitofrontal cortex includes the orbital periallocortex [area OPAlI (Barbas & Pandya, 1989); or area OFap (Morecraft et al. 1992)]. References to architectonic areas in this review and in Fig. 1 are according to the map of Barbas & Pandya (1989), which was modified from the classic map of Walker (1940).

### Cortical areas vs. cortical types

Each of the above areas has unique architectonic features that distinguish it from its neighbours. In fact, finer subdivisions for the orbitofrontal cortex have been suggested (Carmichael & Price, 1994). Architectonic maps, in general, are based on features that give each area its unique signature, such as the size and the shape of neurons in individual layers. For example, the giant Betz cells in layer 5 characterize the primary motor cortex of gyrencephalic primates and help distinguish it from its neighbouring and rostrally situated premotor areas. In recent years several cellular and molecular markers that are differentially distributed in cortical areas have helped delineate architectonic areas.

Cortical type, by contrast, refers to broad structural features of areas, such as the number of layers present, the width and density of layer 4, and overall neuronal density, as summarized in the cartoon in Fig. 1(B). If particular cellular features define an architectonic area, as facial features



**Fig. 1** Cortical types in the orbitofrontal and anterior temporal region. (A) Shades of grey depict cortical type, with agranular areas shaded in the darkest grey. Progressively lighter shades of grey show dysgranular and granular (eulaminate) cortices. Cortical areas (without delineation of their borders) are indicated by numbers. O, before architectonic areas refers to orbital. Abbreviations: OPAlI, orbital periallocortex (agranular cortex); OPro, orbital proisocortex (dysgranular type); TE, inferior temporal visual association area (eulaminate cortex); sts, superior temporal sulcus. (B) Cartoon showing the broad laminar features of different types of cortex. Two types of eulaminate cortices are depicted, differing in the density of granular layer 4 and in the density of the supragranular layers 2–3. Note that orbitofrontal cortex does not have areas with the type of cortex depicted on the far right, found only on the lateral surface of the prefrontal cortex.

identify a person, cortical type unifies architectonically disparate areas into groups by focusing on common features, analogous to grouping people by a common characteristic, such as height or weight. The quintessential feature that readily distinguishes cortical type, namely differences in the number of layers or sublayers among cortical areas, is prominently seen in the drawings and descriptions of Cajal (see DeFelipe & Jones, 1988). Notwithstanding its significance in understanding cortical organization, the concept of cortical type is seldom appreciated in discussions of the cortex.

By cortical type, the rostrally situated orbitofrontal cortices (areas 10, 11, 12 and 14) are eulaminate, signifying that they possess six layers, including a distinct granular

layer 4, comparable with the cartoon in Fig. 1(B) (granular, eulaminar 1). The caudally adjacent areas, including areas 13, OPro and orbital area 25, are dysgranular in type, characterized by the presence of a thin and incipient granular layer 4 (Fig. 1B). The most caudally located orbitofrontal cortex lacks a granular layer 4, and is thus agranular in type (Fig. 1A, darkest grey). The above description indicates that orbitofrontal areas belong to one of three types of cortex, and that each type is identified by the number of layers. Cortical systems composed of many areas, such as the visual, can be described by cortical type as well, as shown for anterior temporal cortices in Fig. 1(A).

The architecture of individual areas, as well as cortical types, can be described objectively using unbiased quantitative methods to determine the distribution of cellular markers that help differentiate them. The best descriptor of cortical type in orbitofrontal cortex in rhesus monkeys is neuronal density in different layers (Dombrowski et al. 2001), where agranular areas have the lowest neuronal density and the eulaminar areas have the highest density. In addition, cortical types in prefrontal cortex can be distinguished by the differential distribution of two classes of inhibitory neurons expressing the calcium-binding proteins parvalbumin (PV) or calbindin (CB). The agranular orbitofrontal cortex has the highest density of CB-positive neurons and the lowest of PV neurons. By contrast, the distribution of CB is comparatively more balanced in the rostrally situated eulaminar orbitofrontal areas, although CB is still more densely distributed than PV (Dombrowski et al. 2001). In the cartoon in Fig. 1 orbitofrontal areas have the first three cortical types (left to right). The type of cortex with a dense granular layer 4 (Fig. 1B, far right) is not seen in orbitofrontal cortex, but is found on the lateral surface of prefrontal cortex, such as areas 46 and 8 (not shown).

The above suggests that the anterior and posterior regions of orbitofrontal cortex are broadly distinguishable by type of cortex, which is granular and eulaminar anteriorly, and dysgranular or agranular progressively posteriorly. As we shall see below, it is the caudal orbitofrontal cortex that appears to sample the entire sensory periphery through cortical connections, and it is the caudal orbitofrontal cortex that has the strongest connections with limbic structures that process signals on the internal environment, and has the most robust and specialized connections with the amygdala. Consequently, the focus of this review will be on caudal orbitofrontal pathways, whose organization may shed light on the possible sequential flow of information for evaluating the emotional significance of events.

