# Dual and opposite effects exerted by orbitofrontal cortices on the amygdala and the emotional motor system

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## Abstract

Orbitofrontal and medial prefrontal cortices in primates have a role in emotions. Here we report that orbitofrontal axons target specific zones in the amygdala, including the intercalated masses. We propose a model whereby orbitofrontal pathways can either drive or dampen the activity of central autonomic structures. These effects are mediated by intercalated neurons, which directly innervate and inhibit autonomic structures, or indirectly disinhibit them through the central amygdaloid nucleus. Medial prefrontal projections are widespread in amygdaloid nuclei that likely drive excitatory projections to autonomic structures. Circuits with opposing influences are likely recruited either to activate autonomic centers for the expression of emotions, or to inhibit them for return to homeostasis, depending on the behavioral situation.

## 1. Introduction

The orbitofrontal cortex in primates has a role in emotions by processing signals about the emotional significance of stimuli through its connections with the amygdala (for review see [2]). The orbitofrontal cortices and the amygdala appear to have a global overview of the environment as recipients of massive input from sensory association cortices (for reviews see [1,5,8]), which seems necessary for processing and remembering the emotional significance of stimuli.

The amygdala, orbitofrontal cortex, and medial prefrontal cortices also have key roles in the expression of emotions by innervating hypothalamic and brainstem autonomic structures (for review see [8]). Disruption of these pathways by damage to the orbitofrontal cortex seriously affects emotional expression, normal social interactions, and the ability to exhibit autonomic responses in emotional situations ([6]; for review see [13]). Thus, even though cognitive function remains intact, decision making is seriously affected, suggesting functional disconnection of cognitive processes from emotionally driven autonomic responses [4]. Here we addressed the extent to which components of prefrontal pathways interact with the output of the amygdala to hypothalamic autonomic centers for the expression of emotions.

## 2. Methods

Experiments were conducted on 13 adult rhesus monkeys. Pathways were studied with the aid of bidirectional tracers injected in the prefrontal cortices, which allowed us to map axonal terminals in the amygdala and projection neurons from the amygdala directed to prefrontal cortices. We used standard immunocytochemical techniques to visualize calbindin (CB) or parvalbumin (PV), which label distinct classes of inhibitory interneurons in order to study their relationship to axonal terminals in the amygdala. We used a computerized system and a motorized stage to quantitatively map labeled axons and neurons in the amygdala, and measured the regional density of anterograde

label in the amygdala using an image analysis system.

## 3. Results

*Orbitofrontal termination zones*

Axons from caudal orbitofrontal areas assumed a u-shaped pattern in the amygdala, in and around the borders of the magnocellular part of the basolateral nucleus (BLmc), terminating heavily in the intercalated masses (IM; Fig. 1A), composed of densely packed small cells between the BLmc and the central nuclei. The neurons in the IM are thought to be inhibitory [17] and we found that they were positive for calbindin (CB), but not parvalbumin (PV), which are calcium binding proteins that label inhibitory interneurons in the amygdala [10]. In another set of experiments we noted that numerous CB-positive neurons in the IM projected directly to hypothalamic autonomic centers. In addition, there were light projections from orbitofrontal cortices to the central nucleus of the amygdala.

*Medial prefrontal termination zones*

Another sector of the prefrontal cortex, the caudal medial prefrontal cortices, are also connected with the amygdala. Our results indicated that axons from caudal medial prefrontal areas terminated heavily in the amygdala, but unlike the orbitofrontal, axonal terminations extended into the parvicellular sector of the BL (BLpc), medial (Me), and cortical (Co) nuclei, but not in the IM (Fig. 1B). Axons from medial prefrontal areas terminated in nuclei of the amygdala that we had earlier found to project to, and likely increase the activity of, hypothalamic autonomic centers.

## 4. Discussion

We provided evidence for a strong and specific input from orbitofrontal cortices to the amygdala, including the intercalated masses, where neurons are largely GABAergic, and project to the central and medial nuclei of the amygdala [18]. The central and medial nuclei, in turn, issue inhibitory projections to autonomic structures in the hypothalamus and brainstem (e.g., [12,20] and personal observations). In addition, the intercalated masses provide direct inhibitory projections to hypothalamic (personal observations) and brainstem [16] autonomic centers.

