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Association of NPSR1 gene variation and neural activity in patients with panic disorder and agoraphobia and healthy controls

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ABSTRACT

Introduction: The neurobiological mechanisms behind panic disorder with agoraphobia (PD/AG) are not completely explored. The functional A/T single nucleotide polymorphism (SNP) rs324981 in the neuropeptide S receptor gene (*NPSR1*) has repeatedly been associated with panic disorder and might partly drive function respectively dysfunction of the neural "fear network". We aimed to investigate whether the *NPSR1* T risk allele was associated with malfunctioning in a fronto-limbic network during the anticipation and perception of agoraphobia-specific stimuli.

Method: 121 patients with PD/AG and 77 healthy controls (HC) underwent functional magnetic resonance imaging (fMRI) using the disorder specific "Westphal-Paradigm". It consists of neutral and agoraphobia-specific pictures, half of the pictures were cued to induce anticipatory anxiety.

Results: Risk allele carriers showed significantly higher amygdala activation during the perception of agoraphobia-specific stimuli than A/A homozygotes. A linear group x genotype interaction during the perception of agoraphobia-specific stimuli showed a strong trend towards significance. Patients with the one or two T alleles displayed the highest and HC with the A/A genotype the lowest activation in the inferior orbitofrontal cortex (iOFC).

Discussion: The study demonstrates an association of the *NPSR1*rs324981 genotype and the perception of agoraphobia-specific stimuli. These results support the assumption of a fronto-limbic dysfunction as an intermediate phenotype of PD/AG.

1. Introduction

Panic disorder with agoraphobia (PD/AG) is one of the most common anxiety disorders with a 12-month prevalence of 2% (Wittchen et al., 2011). This disorder is characterized by panic attacks, avoidance behavior or anticipatory anxiety in or before situations in which an escape would be impossible or embarrassing. These situations include, among others, public transportation, crowds or using an elevator (American Psychiatric Association, 2013). Some brain areas which are involved in the processing of anxiety in PD and PD/AG have been identified. The amygdala plays a pivotal role in the so-called "fear network" and fMRI studies prove increased amygdala activation during

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the perception of anxiety related stimuli (Etkin and Wager, 2007; Ledoux, 2004). Furthermore, the amygdala is engaged in adaptive and detrimental threat responding and the encoding of affective value of stimuli (Fox et al., 2015; Morrison and Salzman, 2011). Patients with PD/AG exhibited not only altered subcortical, but also altered cortical activation patterns. Aside from the amygdala, there are the brainstem, the hippocampus, the insula, the anterior cingulum and different temporal and prefrontal structures which make up the fear network (Dresler et al., 2013; Gorman et al., 2000). Although there is no agreement on the exact prefrontal structures involved, the medial prefrontal cortex (mPFC), the ventromedial prefrontal cortex (vmPFC), the dorsomedial prefrontal cortex (dmPFC), the inferior frontal gyrus and the orbito frontal cortex (OFC) are discussed as central structures (Atmaca et al., 2013; Engel et al., 2016; Hettema et al., 2001; Kircher et al., 2013; Klahn et al., 2017; Lueken et al., 2013; Sobanski and Wagner, 2017). It is not certain to what extent these alterations in brain responses are valid for PD/AG, because many studies did not report the possible comorbidity of agoraphobia (Dresler et al., 2013).

Based on the fact of a moderate to high heritability of PD/AG (Hettema et al., 2001), genetic risk factors are assumed to modulate the activation of the neural fear circuit. The neuropeptide S receptor gene (*NPSR1)* is an often discussed gene in matters of PD/AG. Neuropeptide S is a neurotransmitter, expressed in the brainstem and its m-RNA occurs in some regions of the fear circuit, like the amygdala, hypothalamus and cortex. It operates as a neuromodulator, especially in the onset of anxiety and arousal (Pape et al., 2010). The *NPSR1* gene is localized on chromosome 7p14.3 and exhibits an A/T SNP (rs324981) leading to an amino acid exchange on position 107 ($Asn^{107}Ile$) (Jüngling et al., 2008; Xu et al., 2004). The more active T allele increases the NPS binding affinity to the receptor about tenfold (Reinscheid et al., 2005). The T allele is associated with panic disorder and elevated heart rate, increased response inhibition and error monitoring (Beste et al., 2013; Domschke et al., 2011; Donner et al., 2010; Okamura et al., 2007). Additionally, this allele is associated with a higher level of anxiety sensitivity in women with panic disorder and healthy T/T homozygotes showed an interaction with childhood maltreatment, leading to a higher anxiety sensitivity score (Domschke et al., 2011; Klauke et al., 2014). Dannlowski et al. (2011) reported a modulation of the amygdala reaction to fear-relevant faces by the *NPSR1* SNP. PD patients carrying the T allele showed a disrupted cortico-limbic connectivity with an increased activation of the amygdala, dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC) and dorsal anterior cingulate cortex (ACC) (Domschke et al., 2011). Healthy A/A homozygotes exhibited a stronger prefrontal activity in an emotional Stroop task and likewise T allele carriers had a higher responsiveness of the dlPFC and medial prefrontal cortex in a working memory task (Guhn et al., 2015; Tupak et al., 2013). In an executive control task, participants with the T/T genotype showed increased activation in the inferior and middle frontal gyrus (Neufang et al., 2015) and different developmental trajectories of fronto-limbic connectivity, dependent on *NPSR1* genotype, have been suggested during adolescence (Domschke et al., 2017).