### **Caudal orbitofrontal cortex has a panoramic view of the external and internal environments**

One of the most striking features of caudal orbitofrontal cortex is its polymodal nature, enriched by connections with

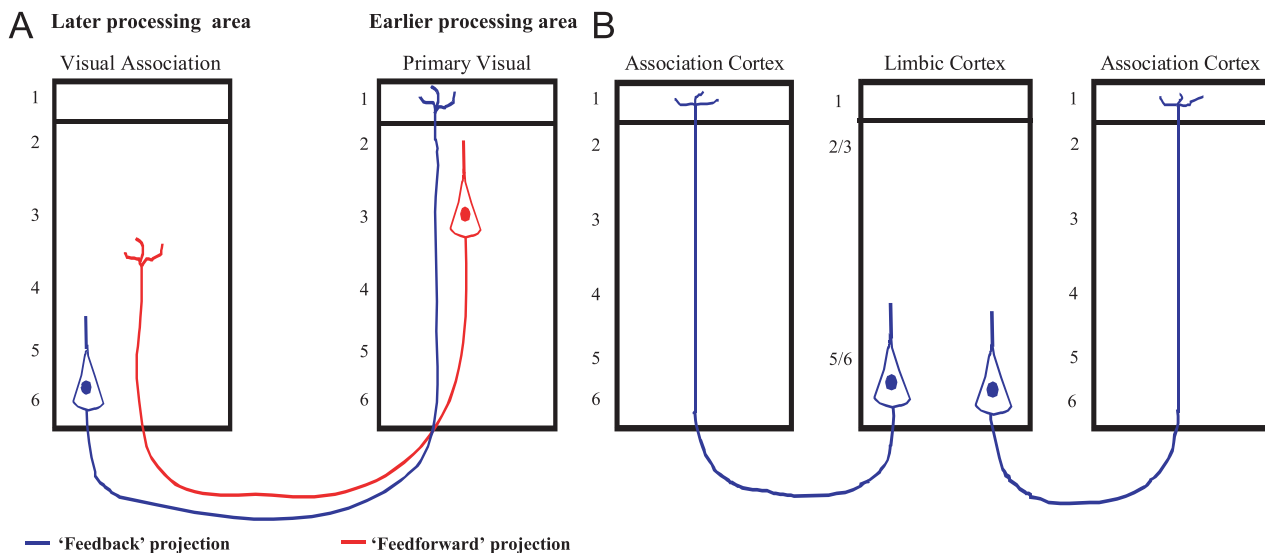
cortices representing each and every sensory modality, including visual, auditory, somatosensory, gustatory and olfactory (reviewed in Barbas, 2000; Cavada et al. 2000). No other cortical region, except perhaps the rhinal/perirhinal region (Van Hoesen et al. 1972; Van Hoesen, 1975; Insausti et al. 1987; Suzuki & Amaral, 1994), has a comparable richness in the sensory information it receives. The caudal orbitofrontal cortex stands apart from the rest of the orbitofrontal cortex for its unique connections with primary olfactory areas (for a review see Takagi, 1986). By contrast, input from the visual and auditory modalities reaches the caudal orbitofrontal cortex through projections from high-order visual, auditory and polymodal association cortices situated in anterior temporal cortices. The orbitofrontal cortex reciprocates with projections to sensory association and polymodal cortices. Some foci within orbitofrontal cortex receive preferential projections from one modality over the others, but the region is essentially polymodal (e.g. Morecraft et al. 1992; Barbas, 1993; Baylis et al. 1995; Carmichael & Price, 1995b; reviewed in Cavada et al. 2000; Barbas et al. 2002). Moreover, the responses of orbitofrontal neurons to sensory stimuli in monkeys are closely linked to reward contingencies and not strictly to their physical properties (Tremblay & Schultz, 1999). Thus, if monkeys learn that a red stimulus signifies reward and a green stimulus does not, orbitofrontal neurons respond to the red stimulus; when the reward contingencies are later reversed, the same neurons respond to the green stimulus.

The orbitofrontal cortex, in general, and the posterior sectors, in particular, are also characterized by the strong bidirectional links they have with cortical limbic structures in the anterior cingulate and the medial temporal cortex, and with subcortical limbic structures, such as the amygdala, the hippocampus, midline thalamic nuclei and the magnocellular sector of the mediodorsal thalamic nucleus (for reviews see Barbas, 2000; Cavada et al. 2000). The robust projections from limbic cortices to the posterior orbitofrontal cortex may provide signals pertaining to the internal, or emotional, environment. In summary, the rich connections of orbitofrontal cortex endow it with a panoramic view of the entire external environment, as well as the internal environment associated with motivational factors.

### **Laminar pattern of connections for inferring sequence of information processing**

#### **Sensory cortices as model systems**

The connections of orbitofrontal cortex with sensory association areas are bidirectional, but the topography of connections does not provide information on the possible sequence of transmission of information between these cortices, which is the focus of this review. The issue of the



**Fig. 2** Laminar patterns of corticocortical connections. (A) Projection neurons from earlier-processing sensory areas originate in the supragranular layers and their axons terminate mostly in the middle–deep layers of later-processing sensory areas, and are called feedforward (red). Projections proceeding in the reverse direction originate in the deep layers and their axons terminate mostly in the upper layers, especially layer 1 of earlier-processing areas, and are called feedback (blue). (B) Limbic cortices (which are either agranular or dysgranular in type) issue projections mostly from their deep layers, and their axons terminate most densely in layer 1 of association areas, akin to feedback projections, regardless of the direction of projections.

