INFLUENCE OF THE CATECHOL-*O*-METHYLTRANSFERASE VAL158MET GENOTYPE ON AMYGDALA AND PREFRONTAL CORTEX EMOTIONAL PROCESSING IN PANIC DISORDER

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INTRODUCTION

Panic disorder is an anxiety disorder characterized by sudden and unexpected attacks of intense fear and anticipatory anxiety with a life-time prevalence of 1-3% (Weissman et al., 1997). Family and twin studies propose a strong genetic contribution to the pathogenesis of panic disorder with an estimated heritability of up to 48% (Hettema et al., 2001). Several biochemical and pharmacological studies suggest that the catechol-O-methyltransferase (COMT) is involved in the pathogenesis of panic disorder. The functional val158met (472G/A) polymorphism in the COMT gene, with the val allele being more active than the met allele, has repeatedly been found to be associated with the disorder (e.g. Hamilton et al., 2002; Domschke et al., 2004). Additionally, in a recent fMRI study the COMT val158met polymorphism has been shown to influence limbic and prefrontal brain activation in response to unpleasant stimuli (Smolka et al., 2005). Given the probable physiological and genetic influence of COMT on the pathogenesis of panic disorder on the one hand and the role of COMT activity in brain regions critical for emotional processes on the other hand, in the present study regional brain activation in response to emotional stimuli as measured by 3T fMRI was used as an endophenotype and investigated for association with the COMT val158met variant in a sample of patients with panic disorder.

METHODS

We investigated regional brain activation in response to visual presentation of happy, fearful and angry face stimuli (Ekman and Friesen, 1976) versus no faces by means of fMRI at 3T in a sample of 20 patients with panic disorder (female=12, male=8). Voxel values of 5 x 2 predefined regions of interest (ROI) were extracted, summarized by mean and tested among the different conditions using the MarsBaR toolbox. Additionally, all patients were genotyped for the functional COMT val158met variant according to the published protocol (Domschke et al., 2004). Genotype group differences in fMRI activation were analyzed using Mann-Whitney-U. An influence of age, gender, marital status, medication and comorbid social phobia or depression could not be observed.

RESULTS

The genotype distribution of the val158met COMT polymorphism (AA: n=7, AG: n=11, GG: n=2) did not significantly differ from the expected numbers calculated according to the Hardy-Weinberg equilibrium (χ^2=0.58, df=2, p=0.75). For further analysis, genotypes were grouped according to functionality and previous studies in panic disorder (AA: n=7 (males: n=3, females: n=4), AG/GG: n=13 (males: n=5, females: n=8)).

COMT val158met genotype and processing of fearful faces

For the COMT val158met genotype groups, regional brain activation changes in response to the presentation of unmasked fearful faces are given in table 1. We observed significantly increased activation in the right amygdala (p=0.026), the right fusiform gyrus (p=0.043) and the left lateral orbitofrontal cortex (p=0.043) in carriers of at least one 472G risk allele (158val) as compared to homozygotes for the 472A allele (158met). Activity differences between the two patient groups (472 AA vs AG/GG) in the right amygdala are visualized on a three dimensional canonical Montreal Neurological Institute brain in figure 1.

Table 1:

COMT 472G/A Genotype		amygdala		fusiform gyrus		lateral orbitofrontal cortex	
		left	right	left	right	left	right
AA (n=7)	mean	0.1257	**-0.0486**	0.1900	**0.3643**	**0.0057**	0.0129
	sd	0.31416	0.35988	0.20744	0.26476	0.19739	0.23970
AG/GG (n=13)	mean	0.2015	**0.2415**	0.3323	**0.6154**	**0.2331**	0.1677
	sd	0.27895	0.17521	0.16130	0.19590	0.20726	0.27170
	U	34.0	17.5	26.5	20.0	20.0	32.0
	p	0.362	**0.026***	0.131	**0.043***	**0.043***	0.284

Tab. 1: Descriptive (mean, sd=standard deviation) and comparative (U=Mann-Whitney-U, p=two-sided p-value at a significance level of p<.05) statistics for COMT val158met effects on regional brain activation as measured by 3 Tesla fMRI in response to presentation of fearful faces. Multiple testing was not corrected for.

Figure 1:

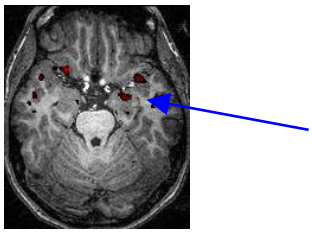

Fig. 1: Random effects statistical parametric map for the fearful vs no faces contrast overlaid on a three dimensional canonical Montreal Neurological Institute brain showing activity differences in the right amygdala between the two patient groups (COMT val158met AA vs AG/GG).

COMT val158met genotype and processing of happy and angry faces

In response to happy faces, the presence of at least one 472G risk allele was associated with significantly elevated activity in the medial orbitofrontal cortex in comparison to homozygotes for the 472A allele (left medial orbitofrontal cortex: AA: mean=-0.3329, sd=0.20798; AG/GG: mean=0.1646, sd=0.26005; U=7.0, p=0.002; right medial orbitofrontal cortex: AA: mean=-0.1871, sd=0.25908; AG/GG: mean=0.0554, sd=0.22467; U=20.5, p=0.047). In response to angry faces, patients carrying at least one 472G risk allele showed higher activation in the left medial orbitofrontal cortex as well (AA: mean=-0.4114, sd=0.23140; AG/GG: mean=-0.2115, sd=0.37233; U=19.5, p=0.039).

DISCUSSION

Our data provides preliminary evidence for a role of the functional val158met COMT polymorphism in orbitofrontal, amygdala and fusiform gyrus activation in response to emotional faces in panic disorder. In patients carrying at least one of the more active COMT val risk alleles, the resilience against anxiety-states in panic disorder might be reduced by altered neuronal integration and validation of anxiety-related emotional stimuli. Replication studies in larger samples are necessary.

LITERATURE

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