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ORIGINAL PAPER

Cognitive-behavioral therapy effects on alerting network activity and effective connectivity in panic disorder

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Abstract

Given the particular relevance of arousal and alerting in panic disorder (PD), here the alerting network was investigated (1) contrasting patients with PD and healthy controls, (2) as a function of anxiety sensitivity constituting a dimensional measure of panic-related anxiety, and (3) as a possible correlate of treatment response. Using functional magnetic resonance imaging (fMRI), 45 out-patients with PD ($f = 34$) and 51 matched healthy controls were investigated for brain activation patterns and effective connectivity (Dynamic Causal Modeling, DCM) while performing the Attention Network Task (ANT). Anxiety sensitivity was ascertained by the Anxiety Sensitivity Index (ASI). Forty patients and 48 controls were re-scanned after a 6 weeks cognitive-behavioral treatment (CBT) or an equivalent waiting time, respectively. In the alerting condition, patients showed decreased activation in fronto-parietal pathways including the middle frontal gyrus and the superior parietal lobule (MFG, SPL). In addition, ASI scores were negatively correlated with connectivity emerging from the SPL, the SFB and the LC and going to the MFG in patients but not in healthy controls. CBT resulted in an increase in middle frontal and parietal activation along with increased connectivity going from the MFG to the SPL. This change in connectivity was positively correlated with reduction in ASI scores. There were no changes in controls. The present findings point to a pathological disintegration of the MFG in a fronto-parietal pathway in the alerting network in PD which was observed to be reversible by a successful CBT intervention.

Keywords Anxiety · Arousal · Alerting system · Neuroimaging · Effective connectivity · Frontal cortex · Locus coeruleus · Fronto-coerulear connectivity

Introduction

Panic disorder (PD) is a frequent anxiety disorder with a 12 months prevalence of 1.8% and substantial limitations in daily functioning and quality of life [1]. Panic attacks

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are characterized by autonomic nervous system symptoms reflecting a state of increased arousal and alertness, i.e. heightened attention towards actual or perceived internal or external threat [2–5]. Anxiety sensitivity (AS) measuring the cognitive vulnerability to catastrophically interpret internal anxiety-related symptoms [6] is suggested as a predictor and dimensional intermediate phenotype of anxiety disorders, particularly PD [7–9].

The alerting system with its anatomical and functional connections influencing cognitive and behavioral dysfunctions in PD [10] seems pivotal for the achievement and maintenance of a state of vigilance toward an impending stimulus, and thus of particular relevance in PD [11]. Attentional processes including the alerting system are measurable by the Attention Network Task (ANT) capturing the effects of cues and targets within a single reaction time task [12]. Efficiency of the alerting system has been shown to be influenced by state anxiety [13, 14], and a CO_2 challenge test as a model of panic attacks led to increased activity of the alerting system accompanied by elevated anxiety [15]. The distinct neural activation pattern underlying the alerting system as elicited by the ANT comprises the locus coeruleus (LC), right lateralized fronto-parietal regions, and is mainly influenced by the norepinephrine system [16]. This is in line with the long-standing notion of alerting and panic-related anxiety states being accompanied by a strong noradrenergic bottom–up signal emerging from the LC, a nucleus in the dorsorostral pons integrating both external sensory and internal visceral data [17–19]. Fronto-parietal regions, in turn, exert a frontal top-down control counterbalancing increased parietal bottom-up signals of spatial or external stimuli [20]. Accordingly, in a neuroimaging study, healthy controls with PD risk factors, i.e. high anxiety sensitivity towards internal bodily stimuli [21] or a genetic risk factor [22], have displayed higher activation in the LC region and—possibly in a compensatory way—the right middle frontal gyrus (MFG) in the alerting condition of the ANT [23].

