International Journal of Neuropsychopharmacology (2006), **9**, 349–355. Copyright © 2005 CINP
doi:10.1017/S1461145705005869

BRIEF REPORT

Association of the functional −1019C/G 5-HT$_{1A}$ polymorphism with prefrontal cortex and amygdala activation measured with 3 T fMRI in panic disorder

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Abstract

Serotonergic genes have been implicated in the pathogenesis of panic disorder and amygdala function in response to fearful stimuli. Regional brain activation on visual presentation of emotional facial stimuli was investigated in 20 patients with panic disorder by means of fMRI at 3 T. All patients were genotyped for the functional −1019C/G 5-HT$_{1A}$ and 5-HTTLPR polymorphisms. In patients homozygous for the 5-HT$_{1A}$ −1019G risk allele ($n=5$), fearful stimuli were associated with a decreased activation of right prefrontal cortex regions. Patients homozygous for the 5-HT$_{1A}$ −1019G risk allele or patients carrying the short risk allele of the 5-HTTLPR ($n=13$) showed higher amygdala activation in response to happy faces. This exploratory study suggests a role of the functional −1019C/G 5-HT$_{1A}$ and 5-HTTLPR polymorphisms on prefrontal cortex and amygdala activation patterns in response to emotional facial stimuli. These serotonergic polymorphisms might increase the risk for panic disorder by contributing to an altered processing of emotional stimuli.

Received 4 April 2005; Reviewed 19 April 2005; Revised 19 May 2005; Accepted 29 May 2005; First published online 5 September 2005

Key words: Amygdala, fMRI, panic disorder, prefrontal cortex, 5-HT$_{1A}$.

Introduction

Panic disorder is an anxiety disorder characterized by sudden and unexpected panic attacks, anticipatory anxiety and a lifetime prevalence of 1–3% (Weissman et al., 1997). Family and twin studies propose that genetic factors contribute to the pathogenesis of panic disorder with an estimated heritability of up to 48% (Hettema et al., 2001).

On the basis of observations from biochemical, physiological and behavioural studies, the serotonergic system has been suggested to play a pivotal role in the aetiology of panic disorder. In particular, the serotonin 1A receptor (5-HT$_{1A}$) is thought to be involved in the pathophysiology of the disease. 5-HT$_{1A}$ gene knock-out mice have been observed to display increased anxiety-like behaviour in various conflict tests (Heisler et al., 1998; Parks et al., 1998; Ramboz et al., 1998). 5-HT$_{1A}$ receptor responsivity has been reported to be reduced in patients with panic disorder (Lesch et al., 1992). A recent PET study showed significant reduction in distribution volumes of a selective 5-HT$_{1A}$ radioligand in patients with panic disorder (Neumeister et al., 2004). In the gene coding for the 5-HT$_{1A}$ receptor located on chromosome 5q12.3, the G allele of the −1019C/G promoter polymorphism has been proposed to derepress 5-HT$_{1A}$ autoreceptor expression by disrupting an inhibitory transcription factor binding site and thereby reducing serotonergic neurotransmission (Lemonde et al., 2003). The −1019G allele was associated with anxiety and depression-related personality traits such as harm avoidance in healthy volunteers (Strobel et al.,

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2003), and with panic disorder with concurrent agoraphobia in patients (Rothe et al., 2004).

The serotonin transporter (5-HTT), which facilitates re-uptake of serotonin from the synaptic cleft, has also been implicated in the pathogenesis of panic disorder. 5-HTT knock-out mice display increased anxiety-like behaviour and abnormal fear conditioning (Holmes et al., 2003). In the promoter region of the 5-HTT gene mapping to chromosome 17q11.1-12, a functional variable repeat sequence polymorphism (5-HTTLPR) resulting in a short (s) and a long (l) variant has been identified, with the l allele promoting the transcription of the gene more efficiently than the shorter s allele. Several studies have reported that carriers of either one or two copies of the s allele are significantly more prone to display abnormal levels of anxiety and neuroticism (e.g. Lesch et al., 1996) and to acquire conditioned fear responses (Garpenstrand et al., 2001) than homozygotes for the l allele. In patients with panic disorder, however, several independent studies failed to detect assocation of the 5-HTTLPR with the disease (e.g. Deckert et al., 1997).

