Acute blockade of 5HT2a receptors reduces orbitofrontal cortex response to angry and fearful faces

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Introduction

The serotonergic transmitter system is involved in modulation of emotions, temperament and individual differences in the risk for developing mood disorders, such as major depression. In a recent PET study, we identified a positive association between frontolimbic serotonin 2A (5-HT_{2A}) receptor binding and specific personality traits, known to be risk factors for development of affective disorders[2]. As a follow-up to that study, we performed pharmacological fMRI in healthy adults to assess the role of 5-HT_{2A} receptors in frontolimbic circuits in emotional processing of faces with negative valence. We used an emotional faces paradigm with and without pharmacological blockade of 5-HT_{2A} receptors by administration of ketanserin. We tested the hypothesis that 5-HT_{2A} receptor blockade leads to an impairment of emotional processing in the orbitofrontal cortex (OFC)[1], since this region has a high 5-HT_{2A} receptor density and is known to be involved in the evaluation of socially relevant stimuli.

Methods

Seventeen subjects (9 males, 8 females), aged 22-40 (32.46 ±2.82,), performed a emotional faces paradigm (Fig. 1) during two fMRI sessions at 3T, at least one week apart. In one session, 5-HT_{2A} receptors were blocked with ketanserin. No drug was given in the other session (control session). The order of sessions was counterbalanced across subjects. Ketanserin was applied intravenously (10 mg bolus followed by 6 mg/h for approx. 75 min; ~ 17.5 mg in total). The paradigm required subjects to discriminate the gender of faces. Faces were shown in blocks consisting of male and female faces with neutral, angry or fearful facial expressions, each intermixed pseudorandomly with null events (1/3 of the total number of images) (Fig. 1). Statistical analyses were performed in SPM5 using a repeated measures ANOVA design including adversive vs. neutral contrasts from the control and ketanserin sessions ($p<0.05$, FWE corrected at cluster level).

Results and conclusion

There were no differences in task performance between the control and the ketanserin session. The amygdalae were consistently activated when viewing fearful or angry faces compared to neutral faces in both sessions. The neuronal response in the amygdalae was unaffected by 5-HT_{2A} receptor blockade. In contrast, 5-HT_{2A} receptor blockade resulted in a bilateral reduction of the neuronal response to angry and fearful faces in medial OFC (Fig.2). This finding is in accordance with previous PET findings showing a high 5-HT_{2A} receptor density in this area. It also demonstrates the involvement of orbitofrontal 5HT_{2A} receptor mediated neurotransmission in emotional processing. In conclusion, our results point to a crucial role of serotonergic neurotransmission in the orbitofrontal regions in emotional processing of human faces with negative valence[3].

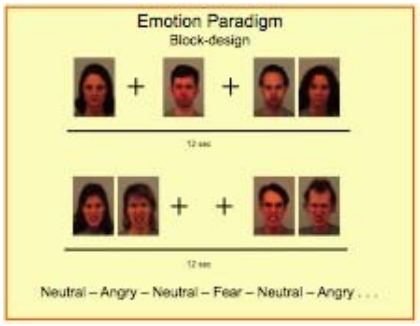

Fig. 1. Task: Gender discrimination of emotional faces. Emotions were blocked, but faces were presented as events pseudorandomly intermixed with null events.

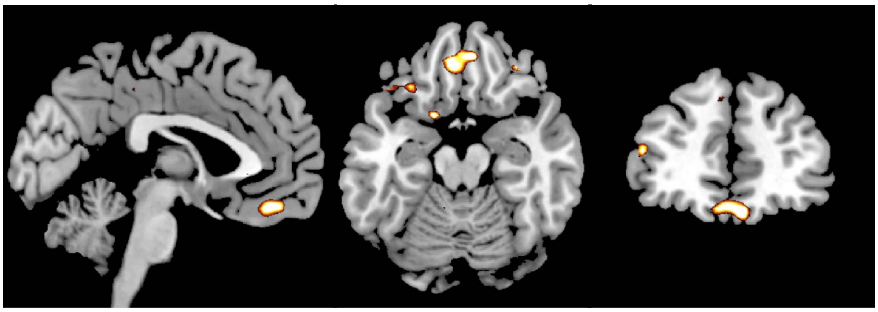

Fig. 2. Bilateral OFC activation in response to emotional faces was reduced after blocking 5-HT_{2A} receptors with Ketanserin ($p<0.001$, uncorrected).

Reference List

1. Blair et al. Brain 1999;122, 883-893
2. Frokjaer et al. .Biol Psychiat 2008;63:569 –576.
3. L. Passamonti et al. NeuroImage 2008; 43, 562–570