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

B. Hornboll1,2, J. S. Wegener1,2, O. B. Paulson1,2, J. B. Rowe3,4, G. M. Knudsen1,2, H. Siebner1,2, and J. Macoveanu1,2

1Danish Research Center for MR, Copenhagen University Hospital, Hvidovre, Hvidovre, Denmark, 2Center for Integrated Molecular Brain Imaging, Copenhagen, Denmark, 3Department of Clinical Neurosciences, Cambridge University, Cambridge, United Kingdom, 4Neurobiology Research Unit, Copenhagen University Hospital, Copenhagen, Denmark

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-HT2A) receptor binding and specific personality traits, known to be risk factors for development of affective disorders2. As a follow-up to that study, we performed pharmacological fMRI in healthy adults to assess the role of 5-HT2A 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-HT2A receptors by administration of ketanserin. We tested the hypothesis that 5-HT2A receptor blockade leads to an impairment of emotional processing in the orbitofrontal cortex (OFC)1, since this region has a high 5-HT2A 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-HT2A 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-HT2A receptor blockade. In contrast, 5-HT2A 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-HT2A receptor density in this area. It also demonstrates the involvement of orbitofrontal 5HT2A 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.

Reference List