Amygdala Activity in Major Depression: Modulation by Serotonergic Genes

H. Kugel[1], U. Dannlowski[2], P. Ohrmann[2], J. Bauer[2], B. T. Baune[2], C. Hohoff[2], A. Kersting[2], V. Arolt[2], W. Heindel[1], J. Deckert[2], T. Suslow[2]
[1]Dept. of Clinical Radiology, University of Muenster, Muenster, NRW, Germany, [2]Dept. of Psychiatry, University of Muenster, Muenster, NRW, Germany

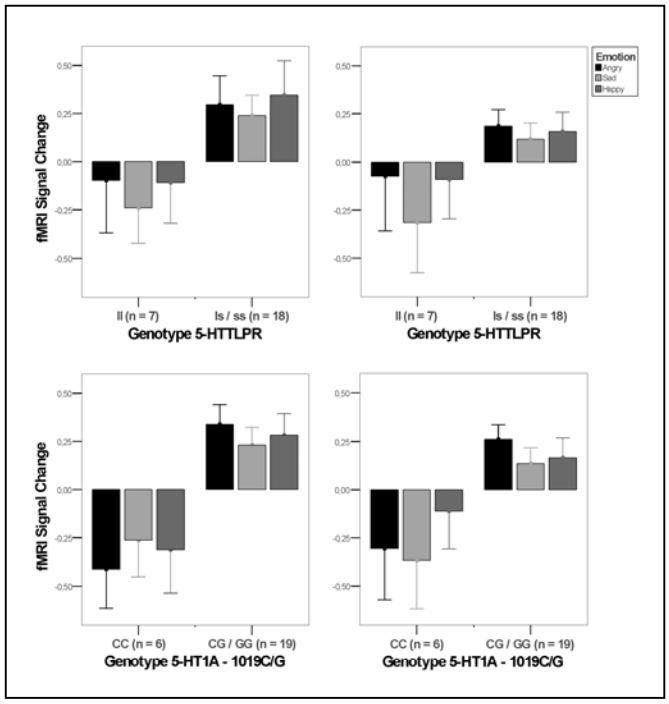
Introduction

Polymorphisms of genes involved in serotonergic neurotransmission, e.g., the serotonin transporter gene (5-HTT) and the serotonin receptor 1A (5-HT_{1A}) gene, have been implicated in the pathogenesis of depression. From studies in healthy controls it was suggested that the gene's effect might be mediated via dysfunctional amygdala activity, a brain structure critical for emotion processing. The present study sought to confirm this idea by for the first time studying amygdala activity dependent on functional polymorphisms in the 5-HTT and the 5-HT_{1A} genes in patients with depression.

Materials and Methods

In 25 patients with major depression (18 w; mean age 36.2, range 20-59; diagnosed with SCID-I interview) amygdala activity was measured in response to visual presentation of happy, sad, and angry facial stimuli (1) by means of fMRI at a 3 T scanner (Gyroscan Intera 3.0T, Philips Medical Systems, Best, NL). Patients were presented with alternating 30 sec blocks of a face category or a no-face stimulus (a grey rectangle). In a passive viewing task facial stimuli were presented twice per second in a random sequence for 500 ms. Each emotion block was preceded by a no-face block and was presented twice, resulting in a total presentation time of 8 min. Functional data were acquired with a multi slice single shot EPI sequence (TR 3 s, TE 30 ms, FA 90°). 25 slices with high resolution (Matrix 128, voxel 1.75 x 1.75 x 3.5 mm) were acquired 160 times (10 times per condition block), in addition to an anatomic dataset (T1w 3DTFE, cubic voxel, .5 mm edge length). Functional imaging data were motion corrected, spatially normalized to standard MNI space, and smoothed using SPM2. The general linear model was used to contrast emotional faces (angry, sad, and happy) with the neutral face condition. Voxel values (2) of bilateral amygdala were extracted, summarized by mean and tested among the different conditions using the MarsBaR toolbox (3).

Patients were genotyped for the functional 5-HT_{1A}-1019C/G and 5-HTTLPR polymorphisms. For each polymorphism, amygdala activity in carriers of one or two risk alleles for either gene was compared with activity in non-risk allele carriers.



Results

The amygdala and surrounding tissue was imaged with only low distortion, allowing a reliable evaluation of BOLD contrast.

Independent of emotion type, risk allele carriers showed higher amygdala activity for the 5-HT_{1A}-1019C/G polymorphism, $F(1,21) = 12.6$, $p = 0.002$, and the 5-HTTLPR - polymorphism, $F(1,21) = 4.8$, $p = 0.041$. No interaction of the genes was observed.

Risk allele carriers for either polymorphism had increased amygdala activity elicited by emotional faces regardless of valence, compared to non-risk allele carriers, 5-HT_{1A}-1019C/G (estimated marginal means ± s.d.): 0.21 ± 0.36 vs. -0.30 ± 0.29; 5-HTTLPR: 0.11 ± 0.39 vs. -0.21 ± 0.30 (see Fig. 1, separately for emotions and laterality).

Discussion

The data suggest that in patients with major depression, amygdala excitability in response to emotionally relevant stimuli is influenced by the 5HT_{1A}-1019C/G and the 5-HTTLPR polymorphism. The findings support the idea that the role of the amygdala in depression is linked to specific genetic risk factors. In risk allele carriers, stronger amygdala activity during emotion processing may reflect a tendency for negatively biased perception of emotionally relevant stimuli and thereby contribute to the onset and maintenance of depression.

Fig 1: fMRI signal change (contrast value) of risk and non-risk alleles, for 5-HTTLPR (top) and 5-HT_{1A}–1019C/G (bottom) genotypes, and for left and right amygdalae (left and right side, resp.). Emotions from left to right: angry, sad, happy.

References

(1) Ekman P, Friesen WV: Consulting Psychologists Press, Palo Alto, CA, 1976; (2) Tzourio-Mazoyer N, et al. Neuroimage 15, 273-289 (2002); (3) Brett M et al., Neuroimage 16, 497 (Abstr.) (2002)