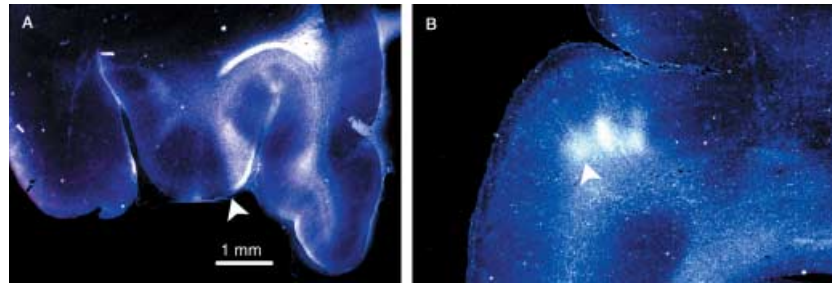
order in signal processing is difficult to tackle using functional or other methods in any system, particularly in complex high-order association cortices. Clues, however, have emerged from processing in the early stages in sensory systems, especially the visual. The sensory systems are useful in this respect because we have a handle on the sequence of signal processing from the periphery to the thalamus, then to the primary sensory cortex, and then to association cortices. Sensory thalamic nuclei that receive input from the sensory periphery relay the signal through axonal projections that terminate in the middle cortical layers of primary cortices, within and around layer 4 (for a review see Jones, 1985). These projections are considered to be feedforward, based on the sequence of signal transmission from the sensory periphery to the cortex. Primary sensory areas, in turn, project in a feedforward manner to neighbouring association areas, issuing projections from the upper layers (mostly from layer 3), and their axons terminate in the middle layers (e.g. Rockland & Pandya, 1979; Friedman et al. 1986; Felleman & Van Essen, 1991; Barone et al. 2000; Fig. 2A). Thus, when corticocortical projections are directed away from the sensory periphery they originate in layer 3 and their axons terminate in the middle layers of sensory association areas, and are considered to be feedforward. Corticocortical projections that proceed in the opposite direction, from sensory association areas back to primary sensory cortex, have a different laminar pattern: they originate in the deep layers (5–6) and terminate most densely in layer 1 (Rockland & Pandya, 1979; Friedman et al. 1986; Felleman & Van Essen, 1991;

Rockland & Van Hoesen, 1994). The latter have been called 'feedback' projections, because they project toward the sensory periphery.

Can we use the patterns of connections between orbitofrontal cortex and sensory areas to infer the possible sequence of information processing between these cortices, by analogy with patterns of connections in early-processing sensory cortices? The pattern of connections between high-order association cortices is quite complex, originating and terminating in varying proportions in different cortical layers. Examples of the complexity of these connections are seen in some interconnections of prefrontal cortices in Fig. 3. Nevertheless, these complex patterns have a consistent laminar organization that can be explained within the context of cortical type, as elaborated upon below.

### Cortical type underlies the laminar pattern of corticocortical connections

An important clue regarding the organization of laminar patterns of connections emerged from the pattern of connections of limbic cortices, which issue projections to association cortices mostly through their deep layers (Barbas, 1986), as seen in Figs 2(B) and 4. Limbic areas were classically named for their topographic placement at the edge of the cortex (Broca, 1878), and by their robust connections with subcortical limbic structures. However, cortical limbic areas also have a common overall structure, being either agranular or dysgranular in type. Projections



**Fig. 3** The varied patterns of laminar terminations linking prefrontal cortices. (A) Dark-field photomicrograph of coronal section through the centre of the orbitofrontal cortex of a rhesus monkey brain showing terminations of axons (white grain) forming a column in orbitofrontal area 13 (white arrowhead), with denser termination in layer 1. (B) Axonal terminations forming three modules restricted to the deep layers of the cortex in the lateral bank of the upper limb of the arcuate sulcus.

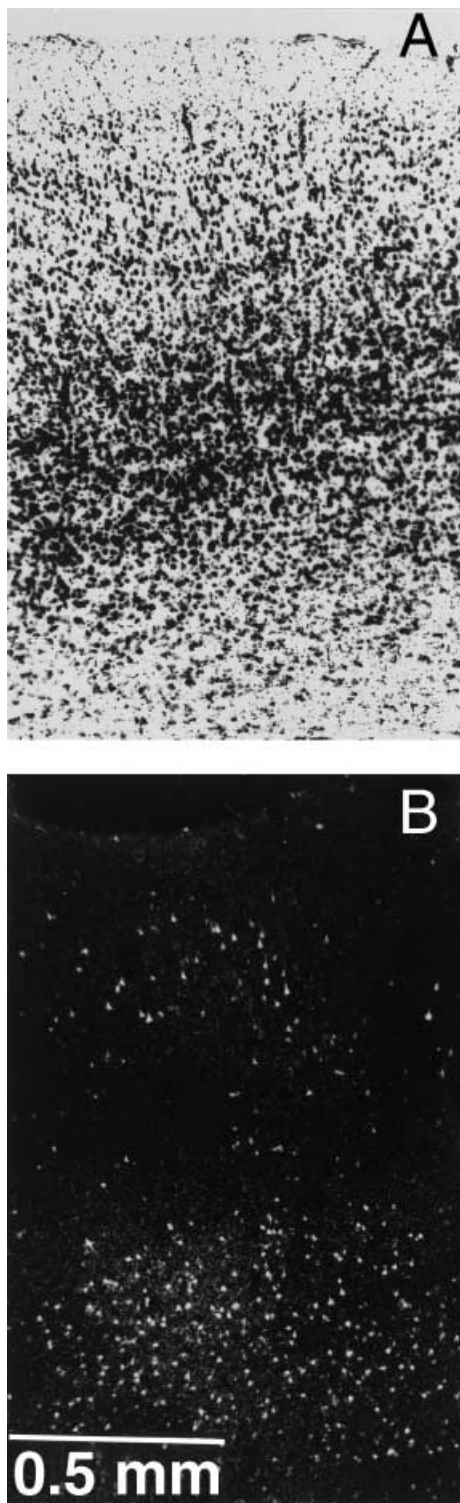
from limbic cortices to association cortices therefore are akin to feedback projections in the sensory systems.

The laminar patterns of corticocortical connections in sensory systems have been attributed to position in processing hierarchy or distance (Barone et al. 2000; reviewed in Felleman & Van Essen, 1991). Cortical distance often coincides with changes in structural type, but when it does not, it is cortical type that can best predict the laminar pattern of connections (see Barbas et al. 2005a). As discussed above and illustrated in Fig. 1(B), laminar structure changes gradually and systematically across a cortical region. These changes can be described quantitatively by the number of layers present, overall neuronal density and the distribution of distinct neuronal markers, such as PV, CB and other cellular and molecular features. Cortical structure changes gradually, but based on broad laminar features areas can be categorized into a few cortical types. We have previously described agranular limbic areas as type 1 cortex and dysgranular limbic areas as type 2 cortex. Eulaminar areas can also be subdivided into cortical types based on the neuronal density of layer 4 and overall neuronal density. In Fig. 1(B) eulaminar 1 cortex (type 3) has lower neuronal density in layer 4 and in the supragranular layers than eulaminar 2 cortex (type 4). Eulaminar areas can be grouped into two or more categories, based on the extent of the cortical region examined, or by how fine a distinction one wishes to make among categories (e.g. Barbas & Rempel-Clover, 1997; Rempel-Clover & Barbas, 2000).