Taken together, there is converging evidence for the *NPSR1* T allele being a risk factor for anxiety related behavior, traits or neural activation patterns. To specifically and for the first time study the assumed relationship between genetic variation and a dysfunctional cortico-limbic network in PD with AG, a disorder-specific fMRI task was selected (Wittmann et al., 2011). Healthy volunteers and patients with PD/AG, (grouped by the *NPSR1* risk allele), had to differentiate during the anticipation and perception between agoraphobia-specific and neutral pictures. Neuroimaging studies in other anxiety disorders (Brinkmann et al., 2017; Heitmann et al., 2014) reported an increased prefrontal activation during the anticipation of fearful stimuli, whereas in PD/AG higher activation in the ventral striatum and insula were observed, so far (Wittmann et al., 2018, 2014). During the perception of fearful stimuli, changes in the amygdala activation were detected most frequently in different anxiety disorders (Brühl et al., 2014; Liebscher et al., 2016; Lueken et al., 2014; Wittmann et al., 2018). Based on previous evidence, the amygdala and the iOFC were chosen as volumes of interest of the neural fear circuit as an a priori hypothesis (Liebscher et al., 2016; Plag et al., 2018; Wittmann et al., 2018). We expected that a successful fear regulation, in terms of a functional fronto-limbic network, is characterized by a higher frontal activation during the anticipation of agoraphobic pictures and a lower activation of the amygdala during the perception of those pictures.

For the *anticipation phase*: a) Healthy controls were hypothesized to show greater activity of the iOFC than patients with PD/AG (main effect diagnosis). b) As a main *NPSR1* genotype effect, participants with the A/A genotype were assumed to show higher responsiveness than participants with one or two T alleles (A/A > T), due to a supposedly better top-down control. c) An exploratory linear interaction group x *NPSR1* genotype (HC A/A > HC T > PD/AG A/A > PD/AG T) was assumed.

In the *perception phase*, d) Patients were expected to show higher activity in the amygdala than HC as a main effect diagnosis. e) As a main NPSR1 genotype effect, participants with the T risk allele were hypothesized to exhibit a stronger amygdala activity than participants with the A/A genotype (T > A/A). f) An exploratory linear interaction of group x *NPSR1* genotype (PD/AG T > PD/AG A > HC T > HC A/A) in the amygdala was assumed.

2. Materials and methods

2.1. Participants

This study was part of the multicenter trial “Mechanisms of action in CBT (MAC)” and experimental add-on studies. The participating fMRI-Centers Aachen, Berlin, Dresden and Münster recruited 89 patients in the first funding period, who met the criteria for panic disorder and agoraphobia (DSM-IV-TR) and matched healthy controls (without any mental disorder). Due to quality controls and missing data, 62 patients and 39 healthy controls (HC) were included in the present study. In the second funding period: “Neural correlates of panic disorder” the participating fMRI-Centers Berlin and Dresden recruited 113 patients with panic disorder and agoraphobia and 99 HC. Data from 60 patients and 38 HC met above defined quality criteria and were included. A flowchart (Figs. S1 and S2) with patient and HC numbers and an explanation of the in- and exclusion criteria can be found in the supplemental information. All 121 patients and 77 HC were of Caucasian decent and underwent an extensive psychological and clinical diagnostic process, consisting of the Composite International Diagnostic Interview (Wittchen and Pfister, 1997), neuropsychological tests and a short medical examination. More than a third of the patients (45) suffered from one or more comorbid diagnoses, like nicotine dependence, depressive disorders or another anxiety disorder. In addition, clinical tests were completed by patients and the control group. Anxiety sensitivity was measured with the German version of the Anxiety Sensitivity Index (ASI, (Reiss et al., 1986)). A detailed description of the diagnostic procedure is added in the supplementary material. All participants were right-handed and comparable in gender, age, smoking status and education (Table 1). Patients and controls enrolled in this study gave their written informed consent, which conformed to the Declaration of Helsinki. The funding periods were approved by the Ethics Committees of the Medical Faculty of the Technische Universität Dresden (EK 164082006), the Medical Faculty of the Philipps-University Marburg, Germany (Project no. 171/09) and by the ethics committees of all participating sites.

