

# fMRI reveals that basolateral amygdala responsiveness to aversive stimuli as a neural correlate of trait anxiety is modulated by Neuropeptide S (NPS) receptor genotype

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**Introduction:** Anxiety disorders are highly prevalent and debilitating psychiatric diseases with a moderate to high degree of heritability (1). Hyperactivity of the amygdala, a central structure in the fear circuit, and insufficient frontal control are considered as neuronal correlates of this vulnerability (2). Understanding the underlying molecular genetic pathomechanism is a major goal of current research.

Recent studies point to a role of neuropeptide S (NPS) in the etiology of anxiety disorders. In animal models, NPS and its receptor (NPSR) were shown to be highly expressed in the amygdala (3). A functional polymorphism in the NPS receptor gene (rs324981 A/T) has been associated with panic disorder and anxiety sensitivity (4). However, the role of NPSR gene variation in the modulation of fear-related amygdala responsiveness remains to be clarified.

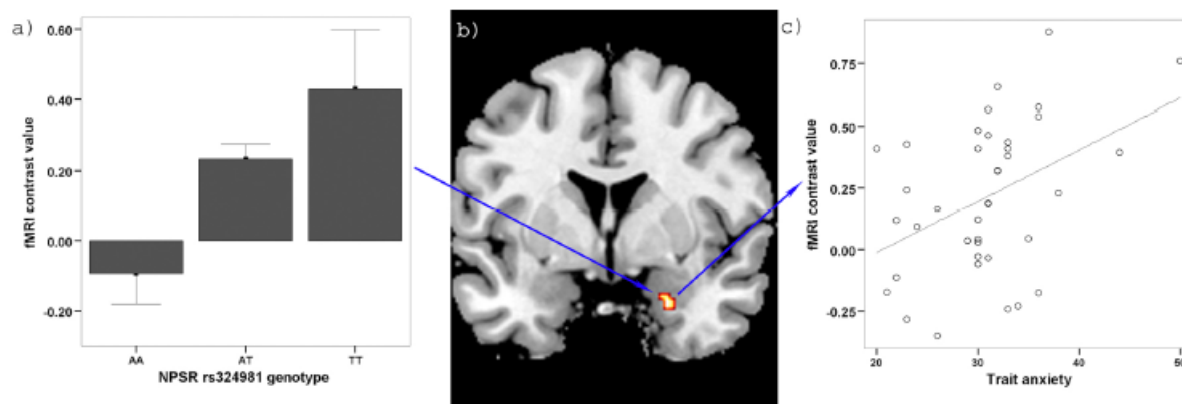
**Methods:** In 40 healthy subjects genotyped for NPSR rs324981, amygdala responses were assessed with a frequently used, robust paradigm for eliciting amygdala responsiveness, based on presentation of emotional faces (e.g. (5)) projected to a screen at the rear end of the scanner. The paradigm consisted of 4 blocks of a face-processing task interleaved with 5 blocks of a sensorimotor control task. During the face processing task, participants viewed a trio of faces (either angry or fearful) from a common stimulus set (6) and selected one of 2 faces at the bottom that was identical to the target face at the top, using a fiber-optic response pad. The sensorimotor control blocks consisted of trios of geometric shapes (circles and ellipses), with the same selection task. All blocks started with an instruction for 2 s, followed by face trios for 4 s with a variable interstimulus interval of 2 to 6 s (mean, 4 s). In the sensorimotor control blocks interstimulus interval was 2 s. Total task time was thus 390 s. Participant's performance was recorded.

Functional MR data were acquired at 3 T (Gyrosan Intera 3T, PMS) using a single shot EPI for volumes of 34 slices (matrix 64x 64, isotropic voxels, edge length 3.6 mm; TR=2.1 s, TE=30 ms, FA=90°). Slices were tilted 25° from the AC/PC line in order to minimize drop out artifacts in the orbitofrontal and mediotemporal region.

fMR data were processed using SPM5 (7). Movement parameters from realignment were entered as additional regressors and the model was corrected for serial correlations. For each participant, one contrast image was generated in each individual fixed-effects 1st level analysis comparing activation in response to fear-relevant faces with the shapes baseline. The resulting contrast images were then entered into 2nd level random-effects group analyses.

**Results and Discussion:** We observed a strong association of NPSR T alleles with right amygdala responsiveness to fear relevant faces. The association peak was located in the basolateral amygdala. Furthermore, responsiveness to aversive stimuli within this basolateral amygdala cluster predicted participant's self reported trait anxiety (STAI scale (8)), but not the depression level.

We conclude that NPSR genotype is associated with amygdala responsiveness to fear relevant stimuli. Thereby, NPSR rs324981 apparently causes an indirect effect on trait anxiety and potentially contributes to the pathogenesis of anxiety disorders by shaping fear-related limbic activity.



a) Activity of basolateral amygdala cluster dependent on genotype  
b) Coronal view depicting amygdala responsiveness modulated by genotype ( $p < .05$ , FWE corrected for amygdala)  
c) Scatter plot showing correlation of cluster response and STAI trait scores ( $r = .42$ ,  $p = .008$ )

**References:** (1) Hettema JM et al., Am J Psych 2001;158:1568-1578 (2) Bishop SJ, Trends Cogn Sci 2007; 11:307-316 (3) Jüngling K et al., Neuron 2008; 59:298-310 (4) Domschke K et al., Molecular Psych 2010; in press, Epub Jul 6 (5) Hariri A et al., Science 2002; 297:400-403 (6) Ekman P and Friesen WV, Pictures of Facial Affect, 1976, Consulting Psychologists Press, Palo Alto (7) www.fil.ion.ucl.ac.uk/spm (8) Laux L et al., Das State-Trait Angstinventar, 1981, Beltz, Weinheim (D)