In the present imaging study, we investigated neural network function of the alerting system (1) contrasting patients with PD and healthy controls, (2) as a function of anxiety sensitivity constituting a dimensional measure of panic-related anxiety and (3) as a possibly dynamic correlate of treatment response. In this effort, we applied the ANT and analyzed brain activation and effective connectivity using Dynamic Causal Modeling (DCM) [24] during the alerting condition in patients and controls. After a 6 weeks course of a standardized cognitive-behavioral psychotherapeutic intervention (CBT) in patients as well as after a comparable waiting time in control subjects, respectively, all participants were re-examined.

It was hypothesized that (1) patients showed alterations predominantly within the fronto-parieto-coerulear interplay with enhanced reactivity in the LC along with impaired frontal control reflecting an excessive reactivity towards internal stimuli in patients. These alterations were (2) assumed to correlate with anxiety sensitivity. (3) The fronto-parieto-coerulear interplay was assumed to be malleable by CBT in terms of an increased recruitment of the MFG after treatment with stronger activation and connectivity. This recovery of alerting processing was expected to correlate with a reduction in anxiety sensitivity after treatment. In controls, no significant changes over time were expected.

Materials and methods

Subjects

Forty-five out-patients (Table 1) with a current diagnosis of PD with ($N=21$) or without comorbid agoraphobia were recruited. Diagnoses were ascertained by an experienced psychiatrist by means of a structured clinical interview (SCID-I) [25]. Comorbid axis I diagnoses (except bipolar disorder, psychotic disorders, current alcohol dependence, current abuse or dependence on benzodiazepines and other psychoactive substances) were allowed if PD was the primary diagnosis (depression: $N=21$; social anxiety disorder: $N=2$ specific phobias: $N=2$). Exclusion criteria were current or previous internal or neurological somatic illnesses, any somatic medication, pregnancy, use of illegal drugs including cannabis (assessed by urine toxicology), excessive alcohol (> 15 glasses of alcohol/week), and excessive nicotine (> 20 cigarettes/day) use. Twenty-three patients (51%) received stable psychiatric medication at baseline (SSRIs: $N=16$; SNRIs: $N=4$; NaSSA: $N=5$; TCA: $N=2$; pregabaline: $N=2$; quetiapine: $N=1$; zopiclone: $N=1$).

Additionally, 51 healthy control subjects were recruited matched for age, gender and education (Table 1). Exclusion criteria were presence of mental axis I disorders based on a structured clinical interview (Mini International Neuropsychiatric Interview, MINI) as administered by an experienced postgraduate psychologist, any psychiatric medication and the criteria applying to the patient sample.

Patients and controls were psychometrically characterized for PD using the German version of the Anxiety Sensitivity Index (ASI) [6, 26] as well as the Stat-Trait Anxiety Inventory [27]. Depressive symptoms were ascertained by means of the Beck Depression Inventory (BDI) [28, 29]. Patients and healthy volunteers were recruited at the Department of Psychiatry, Psychosomatics and Psychotherapy, University of Wuerzburg, Germany, within the Comprehensive Research Centre CRC-TRR-58 "Fear, Anxiety, Anxiety Disorders" funded by the German Research Foundation (DFG).