2.2. Genotyping

DNA isolations and genotyping for the functional neuropeptide S

Table 1
Sociodemographic and clinical data.

Characteristics		PD/AG T $n = =90$ (45.4%)	PD/AG A/A $n = =31$ (15.7%)	HC T $n = =58$ (29.3%)	HC A/A $n = =19$ (9.6%)	total $n = =198$	chi^2/F	p
Sex	Male [*n* (%)]	33 (16.7)	11 (5.7)	21 (10.6)	10 (5.0)	75 (37.9)	1.958	.581
	Female [*n* (%)]	57 (28.8)	20 (10.1)	37 (18.7)	9 (4.6)	123 (62.1)		
Years of school education	8 [*n* (%)]	9 (4.6)	3 (1.5)	2 (1.0)	2 (1.0)	16 (8.0)	6.503	.369
	10 [*n* (%)]	39 (19.7)	9 (4.6)	20 (10.1)	5 (2.5)	73 (36.7)		
	13 [*n* (%)]	42 (21.2)	19 (9.6)	36 (18.1)	12 (6.6)	109 (55.0)		
Smoking status	Non-smoker [*n* (%)]	46 (23.2)	17 (8.6)	39 (19.7)	10 (5.0)	112 (56.6)	5.529	.478
	Smoker [*n* (%)]	34 (17.1)	14 (7.0)	19 (9.6)	9 (4.6)	86 (43.4)		

						main effect diagnosis		main effect *NPSR1*		interaction group x *NPSR1*	
						F	p	F	p	F	p
Age	M *(SD)*	35.19 *(10.04)*	38.32 *(11.69)*	35.67 *(10.45)*	33.16 *(12.55)*	1.627	.204	0.021	.885	2.386	.124
Clinical characteristics											
SIGH-A	M *(SD)*	22.03 *(7.69)*	20.1 *(6.56)*	1.48 *(2.29)*	2.11*(2.03)*	378.112	<.001	0.469	.494	1.719	.191
BSI	M *(SD)*	1.06 *(0.57)*	0.96 *(0.54)*	0.98 *(0.11)*	0.95 *(0.12)*	148.963	<.001	0.574	.45	0.509	.476
BDI	M *(SD)*	15.23*(8.61)*	12.48 *(10.61)*	1.37*(2.0)*	1.21 *(2.1)*	150.535	<.001	1.403	.238	1.118	.292
ASI	M *(SD)*	30.21*(10.59)*	23.97*(10.53)*	8.90 *(7.3)*	8.63 *(7.29)*	132.054	<.001	4.171	.43	3.503	.063
MI alone	M *(SD)*	2.60 *(1.07)*	2.61 *(0.79)*	1.06 *(0.14)*	1.02 *(0.04)*	53.705	<.001	0.002	.964	0.018	.893
MI accompanied	M *(SD)*	2.05 *(0.87)*	2.08 *(0.72)*	1.02 *(0.05)*	1.02 *(0.03)*	35.509	<.001	0.005	.947	0.004	.951
NEO-FFI neuroticism[a]	M *(SD)*	2.0 *(0.31)*	1.8 *(0.31)*	1.34 *(0.52)*	1.6 *(0.36)*	19.005	<.001	0.125	.724	5.111	.026
NEO-FFI extraversion[a]	M *(SD)*	2.01 *(0.3)*	2.05 *(0.25)*	2.41 *(0.45)*	2.32 *(0.33)*	15.803	<.001	0.082	.775	0.553	.459
NEO-FFI openness-to-experience[a]	M *(SD)*	2.1 *(0.34)*	2.12 *(0.16)*	2.31 *(0.39)*	2.21 *(0.44)*	3.367	.069	0.306	.581	0.6	.44
NEO-FFI agreeableness[a]	M *(SD)*	2.05 *(0.3)*	1.87 *(0.97)*	2.4 *(0.45)*	2.3 *(0.46)*	12.087	.001	1.616	.206	0.139	.71
NEO-FFI conscientiousness[a]	M *(SD)*	2.3 *(0.24)*	2.12 *(0.34)*	2.68 *(0.46)*	2.44 *(0.5)*	15.126	<.001	6.058	.015	0.09	.765
Rating neutral pictures	M *(SD)*	1.36 *(0.70)*	1.39 *(0.75)*	1.13 *(0.39)*	1.03 *(0.83)*	8.457	.004	0.087	.768	0.463	.497
Rating panic pictures	M *(SD)*	2.62 *(0.98)*	2.59 *(0.97)*	1.34 *(0.52)*	1.25 *(0.48)*	86.306	<.001	0.153	.696	0.042	.838