By relating connections to cortical type, we see a clear trend: projection neurons from a given area originate mostly in the upper layers and their axons terminate predominantly in the middle–deep layers (4–6) of areas with comparatively fewer layers or lower neuronal density than the cortex of origin (e.g. projections from eulaminar 1 to agranular cortex, in Fig. 1B). Connections proceeding in the opposite direction, from areas with fewer layers or lower neuronal density, originate mostly in the deep layers and their axons terminate predominantly in the upper layers (1–3) of areas with either more layers or higher neuronal density.

We have referred to the relationship of cortical structure (type) to laminar connections as the ‘structural model’, and just as cortices show graded differences in structure, so do the patterns of connections. The structural model is thus relational, i.e. the proportion of projection neurons or axonal terminals in the upper to the deep layers varies according to the relative difference in structure of the connected areas (Barbas & Rempel-Clover, 1997). The pattern is accordingly exaggerated when structurally dissimilar areas are connected (e.g. agranular areas with eulaminar areas), than when structurally similar areas are interconnected (e.g. agranular areas with dysgranular areas). When areas of a similar type are interconnected, the pattern of terminations in each cortex is columnar, encompassing all cortical layers (as seen in Fig. 3A), and projection neurons originate in roughly equal numbers in layers 2–3 and 5–6. The above discussion suggests that just as cortices show a graded pattern in structure (Fig. 1B), so does the distribution of connections in cortical layers, in a pattern correlated with the difference in laminar structure of the linked areas. We have previously discussed that the regularity of corticocortical connections and cortical architecture is probably explained by developmental events (see Dombrowski et al. 2001; Hilgetag & Barbas, 2006).

The concept of cortical type in describing the pattern of corticocortical connections applies to all cortical systems because each system, such as the visual, the somatosensory or auditory, is composed of areas belonging to different cortical types (see Barbas, 1986; reviewed in Pandya et al. 1988; Barbas et al. 2002), as seen for anterior temporal cortices in Fig. 1(A). The structural model has been supported in the pattern of connections not only within the prefrontal cortex of rhesus monkeys (Barbas & Rempel-Clover, 1997), but also in the connections between prefrontal cortices and superior or inferior temporal cortices and prefrontal and intraparietal cortices (Barbas et al. 1999, 2005b; Rempel-Clover & Barbas, 2000; Medalla & Barbas, 2006), and in the sensory systems of other species (Grant & Hilgetag, 2005). These studies have shown that broad structural attributes,



**Fig. 4** The laminar pattern of connections in a limbic area of orbitofrontal cortex. (A) Bright-field photomicrograph shows the architecture of a limbic orbitofrontal area, which has fewer than six distinguishable layers. (B) Dark-field photomicrograph shows that when this limbic area projects to a eulaminar association area the majority of projections neurons (white neurons) are found in the deep layers (5–6) and fewer are found in the upper layers (2–3). Adapted from Barbas (1986).

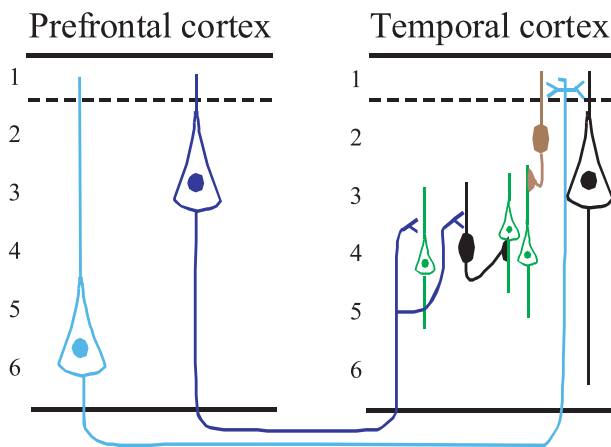
described as different types of cortices, underlie common patterns in corticocortical connections.

#### The functional significance of laminar-specific connections

Laminar-specific connections have implications for function, as axons terminating in the upper layers probably influence different populations of neuronal elements than axons terminating in the deep layers. Specifically, the laminar microenvironment varies considerably in inputs and outputs, and influence from neurochemically specific subcortical structures (e.g. De Lima et al. 1990; Goldman-Rakic et al. 1990; Hof et al. 1995; Zaborszky et al. 1999; Ghashghaei & Barbas, 2001). One key laminar-specific difference that connections encounter in their origin or termination is in the predominant classes of inhibitory neurons. In the primate cortex, for example, two key neurochemical classes of inhibitory neurons that express PV or CB show marked differences in their laminar distribution and in the mode of inhibitory control they exercise on neighbouring neurons. PV is expressed in basket and chandelier cells in the cortex (DeFelipe et al. 1989; Kawaguchi & Kubota, 1997), which are found predominantly in the middle layers of the cortex. PV inhibitory neurons synapse with neighbouring pyramidal neurons, by innervating their proximal dendrites and axon initial segments (DeFelipe et al. 1989; Shao & Burkhalter, 1999). By contrast, CB-positive inhibitory neurons include double bouquet neurons in the cortex, they are most prevalent in cortical layer 2 and upper layer 3, and innervate the distal dendrites and spines of neighbouring neurons (e.g. Peters & Sethares, 1997). A model of the relationship of axonal terminations in the middle vs. the deep layers in corticocortical pathways from prefrontal to temporal cortex is shown in Fig. 5.