Inconsistencies in association findings with panic disorder have been suggested to be in part due to the heterogeneity and complexity of the clinically defined panic disorder phenotype. Consequently, the examination of regional brain activation critical for emotional and learning processes as measured by fMRI might more closely reflect the influence of genes on the pathogenesis of the disorder. The direct combination of fMRI activation data and analyses of genetic polymorphisms is a new emerging field called 'Imaging Genomics' with few studies available to date, most in healthy volunteers. First in the field, Hariri et al. (2002) reported enhanced amygdala response to fearful and angry facial stimuli in carriers of at least one short allele as compared to homozygotes for the long allele of the 5-HTTLPR in two independent samples of healthy volunteers. This finding was confirmed in independent samples (Hariri et al., 2005; Heinz et al., 2005). A recent PET study in social phobia showed that this approach can be successfully applied in anxiety disorders (Furmark et al., 2004).

In panic disorder patients, the differential influence of 5-HT_{1A} and 5-HTT genes on neuronal activation patterns has not yet been studied to the best of our knowledge. In the present study, we therefore investigated regional brain activation in response to relevant emotional stimuli (angry, fearful and happy faces) in relation to genetic variations in the 5-HT_{1A} and 5-HTT genes in a sample of patients with panic disorder.

Methods

Subjects

A sample of 20 unrelated German patients with panic disorder was investigated in this study (12 female, 8 male, average age 36.75 ± 9.39 yr). Panic disorder was diagnosed by experienced psychiatrists on the basis of medical records and a structured clinical interview (SKID-I) according to DSM-IV criteria (Wittchen et al., 1997). Only patients with primary panic disorder were included, secondary lifetime diagnoses were social phobia in 10 and major depression in 5 patients. Ten patients were treated with a selective serotonin re-uptake inhibitor (SSRI), the other 10 patients were free of medication. The study was approved by the local Ethical Committee and informed consent was obtained from all participating subjects.

Facial emotion presentation

Facial stimuli consisted of grey-scale normalized fearful, angry, happy and neutral expressions of 10 individuals (Ekman and Friesen, 1976). Patients were presented with alternating 30-s epochs of the emotional faces or a no-face control stimulus (a grey rectangle). Within unmasked epochs, emotional stimuli were presented twice per second in a random sequence for 500 ms. Within masked epochs, emotional faces were shown twice per second for 33 ms followed by a neutral face mask of 467 ms duration. The order of blocks was counterbalanced across subjects, each face epoch was preceded by a no-face control epoch and was presented twice. The masked-faces experiment always preceded the unmasked-faces experiment. The overall presentation time of each experiment was 8 min. Patients were told that they would see human faces and that they should pay attention to them. Images were presented via projection to the rear end of the scanner (Sharp XG-PC10XE with additional HF shielding). The head position was stabilized with a vacuum head cushion.

fMRI methods

T2* functional data were acquired with a 3 T scanner (Gyroscan Intera 3.0 T, Philips Medical Systems, Best, The Netherlands) using a single-shot echo-planar sequence with parameters selected to minimize distortion in the regions of central interest while retaining adequate S/N and T2* sensitivity. Volumes consisting of 25 axial slices were acquired (matrix 128×128, resolution $1.75 \times 1.75 \times 3.5$ mm; TR = 3 s, TE = 30 ms, FA = 90°) 160 times in block design, 10 times per condition. To optimize the following normalization

procedures the same sequence parameters were used to cover the whole brain with 43 slices. Additionally, two anatomical datasets were acquired: T1 weighted inversion recovery and a high-resolution T1 weighted 3D sequence (isotropic voxel, 0.5 mm edge length).

Functional imaging data were motion corrected, using a set of six rigid body transformations determined for each image, spatially normalized to standard MNI space (Montreal Neurological Institute) and smoothed (Gaussian kernel, 6 mm FWHM) using Statistical Parametric Mapping (SPM2, Wellcome Department of Neurology, London, UK). Statistical analysis was performed by modelling the different conditions (angry, fearful, happy, neutral, no face) as variables within the context of the general linear model (modelled with a standard haemodynamic response function). Voxel values of 5×2 predefined regions of interest (ROI) (Tzourio-Mazoyer et al., 2002) were extracted on the basis of a-priori hypotheses regarding potential involvement of these regions in emotional stimuli processing (amygdala, ventromedial prefrontal cortex, orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex), summarized by mean and tested among the different conditions using the MarsBaR toolbox (Brett et al., 2002).