Abbreviations: PD/AG, patients with panic disorder and agoraphobia; HC, healthy controls; T: T/T & A/T carrier; *M*, mean; *SD*, standard deviation; SIGH-A, Hamilton Anxiety Rating Scale; BSI, Brief Symptom Inventory, BDI II, Becks Depression Inventory-II, ASI, Anxiety Sensitivity Index, MI, Mobility Inventory; NEO-FFI, Revised NEO Personality Inventory.

[a] Due to study design changes between the both funding periods and missing data, NEO-FFI data was only available in 50 patients (40 TT, AT carriers and 10 A/A carriers).

receptor (*NPSR1*) A/T variant (rs324981) were conducted at the Department of Psychiatry, Psychosomatics and Psychotherapy, at the University Hospital of Würzburg, according to published protocols (Domschke et al., 2012, 2011). Genotypes were determined by investigators blinded for phenotypes and independently by two investigators. In both groups, *NPSR1* genotype distribution (PD/AG: AA = =31, 15.7%; AT = 63, 31.8%: TT = =27, 13.6%, p (Exact) = 0.72; HC: AA = 19, 9.6%; AT = 39, 19.7%: TT = 19, 9.6%, p (Exact) = 1.0) did not significantly differ from the expected numbers calculated according to the Hardy–Weinberg equilibrium, using the program DeFinetti provided as an online source (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl; Wienker TF and Strom TM).

2.3. Self-report data and statistical analyses

To assess group differences between patients with PD/AG and healthy controls, as well as differences between the genotype variations, self-report data and clinical data were analyzed with IBM SPSS Statistics 19. To compare patients and HC by demographical data including sex, handedness, smoking status and years of education, χ^2-tests were used. Variances in clinical questionnaires and tests between the PD/AG group and HC and between the different genotype groups were examined with a 2 × 2 ANOVA and post-hoc Bonferroni-corrected t-tests. The picture ratings were analyzed in an analogous manner.

We carried out a post hoc statistical power analysis to calculate the achieved power to detect main or interaction effects using G* Power 3.1.9.4 (Heinrich-Heine-Universität, Düsseldorf, Germany; Faul et al., 2007). Power analysis indicated an 88% chance of detecting a small effect size (f = 0.25) between the four groups as significant at the 5% level (two tailed) and n = 198.

2.4. fMRI: experimental design, data acquisition and analyses

Both groups performed the Westphal-Paradigm (Wittmann et al., 2014, 2011), which is composed of 48 agoraphobia-related (e.g., scenes of subways, crowds) and 48 neutral pictures from the International Affective Picture System (Bradley and Lang, 1994). The pictures were presented randomly to produce reciprocal emotions and anxiety specific brain activation (supplemental material Fig. S3). Half of the pictures were cued by the words “panic” or “neutral” and the other half with a non-specific letter combination “DGHNTFJ”. Each picture was presented 2000 ms and each cue 250 ms. The stimuli were separated by the presentation of a fixation cross (variable period of 2–4 s) with the objective of minimizing eye movements. The duration of the inter-trial intervals varied between 2 and 6 s. The participants were instructed to pay attention to the picture content, to imagine being in the shown situation and to confirm each presentation of a picture with a button press. All pictures were rated related to agoraphobic anxiety after the fMRI scan.