Moreover, prefrontal axons that terminate in different layers are also synaptically distinct. Thus, boutons from prefrontal axons synapsing in the superficial layers of superior temporal cortex are smaller in size and contain fewer synaptic vesicles than boutons terminating in the middle cortical layers. These laminar-specific pathways probably differ in efficacy of synaptic transmission (Germuska et al. 2006). Moreover, the relationship of bouton size to laminar terminations holds for boutons from axons originating in distinct prefrontal areas and terminating in the same temporal area, or originating in the same prefrontal area and terminating in different superior temporal cortices. This laminar-specific pattern of connections at the synaptic level is consistent with physiological features of feedforward pathways in the cortex, which are considered to be 'driver' pathways, and feedback pathways, which are considered to have a modulatory role (e.g. Sandell & Schiller, 1982; Sherman & Guillery, 1998; Shao & Burkhalter, 1999; Reichova & Sherman, 2004).





**Fig. 5** The microenvironment of projections originating and terminating in different layers varies. Model of corticocortical projections, using as an example projections from prefrontal cortex to temporal cortex, indicating that projections originating in layer 3 (left) and terminating in the middle layers (right) encounter an environment that differs from projections originating in the deep layers (left) and terminating in layer 1 (right). The model shows specifically the differences in the microenvironment with respect to inhibitory neurons at the site of termination (right). The neurochemical class of parvalbumin inhibitory neurons (depicted in black) are most prevalent in the middle cortical layers, and innervate the proximal dendrites or axon initial segment of neighbouring neurons. Axons terminating in layer 1 encounter a microenvironment where the neurochemical class of calbindin inhibitory neurons are most prevalent (depicted in grey), which innervate the distal dendrites of neighbouring neurons.

## Laminar-specific pathways for emotions

### Feedforward projections from temporal sensory areas reach posterior orbitofrontal cortex

The connections between orbitofrontal cortices and medial and inferior temporal cortices are organized according to the rules of the structural model for connections. For example, eulaminate temporal visual or auditory association cortices issue projections to caudal orbitofrontal cortex in laminar patterns that are predominantly, though not exclusively, of the feedforward type. In the reverse direction, axons originating in dysgranular orbitofrontal cortex terminate mostly, though not exclusively, in the upper layers of granular (eulaminate) anterior temporal area TE, akin to feedback projections. By contrast, axons from the same orbitofrontal cortex target mostly the middle to deep layers of agranular temporal cortex (entorhinal area 28). In addition, the majority of terminations from axons originating in dysgranular area 36, which is polymodal, terminate in the middle to deep layers of agranular orbitofrontal cortex in a feedforward manner (Rempel-Clower & Barbas, 2000).

### Sequential feedforward projections from sensory cortices to the amygdala and to orbitofrontal cortex

We have seen thus far that the posterior orbitofrontal cortex has strong connections with sensory association cortices,

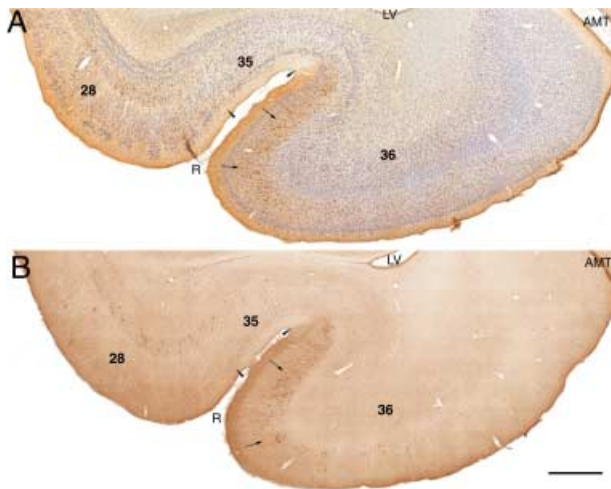
originating mostly from anterior temporal cortices, and that the connections between these structures are organized according to the rules of the structural model for connections. Thus, neurons from sensory association cortices in the anterior temporal region project mostly in a feedforward manner to posterior orbitofrontal cortex.

Can the above connections provide information as to how signals from sensory association cortices convey information on the emotional significance of the environment? To address this issue, information from other pathways is relevant, namely the robust bidirectional pathways that link the posterior orbitofrontal cortex as well as anterior temporal cortices with the amygdala. In fact, the same parts of anterior temporal cortices that project to posterior orbitofrontal cortex project to the amygdala (Ghashghaei & Barbas, 2002). Thus, the posterior orbitofrontal cortex receives direct projections from sensory association cortices, and potentially indirect projections from sensory cortices through the amygdala. We have previously suggested that the pathways from the amygdala to the posterior orbitofrontal cortex convey information about the emotional significance of the environment (Barbas, 1995). Can the laminar patterns of connections between the temporal sensory association areas, the amygdala and the orbitofrontal cortex provide information about the sequence of information processing for emotions, by analogy with connections linking early-processing sensory areas?

We recently found that anterior temporal polymodal areas (e.g. area 36) and the adjacent visual area TE1 issue projections to the amygdala primarily from layers 2–3 (Höistad & Barbas, 2007), resembling feedforward projections in sensory cortices, as shown in Fig. 6. These findings suggest that sensory association and polymodal cortices in the anterior temporal cortex issue mostly feedforward projections to both caudal orbitofrontal cortex and to the amygdala.

