



Modulating amygdala responses to emotion: Evidence from pharmacological fMRI

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ABSTRACT

The use of functional MRI (fMRI) in combination with pharmacological challenges has increased exponentially in recent years, motivated by the idea not only to elucidate the neurochemical foundations of human emotional and cognitive faculties, but also to optimize human brain function in healthy individuals and identify novel drug targets, with the ultimate goal to design more specific pharmacological therapies for the various disorders of human emotion and cognition. In particular, emotional responding of the amygdala has become a central interest, and pharmacological fMRI has been used to specifically probe, and modulate, amygdala activation in response to facial expressions of emotion and emotionally laden scenes. This article reviews recent fMRI experiments manipulating the amygdala's physiological response to such stimuli by pharmacological means and lays a particular focus on monoaminergic, glutamatergic, GABAergic, and hormonal/peptidergic challenges.

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1. Introduction

1.1. The amygdala: structure and connectivity

The amygdala, or 'almond' as its Latin etymology depicts, has become one of the focal centers in research surrounding emotional processing. What was once thought of as a solid, almond shaped mass within the limbic system continues to expose itself as a conglomerate of nuclei and subnuclei, collectively referred to as the amygdaloid complex and distinguished on the basis of cytoarchitectonics, chemoarchitectonics, and fiber connections (Brockhaus, 1938, 1940). The amygdala's subregions have been described using different parcellation schemes (LeDoux, 2007). One of the most widely accepted classification schemes distinguishes the superficial (cortical) subregion from the centromedial subregion and the laterobasal complex (basolateral amygdala, BLA) (Amunts et al., 2005; Heimer et al., 1999).

The flow of information within the amygdala is modulated by a large variety of neurotransmitter systems. Receptors for these neurotransmitters are differentially distributed across amygdala subregions. Also differentially distributed are receptors for various steroid hormones, including glucocorticoid and estrogen

hormones. Numerous peptide receptors are also present in the amygdala, including receptors for opioid peptides, oxytocin, vasopressin, corticotropin releasing factor and neuropeptide Y, to name a few. An important challenge is to understand how these neurochemical systems act together to set the overall tone of the amygdala and thereby modulate activity in interconnected brain regions (LeDoux, 2007).

In a comprehensive quantitative analysis including amygdala connectivity, it was found that the amygdala is richly interconnected with almost all cortical areas analyzed (Young, Scannell, Burns, & Blakemore, 1994), suggesting that, in addition to its well-established role in fear conditioning (LeDoux, 2007), it is fully capable of integrating and modulating multiple emotional processes (Pessoa, 2008; see also Barbas, 1995; Swanson, 2003). In fact, the numerous reciprocal connections of the amygdala form an intricate network supporting a large variety of emotional behaviors related to fear, reward, and motivation. The amygdala has also been implicated in emotional states associated with aggressive, maternal, sexual, and ingestive behaviors (LeDoux, 2007). In addition, the amygdala is involved in the emotional modulation of cognitive functions, such as perception, attention, declarative (explicit) learning and memory, and decision making (Aggleton, 2000; Seymour & Dolan, 2008; LeDoux, 2007; Phelps, 2004; Swanson & Petrovich, 1998). The amygdala's contribution to the detection of emotional events and the production of appropriate responses to these events, is the most extensively investigated and best understood function of this brain region. Recently developed

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cytoarchitectonic probability maps based on histological analysis of post-mortem human brains (Amunts et al., 2005) have even made it possible to shed light on the in vivo intra-amygdalar functional organization with functional magnetic resonance imaging (fMRI) and hypothesize about the particular role of human amygdala subdivisions in specific behaviors. Animal models focusing on a crucial role of the BLA subregion in responding to social–emotional stimuli have been expanded via these maps to include other amygdala regions in humans as well, such as the superficial amygdala (Goossens et al., 2009).

1.2. Imaging drug effects on amygdala activation

fMRI studies examining amygdala function in the face of emotional stimuli have evolved from clinical studies focusing on brain lesion, substance abuse, and affective disorder patients, to in more recent years using single or combined pharmacological challenges to exploit amygdala reactions in healthy individuals. There are several advantages to studying healthy subjects with pharmacological fMRI (phMRI). Honey and Bullmore (2004) mention for example the ability to discern the pharmacodynamics of the drug, as well as the ability to identify the neurochemical players involved in emotional and cognitive functions during various tasks; selective drug action can help to isolate the contribution of specific neuroreceptors (Honey & Bullmore, 2004). Studies listed in this review focus on single-drug challenges as well as combination drug challenges that target the interaction of multiple neurochemical pathways.