The functional imaging of the MAC study was performed at four sites: Berlin (3-T General Electric Healthcare), Dresden (3-T Siemens Trio), Münster (3-T Philips Achieva) and Aachen (3-T Philips Achieva). In the second trial phase, the participating fMRI sites Berlin and Dresden measured with a 3-T Siemens Trio. A table with the sample sizes per scanner can be found in the supplement (Table S1). The variety of scanners was controlled by using corresponding dummy variables as covariates in the statistical analyses. Functional images were collected using an echoplanar imaging (EPI) pulse (repetition time (TR) = =2 s, echotime (TE) = 30 ms, matrix size = =64 × 64, voxel size = =3.6 × 3.6 × 3.8, flip angle = =90°) to reduce data loss and artifacts at all sites. 446 volumes were acquired with thirty slices positioned parallel to the anterior commissure–posterior commissure (AC–PC).

Statistical Parametric Mapping (SPM 8, http://www.fil.ion.ucl.ac.uk/spm) was used for the data analysis. All functional images were slice-time corrected, realigned to the individual mean EPI, spatially normalized to the standard EPI template and spatially smoothed with 8 mm full width at half-maximum during the preprocessing. On the first level, a single-subject statistic was conducted and two contrast images were computed and taken to the second level. For the anticipation phase the contrast: “panic cue minus neutral cue” and for the picture perception phase the contrast: “all panic pictures minus all neutral pictures“ were created. On the group level, for each of the two contrasts (anticipation and perception) separate full factorial design ANOVAs with the factors group (PD/AG vs. HC) and grouped *NPSR1* genotype (AT/TT vs. A/A) and the covariate site were used. We tested *NPSR1* genotype effects using an F-contrast comparing the risk allele carriers and non-risk allele carriers in PD/AG and HC. Furthermore, the diagnosis by genotype interaction was tested in order to assess differences in genotype effects between both groups. Significant results were followed up with appropriate Bonferroni-corrected t-tests. In an explorative analysis, a linear effect over both groups was tested and corrected for multiple comparisons using small volume correction. Specifically, we assumed that existence of the T risk allele would lead to higher activation in both groups and that this effect would be higher in patients than in controls using the contrast [2 1 -1 -2].

With regard to the a priori hypotheses, the amygdala and the inferior orbitofrontal cortex were defined as volumes of interest (VOI) in the anticipation and the perception phase. A small volume correction (SVC) was applied to the amygdala and iOFC VOIs, which was generated using the AAL- Atlas (Tzourio-Mazoyer et al., 2002) within the WFU Pick Atlas software toolbox (Maldjian et al., 2003) voxel-level threshold of $p_{\text{FWE-corrected}} < 0.05$. Outside these VOIs we applied a whole brain threshold of $p_{\text{FWE-uncorrected}} < 0.001$. Associations between the neural activation (using mean parameter estimates extracted from the VOIs) and ASI respectively NEO-FFI scores were computed for each of the four groups using Bonferroni-corrected Pearson's correlations within SPSS.

3. Results

3.1. Self-report data

The patient group differed significantly from healthy controls in all disorder-specific questionnaires and tests (see Table 1). There was a significant main effect of *NPSR1* genotype regarding in the ASI scores, with T allele carriers displaying higher scores than A/A homozygotes ($F_{1,198}$ = 4.17, p = .043). The genotype x group interaction showed a tendency towards significance ($F_{1,198}$ = 3.50, p = .063). The PD/AG group showed significantly higher scores than the HC group in the neuroticism subscale of the NEO-FFI ($F_{1,127}$= = 19.005, p = <.001). There was a main effect of *NPSR1* regarding the conscientiousness subscale ($F_{1,127}$= = 6.058, p = .015), with T allele carriers displaying higher means than A/A homozygotes. A significant genotype x group interaction was found regarding the neuroticism scale of the NEO-FFI ($F_{1,127}$ = 5.111, p = .026). This interaction showed that PD/AG patients with one or two T alleles had higher neuroticism scores than PD/AG patients homozygous for the A allele. In contrast, HC with the A/A genotype had higher scores on that scale than healthy risk allele carriers. The anxiety rating of the agoraphobic-specific and neutral pictures revealed a significant group and picture difference. Over all groups, the panic pictures were rated as more anxiety-inducing than the neutral pictures. However, the patients evaluated the agoraphobic-specific and the neutral pictures as more alarming than the HC (panic pictures: $F_{1,198}$ = 86.306, p < .001, neutral pictures: $F_{1,198}$ = 8.457, p = .004). No influence of *NPSR1* genotype on these ratings was detected.