The circuitry is summarized in figure 2, and implies a dual role for the specific and strong projections from orbitofrontal cortices to the intercalated masses. First, orbitofrontal axons can indirectly suppress the inhibitory output of the central and medial nuclei of the amygdala to autonomic centers, suggesting a permissive effect on the hypothalamus [Fig. 2, pathways (a)]. The activity of the hypothalamus could be further augmented by direct excitatory projections from the same orbitofrontal cortices to the hypothalamus [19]. We propose that the pathways shown in (a) may be recruited when the environment signals an emotionally charged circumstance. Second, direct orbitofrontal projections to the central nucleus would effectively inhibit hypothalamic and brainstem autonomic centers [Fig. 2; pathways (b)]. In addition, projections from orbitofrontal cortices to intercalated neurons that directly innervate autonomic centers of the hypothalamus and brainstem, would also inhibit the activity in these structures [Fig. 2; pathways (b′)]. Both of these pathways (b and b′) likely mediate fast suppression of autonomic responses. These pathways are likely recruited for a return to autonomic homeostasis when the environment no longer signals for emotional vigilance.

Our proposed dual control by the orbitofrontal cortex on autonomic responses is consistent with the functional role of orbitofrontal cortices in cognitive processes and decision making in complex emotional situations, including response selection and reward associations (e.g., [3,7,11,15]). Hence, orbitofrontal projections to the amygdala can either increase or decrease autonomic responses depending on the demands of the situation. The mechanisms for recruitment and function of the dual inhibitory projection systems in the intercalated masses remain to be investigated.

In contrast to the orbitofrontal terminations in the amygdala, medial prefrontal terminations in the amygdala appear to recruit, and presumably excite, hypothalamic and brainstem autonomic centers for the expression of emotions. These effects are mediated by strong projections from medial prefrontal cortices to a separate system in the amygdala with excitatory projections to hypothalamic autonomic centers, as suggested by our data (Fig. 2). This projection system involves the parvicellular sector of the basolateral nucleus, and the cortical nuclei of the amygdala which provide strong projections to autonomic centers, and do not appear to be GABAergic. Thus, medial prefrontal projections to the amygdala may amplify the output of the amygdala to the hypothalamus, a pathway that may be recruited in concert with a robust direct projection from medial prefrontal cortices to hypothalamic autonomic centers [9,19]. The recruitment of autonomic structures by medial prefrontal cortices is consistent with their role in vigilance and monitoring conflict before the selection of a behavioral response (e.g., [14]).

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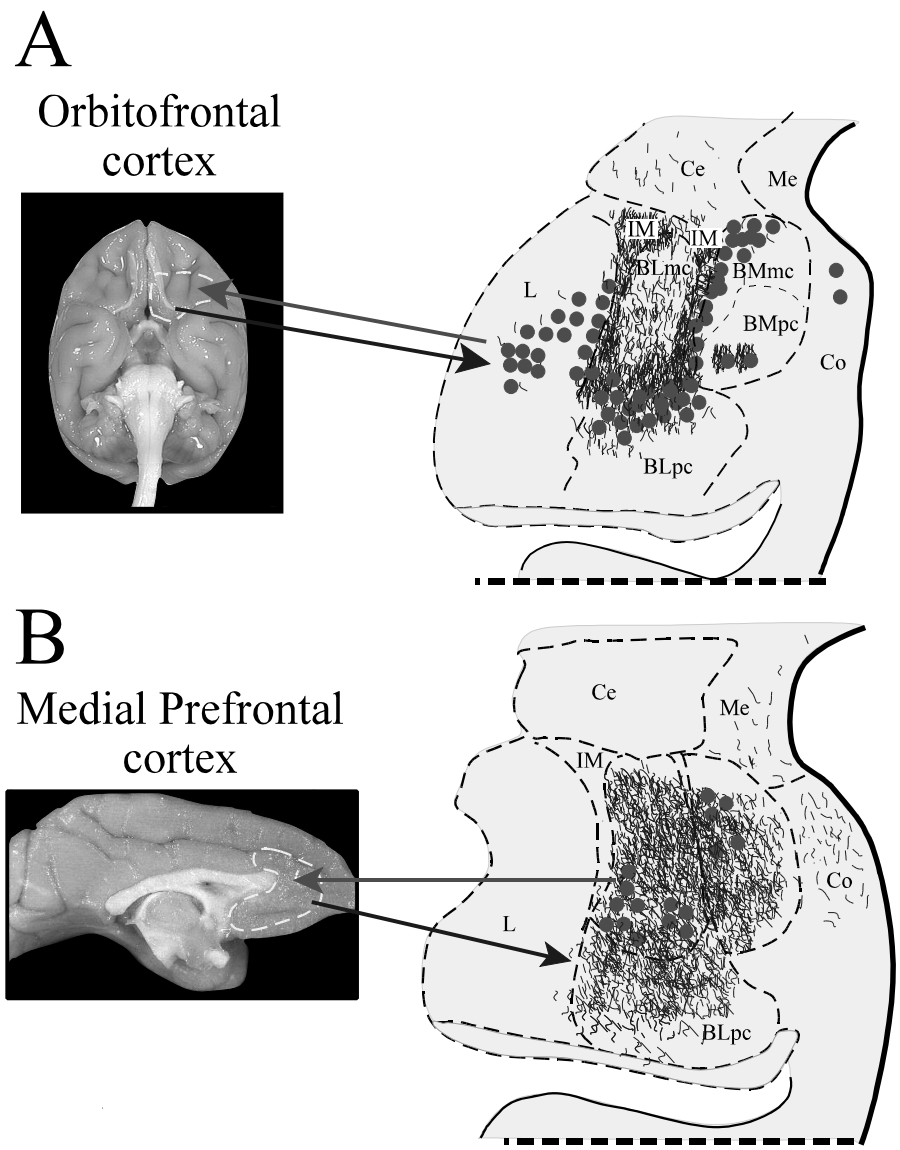