Another benefit to using phMRI in healthy individuals is the ability to identify potential biomarkers of behavioral changes, useful in applying to mental disorders, by inducing such changes with one drug or a combination of drugs. The utility of biomarkers stems from their potential to provide reliable and precise data regarding the probability and course of a disease. Following genetic and environmental factors, biological events often precede clinical pathologies (see for example Bonassi & Au, 2002), and are furthermore better predictors of disease than self-reports (Goldman, 2007), resulting in a more objective and reliable diagnosis and thus earlier treatment. In proof of concept studies, specifically in the preclinical and phase I development stages, biomarkers can help to identify the most ideal candidate pool in terms of toxicity and drug interactions (see for example Kuhlmann and Wensing, 2006). Research shows that by making use of biomarkers identified by pharmacological models in healthy volunteers, treatment development can be greatly enhanced in the first stages (Gilles & Luthringer, 2007). In a review of imaging in drug development, Wong, Tauscher, and Gruender (2009) noted that phMRI can be viable in studies on dose response and development of treatment. This field is dominated by positron emission tomography (PET) because of the necessity in most cases to determine dose-dependent receptor occupancy and thus mechanism of action. However, phMRI poses a viable option of measuring response to drugs for which the mechanism of action is known or possibly not dependent on receptor occupancy or enzyme activity (see Wong et al., 2009). Moreover, some drug responses are driven by a second or third messenger effect which cannot be easily measured with traditional PET (see Wong et al., 2009). The advantage of phMRI in this field lies in its ability to fill the void left by PET, when considering target engagement or receptor occupancy, in that it can measure intrinsic activity at the target. For instance, fMRI has led to the identification of brain regions associated with given symptoms on the basis of invoking activation or deactivation (Wong et al., 2009). In this vein, phMRI can allow researchers to isolate functional and behavioral changes with less risk of measuring artifacts or confounding factors caused by a relatively subjective clinical picture in patients, who often show symptoms of more than one illness (comorbidity), through the selective hypo- and hyper-sensitization of the amygdala in

healthy volunteers. PhMRI can in this case act as a pre-biomarker when the proof of concept of the target is unknown or uncertain (Wong et al., 2009).

1.3. Experimental paradigms

There are two basic approaches to eliciting amygdala responses used in the phMRI studies discussed below. One method is to ask participants to view, rate, or identify a set of emotional scenes, such as those from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1995) or facial expressions of emotion from various databases. The first paper here, by Hariri et al. (2002), used an alternative approach which engaged participants in a faces matching task. In this task, participants are instructed to match the angry or fearful face on top to one of two faces below displaying the same emotion. Importantly, this task engages amygdala–prefrontal cortex circuitry, which has led authors to explore amygdala connectivity under different pharmacological conditions, as presented in the following review. Since this original task, authors have created several variations of this paradigm, including matching the sex of the face or varying the emotions. For each study below, the specific type of phMRI paradigm is named. Another approach to measuring amygdala response to different emotions is to mask faces shortly after presentation. In this type of paradigm, faces showing a specific emotion are presented for a fraction of a second (e.g., 30 ms) and subsequently replaced by a neutral facial expression. This can have the effect that participants report only seeing a neutral face, but that the amygdala is despite this differentially activated according to the previous emotion. The concept of examining emotional processing of faces and scenes in healthy individuals has critical implications for patient studies, especially in affective disorders such as major depression, of which approximately 17% of US Americans suffer during their lifetimes (Kessler et al., 2003; see also Andrade et al., 2003). Already, research has shown a cognitive bias in depressed patients towards negative and away from positive facial emotions (see Leppanen, 2006). Contrasting such reactivity patterns between healthy individuals and patients, and furthermore pharmacologically reproducing such biases in healthy individuals can lead to more effective and honed treatments both in terms of pharmacological intervention as well as cognitive behavioral therapy (CBT).

1.4. Aims and structure of the review

This review is a summary of >30 published journal articles published up until May 2010, containing the criteria pharmacological modulation of emotional processing of faces and scenes in the amygdala. Search methods included an extensive search of PubMed with search criteria including 'amygdala', 'drug', 'emotion', 'fMRI', 'healthy', and 'human'. Included are only pharmacological challenge studies on healthy individuals. Studies reviewed are divided according to the following pharmacological challenges: serotonergic, dopaminergic, noradrenergic, glutamatergic, hormonal/peptidergic, and GABAergic.

2. Overview

2.1. Serotonergic system

Serotonergic neurotransmission can be influenced by serotonin (5-HT) reuptake inhibitors (SSRIs), which act by blocking 5-HT reuptake via the presynaptic 5-HT transporter (5-HTT or SERT). This increases the intrasynaptic concentration of 5-HT and the interaction with pre- and postsynaptic 5-HT receptors. Clinically, this mechanism of action is extremely relevant to treat major depressive disorder and anxiety disorders, including

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