3.2. fMRI

3.2.1. Anticipation phase

In the anticipation phase neither significant main effects nor a

Table 2
Brain activation in fMRI 2 × 3 Design Westphal-Paradigm. Brain activation during perception phase (agoraphobia-specific pictures vs. neutral pictures) depending on NPSR1 rs324981 genotype (T > A/A) in HC compared to PD/AG.

Contrast	ROI	Voxels	*x*	*y*	*z*	*t*	*p*FWE
Main effect diagnosis: PD/AG > HC							
	Amygdala bilateral						n.s.
	iOFC bilateral						n.s.
Main effect *NPSR1*: T > AA							
	Amygdala bilateral	47	27	2	−29	3.95	0.006[a]
	iOFC bilateral						n.s.
Linear Interaction: PD/AG > HC, T > AA							
	Amygdala bilateral						n.s.
	iOFC bilateral	100	−51	23	−14	3.48	0.054

Abbreviations: x, y, z, MINI-Coordinates; n.s., not significant; PD/AG, patients with panic disorder and agoraphobia; HC, healthy controls; iOFC, inferior orbitofrontal cortex.
[a] Bonferroni-corrected.

diagnosis by genotype interaction were observed in the a priori defined ROIs. In the exploratory whole brain analysis, we detected a main effect genotype in the medial superior frontal gyrus ($F = 18.29$). This area is part of the anterior or medial PFC (BA10). The whole brain results are reported in the supplement (Table S2).

3.2.2. Perception phase

During the perception of agoraphobic pictures, we observed a significant main effect of *NPSR1* genotype on the bilateral amygdala ($F = 15.65$, $x = 27$, $y = 2$, $z = -29$, $p_{FWE\ Amygdala} = = .006$;Table 2). Across groups, participants with two A alleles displayed a significantly reduced activation in the bilateral amygdala compared to T carriers ($T = 3.95$, $x = 27$, $y = 2$, $z = -29$, $p_{FWE\ Amygdala} = .006$, see Fig. 1). Areas in the left lingual gyrus and in the right amygdala survived the exploratory whole-brain correction (Table S1). The NEO-FFI trait neuroticism was trendwise negatively correlated with the amygdala activity ($r = -0.488$, $p = .068$) in healthy controls carrying A/A genotype. In an exploratory approach, we tested the assumed linear interaction in the ROIs with the highest activation in the PD/AG group with one or two risk alleles and the lowest activation in HC homozygous for the A allele. This effect showed a strong trend towards significance in the bilateral iOFC ($T = 3.54$, $x = -51$, $y = 23$, $z = -14$, $p_{FWE\ iOFC} = .054$).

Contrary to our expectations, no significant differences between patients and HC were found in the perception phase.

4. Discussion

This study aimed to explore the interaction between risk allele status of the *NPSR1*rs324981 variant and a disrupted cortico-limbic dysfunction in PD/AG. Using a disorder-specific task, the neural activation patterns of anticipation and perception of agoraphobia-specific stimuli were examined in patients with PD/AG and HC, as a function of *NPSR1* genotype. The main findings are a higher amygdala activation in risk allele carriers and a trendwise diagnosis x genotype interaction in the iOFC during the perception of agoraphobia-specific stimuli. Unlike initial expectations, no effects of genotype or diagnosis were obtained in the a priori defined ROIs of the fear network during the anticipation phase. Though, we detected a *NPSR1* genotype effect on the activation on a part of the medial PFC in the exploratory whole brain analyses.

As a first main result, during the perception of agoraphobia-specific pictures, participants with one or two risk alleles were observed to show increased bilateral amygdala activation, while A/A homozygotes displayed a reduced activation. The amygdala is an important interface