The next pathway is from the amygdala to orbitofrontal cortex, which terminates in a complex pattern involving all layers (Ghashghaei et al. 2007). Interestingly, this pathway includes significant projections from the amygdala that target the middle layers of limbic prefrontal cortices, especially the caudal orbitofrontal cortex. This evidence indicates that there is a 'feedforward' projection from polymodal and unimodal sensory association cortices to the amygdala, and a 'feedforward' projection from the amygdala to posterior orbitofrontal cortex.

The above evidence indicates that feedforward projections from temporal sensory association cortices reach the orbitofrontal cortex. In addition, there is a potential indirect route from temporal sensory cortices to posterior orbitofrontal cortex through the amygdala, and both pathways are feedforward. Based on the role of the amygdala in vigilance in emotional situations (Whalen et al. 1998; Davis & Whalen, 2001), it may be assumed that a feedforward projection from the amygdala to orbitofrontal



**Fig. 6** Feedforward projections from the upper layers of anterior temporal polymodal cortices project to the amygdala. (A) Cross-section through the entorhinal and perirhinal cortex showing projection neurons (small arrows) found mostly in the upper layers in the lateral bank of the rhinal sulcus (R) after injection of biotinylated dextran amine (BDA) in the basal nuclei of the amygdala. These projection neurons that are directed to the amygdala are found mostly in layer 3 of polymodal area 36, within the lateral bank of the rhinal sulcus, and in visual association area TE1, situated more laterally in the inferior temporal cortex. The section was counterstained with Nissl. (B) An adjacent unstained section shows the same pattern of projections to the amygdala from the above areas (arrows). Note that projection neurons in the entorhinal cortex (area 28), a limbic area, situated medial to the rhinal sulcus, are found in layer 5. Medial is to the left.

cortex may convey signals about the emotional significance of the environment.

Information about the synaptic organization of these pathways is lacking, but several connectional features at the level of systems are consistent with a co-operative interaction of posterior orbitofrontal, anterior temporal cortices and the amygdala in evaluating emotional significance. One is based on the common topography of projections from sensory association and polymodal cortices directed to both orbitofrontal cortex and to the amygdala (e.g. Herzog & Van Hoesen, 1976; Turner et al. 1980). Both structures receive projections from late-processing visual, auditory and somatosensory cortices, which have a role in the analysis of features of stimuli and their memory. Another common feature is the relationship of connections of orbitofrontal and temporal cortices in the amygdala. This issue is relevant because the amygdala is a comparatively large structure, extending 6–8 mm in the antero-posterior axis, 8–10 mm in the dorso-ventral dimension and at its widest is about 10 mm in the medio-lateral dimension in the rhesus monkey. In this regard, the heaviest projections between posterior orbitofrontal cortices are with the posterior half of the amygdala (Barbas & De Olmos, 1990; Barbas et al. 2002), the same parts linked with anterior temporal visual/polymodal and auditory association cortices

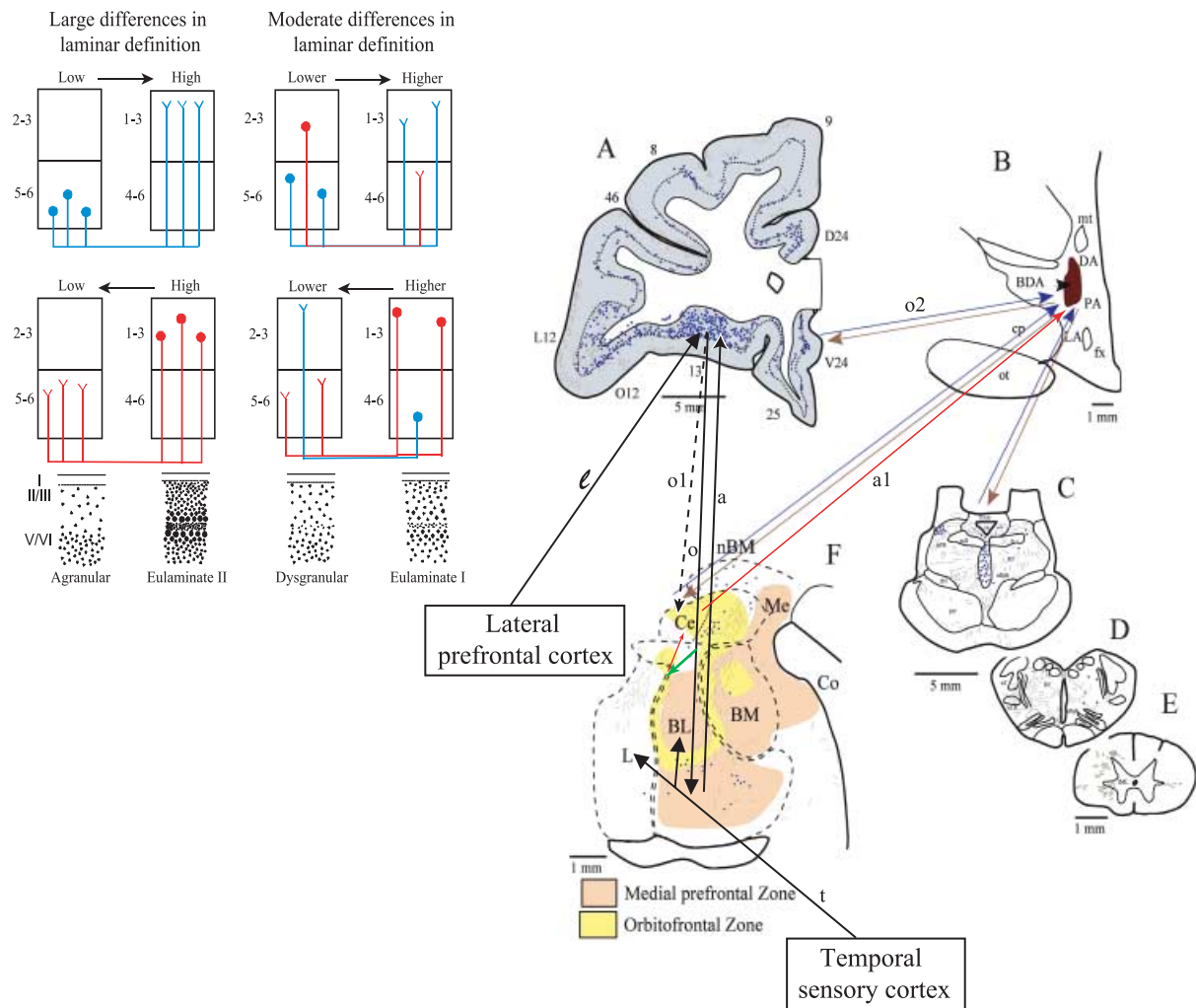
(Ghashghaei & Barbas, 2002). Moreover, connections of the posterior orbitofrontal cortex and anterior temporal sensory cortices overlap extensively in the amygdala (Ghashghaei & Barbas, 2002). This evidence suggests that there may be an interaction between these pathways, even though the extent to which they interact directly at the synaptic level is unknown.