Genotyping

All patients were subsequently genotyped for the 5-HT$_{1A}$ −1019C/G polymorphism and the 5-HTTLPR according to published protocols (Deckert et al., 1997; Rothe et al., 2004). For each of the polymorphisms, genotypes were placed into high-risk and low-risk groups according to functionality and previous association studies in panic disorder [5-HT$_{1A}$ −1019C/G: GG ($n=5$) vs. CC ($n=6$) and CG ($n=9$); 5-HTTLPR: SS ($n=1$) and SL ($n=12$) vs. LL ($n=7$)]. Group differences in fMRI activation were analysed using the Mann–Whitney U test. The relationship between genotype groups and age, gender, marital status, medication and the presence of social phobia and depression was tested by application of the Mann–Whitney U test or Fisher's exact test respectively. Effects of age, gender, marital status, medication and psychiatric comorbidity on regional brain activation were tested by means of regression analysis (age) or Mann–Whitney U test (female vs. male, married vs. not married, with vs. without medication, comorbidity vs. no comorbidity) to probe if they could explain genotype effects. All statistics were calculated by means of the SPSS statistical package, version 12.0.1 (SPSS Inc., Chicago, IL, USA). Hardy–Weinberg equilibrium was examined using the program DeFinetti provided as an online source (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl; T. F. Wienker, T. M. Strom; accessed February 2005). The genotype distribution of both the 5-HT$_{1A}$ −1019C/G polymorphism ($p=0.67$) and the 5-HTTLPR ($p=0.33$) did not significantly differ from the expected numbers calculated according to the Hardy–Weinberg equilibrium.

The statistical threshold was set at $p<0.05$. Statistical analyses were basically explorative and were, therefore, not corrected for multiple testing.

Results

Subjects in the respective genotype groups were not significantly different with respect to gender, marital status, medication with SSRIs, or psychiatric comorbidity. Of those, only gender and psychiatric comorbidity with social phobia had a differential effect on brain activation in some ROIs, which, however, only partially overlapped with those differentially activated between the genotype groups. Genotype groups were partly different with respect to age (5-HT$_{1A}$ −1019C/G, $p=0.04$; 5-HTTLPR, $p=0.34$), but regression analysis did not reveal any effect of age on brain activation in the ROIs.

For the 5-HT$_{1A}$ −1019C/G genotype groups, regional brain activation changes in response to the presentation of unmasked fearful vs. neutral faces are given in Table 1. We observed significantly decreased activation in the right ventromedial prefrontal cortex ($p=0.01$), right orbitofrontal cortex ($p=0.04$), and the right anterior cingulate cortex ($p=0.03$), as well as a trend to decreased activation in the right dorsolateral prefrontal cortex ($p=0.06$) in homozygotes for the −1019G allele compared to carriers of either one or two −1019C alleles (Figure 1). A trend towards differential activation in the right ventromedial prefrontal cortex region for different 5-HT$_{1A}$ genotype groups was also observed during processing of angry faces ($p=0.06$). In response to unmasked happy faces, patients homozygous for the 5-HT$_{1A}$ −1019G allele showed significantly higher activation in the left amygdala ($p=0.03$) in comparison to −1019C allele carriers, with a trend in the same direction in the right amygdala ($p=0.12$) as outlined in Table 2. On masked presentation of emotional faces, activation in the right ventromedial prefrontal cortex in response to fearful faces was significantly decreased ($p=0.02$) in homozygotes for the −1019G genotype.

Statistical analysis of 5-HTTLPR influence on brain activation in response to unmasked angry or fearful faces did not reveal any significant results.

