Modulation of normal orbitofrontal function by serotonergic manipulation and by clinical depression: evidence from functional imaging

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The orbitofrontal cortex (OFC) is a functionally heterogeneous structure known to be involved in various aspects of higher cognition. Recent evidence from human neuropsychology and functional neuroimaging has implicated the region in aspects of motivational and emotional processing, that underpin social interactions and decision-making. Additionally, studies with clinical populations have suggested that orbitofrontal dysunction may be involved in the psychopathology of several disorders, including clinical depression.

In a recent series of studies using functional magnetic resonance imaging (fMRI), we have investigated the role of the OFC in mediating responses to financially and socially reinforcing stimuli and demonstrated that in normal volunteers, the OFC responds to both social and financial reinforcement.

Using similar paradigms, we have also demonstrated significant modulation of OFC function in response to acute administration of serotonergic drugs. Data will be presented from studies of citalopram, mCPP and mirtazepine, showing that all three serotonergic agents significantly modulate OFC response to motivational and emotional challenge tasks.

Finally, we have demonstrated that patients with unipolar depression show abnormal OFC responses to motivational tasks relative to normal controls, with different stages of the disorder associated with hypo- or hyperfunction of the OFC.

These findings indicate that abnormal function of the OFC plays a role in the pathophysiology of depression. Acute administration of serotonergic drugs, including drugs with clinical use as antidepressants, also modulates OFC response to cognitive challenges. Taken together, this pattern of results suggests that serotonin is an important mediator of the emotional and motivational functions that are normally subserved by the OFC. This has significant implications for our understanding of serotonergic mechanisms of psychiatric disorders, particularly depression.

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