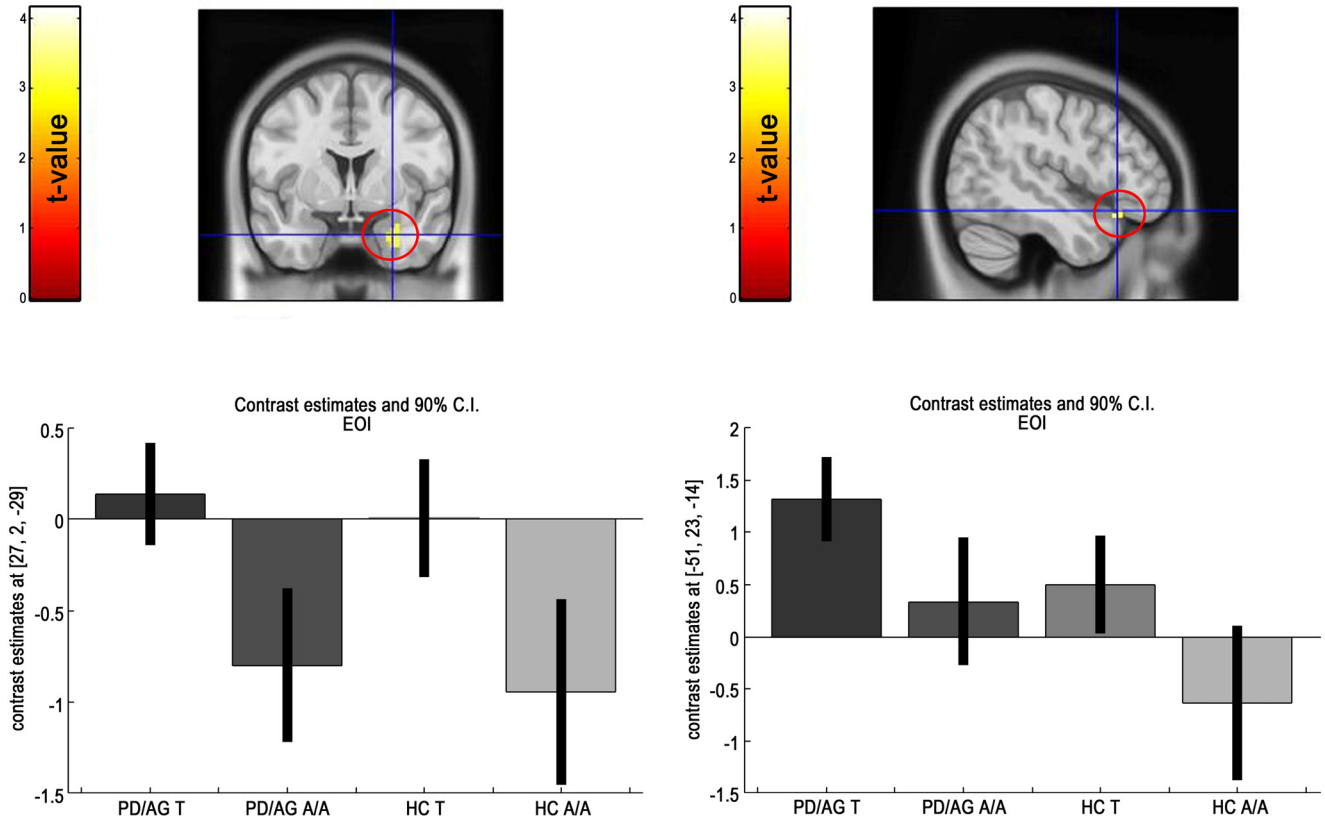

Fig. 1. BOLD responses during perception phase: (a) main effect of *NPSR1 rs324981* in the right amygdala (b) interaction: group x *NPSR1* genotype in the left iOFC. Abbreviations: PT: patients with panic disorder and agoraphobia; HC: healthy controls T: T/T and A/T carriers; A/A: A/A homozygotes; iOFC: inferior orbitofrontal cortex

in the neural fear circuit and is associated with the processing and transition of emotional information regarding its valence and affects related behavior (Janak and Tye, 2015; Ledoux, 2004; Morrison and Salzman, 2011). In line with the present results, the amygdala has been proposed to be significantly more involved in the perception than in the anticipation of fear related objects (Etkin and Wager, 2007; Gorman et al., 2000). Also, the *NPSR1* T allele has previously been linked to a stronger amygdala activity, partly to a stronger amygdala activity in a gene x environment interaction (Dannlowski et al., 2011; Streit et al., 2014). The reported results are thus in accordance with the current state of research and imply an association of the *NPSR1* risk allele on amygdala activation during the perception of agoraphobia-specific pictures. Furthermore, in HC homozygous for the A allele amygdala activation correlated trendwise negatively with the trait 'neuroticism'. This result points to a possibly protective, i.e. resilience-increasing function of the A/A genotype, as described by Domschke et al. (2011).