Table 1. Descriptive and comparative statistics for 5-HT_{1A} −1019C/G effects on regional brain activation as measured by 3 T fMRI in response to presentation of fearful vs. neutral faces

5-HT_{1A} −1019C/G	Amygdala		Ventromedial prefrontal cortex		Orbitofrontal cortex		Dorsolateral prefrontal cortex		Anterior cingulate cortex	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
CC/CG ($n=15$)										
Mean	−0.1287	−0.1040	0.0120	0.1000	−0.0260	−0.0193	−0.0500	−0.0827	−0.0853	−0.0260
S.D.	0.3781	0.3806	0.6215	0.4442	0.3503	0.2722	0.3077	0.2539	0.4494	0.3414
GG ($n=5$)										
Mean	0.1520	0.0140	−0.1620	−0.4860	−0.0820	−0.4800	−0.1720	−0.4700	−0.5180	−0.5220
S.D.	0.3628	0.1422	0.5582	0.3233	0.1152	0.4082	0.3714	0.4604	0.6455	0.5720
U	24.0	31.0	37.0	9.0	34.0	14.0	31.5	15.5	21.5	13.0
p	0.238	0.570	0.965	0.013*	0.760	0.040*	0.600	0.055	0.162	0.032*

S.D., Standard deviation; U, Mann–Whitney U; * p value at a significance level of $p<0.05$.

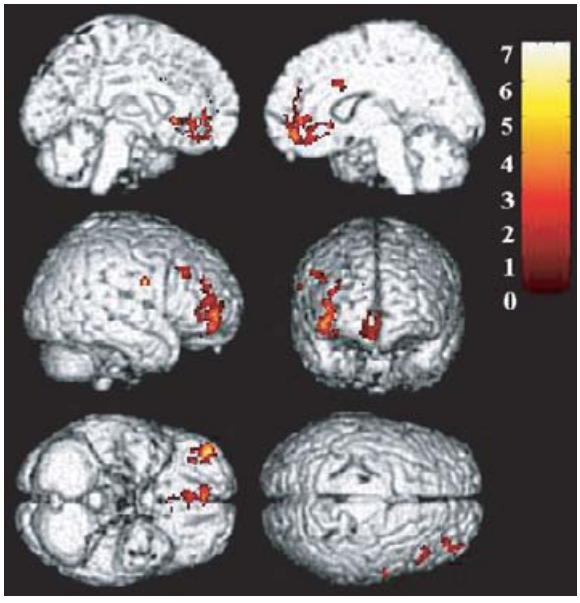

Figure 1. Random effects statistical parametric map for the fearful vs. neutral faces contrast overlaid on a three-dimensional canonical Montreal Neurological Institute brain showing right-lateralized activity differences in the prefrontal cortex between the two patient groups (5-HT_{1A} −1019GG vs. CC/CG; $p<0.001$, uncorrected).

Presentation of unmasked happy faces, however, was associated with higher amygdala activation in carriers of at least one short allele compared to homozygotes for the long allele (right amygdala: LL, mean = −0.2871, S.D. = 0.4199; SS/SL, mean = 0.0854, S.D. = 0.3543; $U=21.0$, $p=0.05$). fMRI activation in response to masked presentation of emotional faces was not influenced by 5-HTTLPR genotypes.

Discussion

Our data suggest that in patients with panic disorder processing of anxiety-related emotional face stimuli might be influenced by the functional 5-HT_{1A} −1019C/G promoter polymorphism in specific right hemispheric prefrontal regions. A significant decrease of activation was observed in the right ventromedial and orbitofrontal cortex regions and the right anterior cingulate cortex in patients homozygous for the G high-risk allele of the 5-HT_{1A} −1019C/G polymorphism. These findings may indicate that depending on the genetic variants of the 5-HT_{1A}, patients with panic disorder are prone to impaired cerebral processing of anxiety-related stimuli in cortical regions known to play a crucial role in the evaluation of emotional stimuli and determining salient events (Bishop et al., 2004; Northoff et al., 2004). It is noteworthy that the orbitofrontal and anterior cingulate cortex regions were implicated in panic disorder with prior PET and fMRI mental imagery studies (Bystritsky et al., 2001; Malizia et al., 1998). The strong right lateralization is in agreement with recent functional neuroimaging findings as well as clinical findings that link conscious processing of emotional facial expressions with the right hemisphere (Adolphs et al., 2000, Schmitt et al., 1997). Our data may thus suggest that the specific role of these regions in the pathophysiology of panic disorder is linked to specific genetic risk factors.