### Specialized linkage of posterior orbitofrontal cortex with the amygdala

As discussed above, the posterior orbitofrontal cortex has multimodal and highly ordered laminar-specific connections with anterior temporal cortices. The caudal orbitofrontal and caudal medial prefrontal cortices have strong and bidirectional connections with the amygdala (e.g. Nauta, 1961; Pandya et al. 1973; Jacobson & Trojanowski, 1975; Aggleton et al. 1980; Porrino et al. 1981; Van Hoesen, 1981; Amaral & Price, 1984; Barbas & De Olmos, 1990; Morecraft et al. 1992; Carmichael & Price, 1995a; Chiba et al. 2001). However, posterior orbitofrontal cortices are distinguished among prefrontal cortices for their specialized connections with the amygdala. The most striking specialization is the partial segregation of input and output connections in the amygdala that link it with posterior orbitofrontal cortex (Ghashghaei & Barbas, 2002). Projection neurons from the amygdala directed to orbitofrontal cortex originate most densely from the basolateral, basomedial (also known as accessory basal) and lateral nuclei, and to a lesser extent in the cortical nuclei of the amygdala (Barbas & De Olmos, 1990; Ghashghaei & Barbas, 2002). The reciprocal projections from caudal orbitofrontal cortex terminate in distinct sectors of several nuclei of the basal complex of the amygdala, and to a lesser extent in the central nucleus, and the cortical nuclei of the amygdala. Importantly, axons from posterior orbitofrontal cortex target most heavily the intercalated masses (IM) of the amygdala (Ghashghaei & Barbas, 2002), which are composed of small neurons found between different nuclei of the amygdala, and are GABAergic (Moga & Gray, 1985; Paré & Smith, 1993, 1994; Pitkanen & Amaral, 1993). The intercalated masses do not project to the cortex, but have significant connections within the amygdala. These findings suggest that the input and output connections in the amygdala that link it with posterior orbitofrontal cortex are at least partly segregated, suggesting a unique relationship among prefrontal cortices.

A significant implication of the projection of orbitofrontal cortex to IM is in the potential influence on the internal processing of the amygdala, because the IM nuclei project and inhibit the central nucleus of the amygdala (Moga & Gray, 1985; Paré & Smith, 1993, 1994). The central nucleus, in turn, issues inhibitory projections to central autonomic structures in the hypothalamus and brainstem. Activation of the orbitofrontal pathway to IM therefore could result





**Fig. 7** Posited sequence of information processing for emotions. Temporal sensory association cortex issues mostly feedforward projections to the amygdala (F, pathway t), and the amygdala issues projections to orbitofrontal cortex (A) terminating in complex laminar patterns (not shown), including substantial feedforward projections to the middle layers (pathway a). The orbitofrontal cortex (A, basal part) has bidirectional and highly specific connections with the amygdala (F), originating robustly from layer 5 and directed to the intercalated masses of the amygdala (pathway o, green branch), and to the basal nuclei of the amygdala (pathway o, black branch). Projections to the intercalated masses influence the internal processing of the amygdala, by inhibiting the central (Ce) nucleus (small red arrow) and thus disinhibiting its output to autonomic structures in the hypothalamus (B), brainstem and the spinal cord (C, D, E). Projections from layer 5 of orbitofrontal cortex are also directed to hypothalamic autonomic centres (B, pathway o2), which is linked with brainstem and spinal autonomic centres (C, D, E). Activation of these pathways would be expected to accompany emotional arousal. Another pathway from orbitofrontal cortex to the central nucleus of the amygdala (o1) would inhibit hypothalamic autonomic centres (long red arrow), leading to autonomic homeostasis. Decision for action in emotional situations may ultimately be directed from lateral prefrontal cortices, which innervate the middle–deep layers of orbitofrontal cortices, including layer 5 (pathway l), according to the rules of the structural model for connections (top, left). Layer 5 of orbitofrontal cortex is the chief output to the amygdala (pathways o, or o1). Black or green arrows show excitatory pathways. Red arrows show inhibitory pathways.

in disinhibition of central autonomic structures, allowing them to be activated, and then activate spinal autonomic structures. The latter innervate peripheral autonomic organs, such as the heart and the lungs, which markedly increase their activity in emotional arousal. Central autonomic structures receive direct innervation from orbitofrontal cortices, but an even stronger innervation from caudal medial prefrontal cortices in the anterior cingulate (Öngür et al. 1998; Rempel-Clower & Barbas, 1998; Barbas et al. 2003), which could thus activate brainstem and

spinal autonomic structures in emotional arousal. The above discussion suggests the presence of a rapid sequential pathway from orbitofrontal cortex to central autonomic structures (Barbas et al. 2003) that may be activated in emotional situations that require vigilance, as summarized in Fig. 7.