Fig. 1. Zones in the amygdala connected with orbitofrontal (A) and medial prefrontal (B) cortices. The position of caudal medial and orbitofrontal cortices is marked by dashed lines in ventral (A) and medial (B) views of the cerebral hemisphere. On the right, projection neurons (circles) and axonal terminals (fibers) are depicted in coronal sections of the amygdala. Amygdaloid nuclei: IM, intercalated masses; Ce, central nucleus; Me, medial nucleus; Co, cortical nucleus; BLmc, magnocellular basolateral nucleus; BLpc, parvicellular basolateral nucleus.

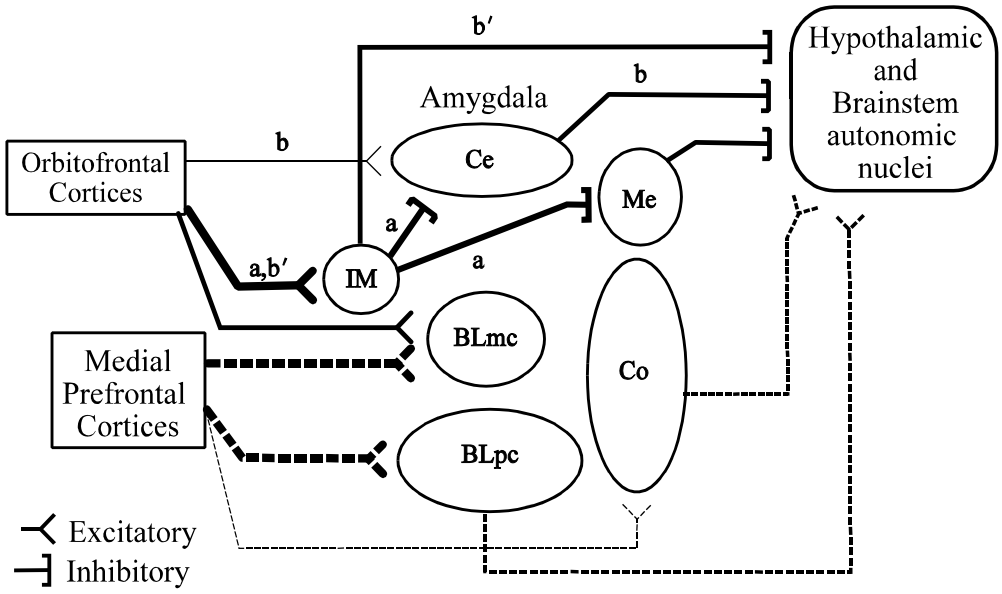


Fig. 2. Summary of differential inputs from orbitofrontal and medial prefrontal cortices to the amygdala in the primate and model of their effect on the output of the amygdala. Pathways from orbitofrontal cortices can influence the amygdala (uninterrupted lines) in opposite ways. Activation of pathways (a) leads to disinhibition of hypothalamic and brainstem autonomic centers. In contrast, recruitment of pathways (b) and (b′) inhibits hypothalamic and brainstem autonomic centers. Pathways recruited by medial prefrontal cortices (dashed lines) are thought to be excitatory to hypothalamic and brainstem autonomic centers. Thickness of the lines represents the density of the projections and strength of pathways. Amygdaloid nuclei: IM, intercalated masses; Ce, central nucleus; Me, medial nucleus; Co, cortical nucleus; BLmc, magnocellular basolateral nucleus; BLpc, parvicellular basolateral nucleus.