

Trait Anxiety and Serotonin Transporter Polymorphism Influence Amygdala Activation as Measured with fMRI during Fear Extinction at 3 T

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Introduction: Anxiety disorders are characterized by an increased fear conditioning and impaired extinction of fear reactions (1). Neuronal hyperactivity of the amygdala and insufficient frontal control are considered as neuronal correlates of this vulnerability (2). Fear related personality traits and genetic factors can increase the risk to develop an anxiety disorder (3, 4). In this fMRI study we investigated the influence of the serotonin transporter polymorphism 5-HTTLPR (panic disorder patients carrying the s-allele suffer from more severe symptoms) and trait anxiety on the activation of the amygdala during fear conditioning and fear extinction.

Methods: A classical fear conditioning paradigm was presented to 32 healthy volunteers (20 f, mean age 23.6 years) during examination with functional magnetic resonance imaging (fMRI) in a 3 T scanner (Gyrosan Intera 3.0T, Philips, Best, NL). Pictures of two faces with neutral expression (NimStim (5)) served as conditioned stimuli (CS+, CS-). The experiment consisted of 4 phases: familiarization, acquisition 1, acquisition 2, and extinction. In the acquisition phases 25 % of the CS+ were paired with an acoustic startle as unconditioned stimulus (UCS, 100 ms, 95 dB) in an event-related design. fMRI data were acquired with a whole head EPI sequence (TR/TE 2s/30 ms, isotropic voxels of 3.6 mm edge length). The (German) State-Trait-Anxiety-Inventory (STAI) (6) was used to determine trait anxiety on an individual basis. fMRI data were analyzed with SPM5. Correlation of BOLD response with STAI scores was determined using linear regression. Volunteers were genotyped for the functional 5-HTTLPR polymorphism, and amygdala activity in carriers of risk alleles was compared with activity in non-risk allele (l-allele) carriers.

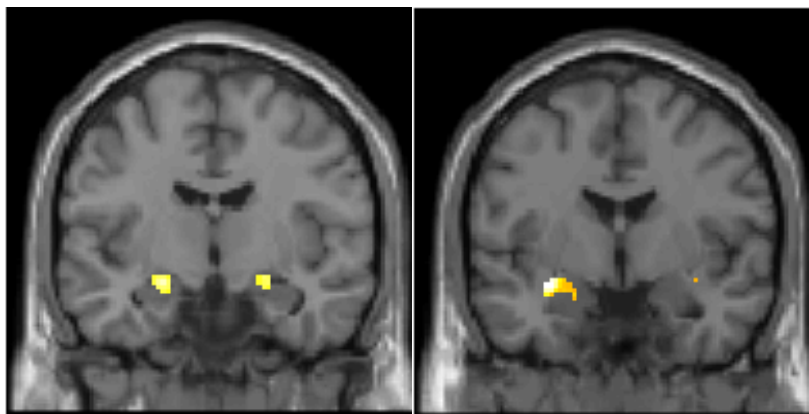


Fig. 1 Extinction and trait anxiety: Influence of trait anxiety during extinction only - trait anxious persons show more amygdala activation (Projection on the T1w template used by SPM5).

Fig. 2 Extinction and 5-HTTLPR: Influence of 5-HTTLPR during extinction only - volunteers carrying the s-allele show more amygdala activation (Projection on the T1w template used by SPM5).

Results: EPI data were sufficiently undistorted to allow reliable evaluation even of sensitive areas as the amygdala. During conditioning significant activations could be detected in the typical fear areas of the insula, anterior cingulate cortex, and striatum. Activations of the amygdala occurred in the late conditioning phase only. The extinction phase showed significant activations of bilateral insulae and a deactivation of the amygdala. Both, Trait anxiety and 5-HTTLPR polymorphism did not influence BOLD response during acquisition, but there was an effect on the extinction phase: Highly trait anxious persons and carriers of the short s-allele showed less deactivation of the amygdala during extinction (Fig. 1, 2).

Discussion: The study revealed that trait anxiety and 5-HTTLPR do not influence the acquisition, but the (learned) extinction of fear, as reflected by amygdala activity. These findings demonstrate that persons with these risk factors do not only react more strongly to fear stimuli, but can also less easily extinguish learned fear reactions.

References: (1) Anderson KC and Insel TR, *Biol Psychiatry* 2006; 60:319-321 (2) Bishop SJ, *Trends Cogn Sci* 2007; 11:307-316 (3) Bienvenu OJ et al., *Psychiatry Res* 2001; 102:73-85 (4) Lonsdorf TB et al., *Prog Neuropsychopharmacol Biol Psychiatry* 2009; in press (5) Tottenham N et al., *Psychiatry Research* 2009; 168:242-249 (6) Laux L et al., *Das State-Trait-Angstinventar*, Belz-Test GmbH, Weinheim (D) 1981