There are further specialized connections that link the caudal orbitofrontal cortex with the amygdala. A lighter pathway from caudal orbitofrontal cortex terminates directly onto the central nucleus of the amygdala (Carmichael &

Price, 1995a; Ghashghaei & Barbas, 2002), as shown in Fig. 7. When this pathway is activated, an opposite effect would be expected, now resulting in inhibition of central autonomic structures. Activation of this pathway would thus suppress hypothalamic autonomic activity and prevent its excitatory influence on spinal autonomic centers. This pathway may be recruited when the emotional significance of the environment changes, such as when a perceived danger in the environment subsides.

## Who decides on action?

### Interaction among functionally distinct prefrontal areas, temporal areas and the amygdala

The above discussion shows that the posterior orbitofrontal cortex has specialized connections with the amygdala that may be active in distinct states of emotional arousal. Physiological studies have shown that neurons in orbitofrontal cortex in non-human primates respond to the value of a stimulus, but do not appear to be part of a decision for a response (Wallis & Miller 2003; Padoa-Schioppa & Assad 2006; reviewed in Miller & Cohen 2001). The question then arises: which part of the cortex has a role in deciding action? Take, for example, a loud noise heard by someone walking through the woods, bringing to mind the alarming thought of a large and potentially dangerous wild animal in the vicinity, perhaps a bear. The heart rate and breathing rate of the frightened person quickly accelerate. But suppose that the walker then sees the object, a fawn, and calms down, as the situation is no longer perceived as dangerous. Figure 7 summarizes the pathways that may be recruited in the above situation.

The noise heard in the forest probably activates the auditory pathways to the amygdala (F, pathway t), and the projections from the amygdala to orbitofrontal cortex convey the emotional significance of the event (pathway a). A massive projection from orbitofrontal cortex (A) to the intercalated masses of the amygdala (pathway o, green branch) results in disinhibition of the hypothalamus, allowing activation of hypothalamic autonomic centres (B) and its downstream pathways to brainstem and spinal autonomic centres (C, D, E) that innervate the heart and other peripheral organs. The entire sequence of events would result in the sounding of a general internal alarm manifested as peripheral autonomic function.

The laminar patterns of connections are consistent with the sequential transmission of information in the above serial pathways. Feedforward projections from temporal sensory association cortices project to both orbitofrontal cortex (not shown) and to the amygdala (t), which then issues robust feedforward projections to orbitofrontal cortex (a), terminating in the middle layers, including layer 5. In turn, projections originating predominantly from layer 5 of orbitofrontal cortex terminate heavily in the

intercalated masses of the amygdala (o, green branch). In addition, projections from layer 5 of orbitofrontal cortex, as well as anterior cingulate cortices (A), project to hypothalamic autonomic centres (pathway o2). Activation of this series of pathways would result in autonomic activation, as seen in emotional arousal.

The second event is seeing the fawn, which quickly calms the walker. Information from temporal areas (t) to the amygdala, here too, may convey the sensory aspects of the environment. The pathway from the amygdala to orbitofrontal cortex (a) could provide information about emotional context. We have seen that there is also a distinct pathway from orbitofrontal cortex to the central nucleus of the amygdala (o1, dotted line), which would lead to inhibition of hypothalamic autonomic centres (Ce to hypothalamus, red arrow), resulting in return to autonomic homeostasis.

But one problem remains unresolved in the above scenario. The orbitofrontal cortex does not appear to be part of the action plan, so what other pathway may be recruited? Lateral prefrontal cortices have been implicated in executive functions (reviewed in Miller & Cohen 2001), and may have a role in decision for action. Several features of prefrontal pathways are consistent with the idea of their collaborative action. First, lateral prefrontal areas receive detailed information from rather early-processing visual and auditory association cortices, suggesting that the information may have the resolution necessary to discriminate the fine features of the environment (see Barbas et al. 2002), to appreciate, for example, the image of a fawn. By contrast, the orbitofrontal cortex receives an overview of the visual and auditory environments through late-processing visual and auditory association cortices (e.g. Barbas, 1993; Barbas et al. 2002; Bar, 2003; Bar et al. 2006). Second, sequential and bidirectional pathways link orbitofrontal cortex with lateral prefrontal cortices. Importantly, the laminar patterns of connections in these pathways are also consistent with a rapid influence of sequential pathways. According to the rules of the structural model for connections (Barbas & Rempel-Clower, 1997), when lateral prefrontal cortices project to orbitofrontal cortices they target predominantly the middle–deep layers in a feedforward manner (pathway l), including the upper part of layer 5, which is the chief output layer to the amygdala (pathway o, or o1). Information between these structures may be used in decision and action in behaviour. Importantly, caudal lateral prefrontal cortices have connections with premotor cortices, suggesting that a decision can be translated into action (reviewed in Barbas, 2000).

The above implies that signals from lateral prefrontal cortices to orbitofrontal cortex would have to be specific, signalling activation of either the orbitofrontal pathway to the intercalated masses in sounding a general alarm (pathway o), or a pathway from orbitofrontal cortex to the

central nucleus of the amygdala for return to autonomic homeostasis (pathway o1, dotted line). The mechanism for selection of each pathway is unknown.

The above posited flow of information for emotions is feasible based on the consistent laminar patterns of connections. But this scheme is only by analogy with processing in the sensory systems, and its confirmation will depend on a convergence of approaches sensitive to the timing of activation of pathways and their laminar distribution in animals and humans. For now it provides a framework to address the issue of sequential activation of pathways, and to investigate how disruption of distinct aspects of these circuits may lead to specific symptomologies. Neuropathology characterized by anxiety, for example, may reflect over-activation of orbitofrontal pathways to the amygdala, leading to overdrive of peripheral autonomic structures.

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