As a second main result, we detected a borderline significant diagnosis x *NPSR1* risk allele interaction during the perception phase in the iOFC. Patients with PD/AG showed a significantly higher activation than HC and within these groups, the activation decreased dependent on the genotype (T > A/A). We assumed, that the frontal activation would primarily be higher during the anticipation phase, not during the perception of agoraphobia-specific stimuli. It appears that the interaction of prefrontal and limbic areas could not be strictly be separated into anticipation and perception. Plag et al. (2018) reported similar findings with activation alterations in the amygdala, insula, ACC and iOFC in a subgroup of patients with PD/AG before and after SS(N)RI treatment during the perception phase of the Westphal Paradigm. Furthermore, the trend in the group x *NPSR1* genotype interaction is in line with the findings by Domschke et al. (2011), who showed a higher activation of the dlPFC and OFC during the processing of fearful faces in patients with at least one T allele. Such activations in prefrontal regions as the OFC have been linked to emotion regulation processes (Buhle et al., 2014; Kohn et al., 2014) and aforesaid activation patterns in the neural fear circuit could therefore be interpreted as attempts of a compensatory top-down control. However, in participants carrying the T risk allele, in particular patients with PD/AG, the down-regulation of the amygdala possibly might be insufficient or fail because of a disrupted connectivity between cortical and limbic areas. This latter hypothesis is supported by findings of a reduced effective fronto-limbic connectivity in healthy children and adolescents, with a higher risk of adolescent subjects with T/T genotype (Domschke et al., 2017). Furthermore, there is evidence for impaired emotion regulation in patients with PD or PD/AG associated with prefrontal activity (Dresler et al., 2013; Reinecke et al., 2015), also specifically in a panic disorder-specific paradigm, similar to the Westphal-Paradigm (Engel et al., 2016). Altogether, the scope of this finding is limited due to its exploratory nature and the less conservative correction for multiple comparisons.

The third main result is that, against our hypotheses, no main or interaction effects were observed in the anticipation phase in the a priori defined ROIs. However, as an exploratory result, we detected a main effect of genotype in the whole brain analysis in the medial superior frontal gyrus, which is part of the anterior or medial PFC (BA10). This region is associated with emotion regulation and emotion action control and down-regulation of the amygdala (Neubert et al., 2014; Tyborowska et al., 2016; Volman et al., 2011). More precisely, the medial PFC is associated with different neural activation patterns in patients with PD/AG respectively PD (Dresler et al., 2013; Feldker et al., 2016) and is linked to the *NPSR1* polymorphism (Guhn et al., 2015; Tupak et al., 2013).

Despite the accordance of the present findings with the hypotheses deduced from the available literature, several limitations have to be considered. Sample size, especially the subgroup of A/A homozygous HC ($n = 19$), were small to medium sized, therefore the degree to which these results can be generalized is limited. Also, the fact that the presently applied "Westphal-Paradigm" has to date uniquely been used in a patient sample recruited within two funding periods of a large German multi-site consortium does not allow for replication at this point, which limits the current candidate gene approach. Future studies could develop designs. Neither main results nor interaction effects were found during the anticipation phase. Expanded examination of the prefrontal areas might be helpful in further elucidating underlying mechanisms of this phase. More research is needed to examine the influence of the *NPSR1* polymorphism on prefrontal areas and top-down regulation. Opposite to the hypotheses, no group differences between patients with PD/AG and HC were detected in the examined ROIs. However, there was a group difference on the behavioral level in the rating of the agoraphobia-specific pictures. This inconsistency between neural and behavioral data could be due to the presentation duration of the stimuli. 2000 ms is, compared to other studies, a longer presentation duration, in which up- or down regulation processes could take place, which were not detected. Recent studies presented disorder-specific stimuli for a duration of 800 ms and showed stronger group main effects (Feldker et al., 2017; Heitmann et al., 2017). For future research, a reduction of the demonstration time could be useful. Also a connectivity analysis to examine the supposed top-down regulation process while considering the *NPSR1* risk allele status would be helpful to understand the interaction of the different parts of the neural fear circuit.

4.1. Conclusions

In sum, the present results for the first time indicate a link between *NPSR1*rs324981 genotype and neural processing of agoraphobia-related stimuli underlying PD/AG psychopathology. The reported results and previous research suggest that a fronto-limbic dysfunction might constitute an intermediate phenotype of PD/AG and thus a valid marker for disease risk. The understanding of the influence of genetic risk alleles on fear processing in patients with PD/AG and HC can be enhanced by our findings. It may help to form the basis of a more personalized treatment of PD/AG, in terms of personalized medicine.

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Supplementary materials

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