Preceding imaging genomic studies on emotional processing and the serotonin system were performed on healthy volunteers and demonstrated increased activation of the amygdala in individuals with the short risk allele after stimulation with threatening facial stimuli (Hariri et al., 2002, 2005; Heinz et al.,

Table 2. Descriptive and comparative statistics for 5-HT$_{1A}$ −1019C/G effects on regional brain activation as measured by 3 T fMRI in response to presentation of happy vs. neutral faces

5-HT$_{1A}$ −1019C/G	Amygdala		Ventromedial prefrontal cortex		Orbitofrontal cortex		Dorsolateral prefrontal cortex		Anterior cingulate cortex	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
CC/CG ($n=15$)										
Mean	−0.1653	−0.1227	0.2247	0.1520	−0.1107	−0.1227	−0.1413	−0.2120	−0.0993	−0.0973
S.D.	0.4698	0.4262	0.5210	0.4324	0.4400	0.4162	0.2753	0.3638	0.4834	0.3486
GG ($n=5$)										
Mean	0.3200	0.1880	0.1860	0.1700	−0.0260	−0.1740	0.0160	−0.1080	0.0620	−0.0100
S.D.	0.1678	0.2697	0.4767	0.2577	0.3555	0.3560	0.2791	0.2440	0.1961	0.2364
U	13.0	19.5	34.5	34.5	36.0	27.0	25.0	32.0	36.5	37.5
p	0.033*	0.116	0.793	0.793	0.896	0.359	0.275	0.631	0.930	1.000

S.D., Standard deviation; U, Mann–Whitney U; * p value at a significance level of $p<0.05$.

2005). In our sample of patients with panic disorder, we did not observe any alteration in neuronal amygdala activation in response to anxiety-related facial stimuli associated with the 5-HT$_{1A}$ −1019C/G polymorphism or the 5-HTTLPR. However, presentation of happy compared to neutral faces elicited significantly higher amygdala activation in patients homozygous for the 5-HT$_{1A}$ −1019G high-risk allele and in carriers of the short 5-HTTLPR high-risk allele. It is conceivable that activation of the amygdala is unspecifically increased in response to presentation of emotional faces in patients with panic disorder. It is only in the case of the presentation of happy faces that patients with low-risk 5-HT$_{1A}$ −1019C and 5-HTTLPR l alleles failed to react with increased amygdala activation. Interestingly, in an anticipatory anxiety paradigm we previously observed a lack of amygdala activation during presentation of an experimental anxiety cue and, rather paradoxically, during the 'safe' condition (Stern et al., 2003). This is possibly due to a differential prefrontal cortex serotonergic tonus in panic patients (Lesch et al., 1992) associated with a lack of inhibition of amygdala activation by the prefrontal cortex as can be hypothesized in particular for patients with the high-risk 5-HT$_{1A}$ −1019G allele.

Some limitations to this study should be mentioned. First, the number of patients is small, albeit in the range of other recently published studies. Accordingly, the statistical analysis was explorative. Only patients were investigated and, thus, the specificity of our findings relative to healthy subjects or other patient groups could not be directly assessed here. However, some published reports on healthy subjects are available and have been discussed above. Owing to these limitations our results might well be false-positive ones and, therefore, replication studies of larger samples of patients and healthy volunteers in parallel are indicated.

In conclusion, our data provide preliminary evidence for a role of the functional 5-HT$_{1A}$ −1019C/G promoter polymorphism in prefrontal cortex activation patterns to anxiety-related stimuli in patients with panic disorder. Our findings also suggest a role of both the 5-HT$_{1A}$ −1019C/G polymorphism and the 5-HTTLPR for amygdala activation to positive emotional stimuli in patients with panic disorder. The two functional polymorphisms might increase the risk of suffering from panic disorder by contributing to an altered processing of emotional facial stimuli.

Acknowledgements

We gratefully acknowledge the skilful technical support of Ms. Kathrin Schwarte. This research was supported by an IMF grant (DE219915).

Statement of Interest

None.

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