Table 1 Baseline sample description

Demographical data											
			Patients	Controls	Statistics	η^2					
N			45	51							
Sex, m/f			12/33	11/40	$X^2=0.3$						
Age			34.3 (9.9)	33.9 (9.0)	$T=0.2$	0.01					
Education MS/HS/C			9/22/14	5/21/25	$X^2=3.9$						
Medication *n*/y			22/23	51/0	$X^2=34.3$**						
BDI			17.3 (11.2)	5.2 (5.6)	$T=14.4$**	0.33					
Anxiety sensitivity and behavioral performance											
Baseline						Treatment effects					
	Patients	Controls	Statistics	η^2		Patients [T0/T1]		Controls [T0/T1]		F_{group}	F_{time}	$F_{groupXtime}$	$\eta^2_{groupXtime}$
ASI	28.5[a] (1.6)	15.7[b] (1.5)	$F=30.6$**	0.50		32.5[a] (1.7)	16.8[a] (1.5)	12.1[b] (1.5)	11.8[b] (1.3)	54.5**	52.1**	40.5**	0.30
acc	96.1[a] (0.8)	97.6[b] (0.7)	$F=0.5$	0.02		96.3[a] (0.9)	97.2[a] (2.2)	97.4[b] (0.7)	95.4[b] (1.8)	0.1	0.8	0.1	0.01
Rt	566[a] (13)	562[b] (12)	$F=2.0$	0.06		562[a] (14)	559[a] (13)	561[b] (11)	558[b] (10)	0.1	2.1	0.4	0.01
Alert	46.4[a] (4.6)	47.8[b] (4.1)	$F=0.6$	0.02		45[a] (5)	43[a] (5)	48[b] (4)	53[b] (4)	1.3	1.1	0.5	0.05
Orient	64.5[a] (5.4)	63.2[b] (4.9)	$F=0.8$	0.03		61[a] (6)	63[a] (5)	64[b] (5)	67[b] (5)	0.1	0.4	0.1	0.00
Exec	83.1[a] (4.8)	84.7[b] (4.4)	$F=2.3$	0.07		84[a] (5)	72[a] (5)	85[b] (5)	74[b] (4)	0.1	0.5	0.1	0.05

Education: *MS* middle school, *HS* high school, *C* college, *BDI* beck depression inventory, *ASI* anxiety sensitivity index, *ms* millisecond, *SD* standard deviation, *acc* accuracy in % correct trials, *Rt* Reaction time [ms], *alert* Alerting network score [ms], *Orient* Orienting network score [ms], *Exec* executive attention network score [ms]

[a]Corrected for sex and medication

[b]Corrected for sex

**$p<0.01$, FDR-corrected for multiple comparisons; η^2: partial squared eta, with $\eta^2<0.06$-small effect, $0.06<\eta^2<0.14$-medium effect, $\eta^2>0.14$ large effect

Study design and experimental paradigm

Patients and controls were psychometrically characterized and scanned using fMRI at baseline (T0). The experimental paradigm was the ANT (Electronic Supplementary Material; ESM I) [12, 23, 30, 31].

Patients subsequently underwent a therapeutic intervention (see below) and were re-scanned and psychometrically characterized within 1–2 weeks after treatment (T1). The total time between T0 and T1 was 6.17 ± 0.99 weeks. To control for potential time effects, healthy controls were also re-examined after an equivalent waiting time (6.27 ± 0.86 weeks, $t(86,2) = 0.6$, n.s.) (in days: patients: 43.80 ± 6.00 days, healthy controls: 42.66 ± 6.91 days). Five patients and three controls did not participate in the post-therapy measurement, so that the sample with complete pre/post data (T0/T1) consisted of 40 patients (30 females) and 48 controls (37 females).

Therapeutic intervention

Patients underwent a shortened, 6-week version of the exposure-based CBT as applied in the "Mechanisms of Action for CBT" (MAC) study within the BMBF network "Improving the Treatment of Panic Disorder" [32] in a regular outpatient clinical setting. This proof-of-principle treatment design consisted of six semi-standardized sessions covering psychoeducational information, exposure exercise sessions and intensive homework. In detail, the first three sessions were conducted within 2–3 weeks each lasting ~ 90 min covering psychoeducational information (for example, physiological, mental and behavioral components of anxiety, vicious circle of anxiety, vulnerability–stress model). A second three-session block within the subsequent 3–4 weeks comprised interoceptive exercises (for example, hyperventilation, straw breathing, running) for all patients. Those exposure exercise sessions were conducted approximately once a week and lasted 100–240 min per session. Furthermore, these sessions were followed by intensive homework adapted to the individual´s particular fears of situations. Within the last session, therapeutic gains and individual plans for continued exposure exercises, as well as relapse prevention were discussed [33]. All therapists were experienced graduate or clinical psychologists having participated in a training workshop on this manual. During the study, therapists were involved in weekly supervision to maintain therapy integrity. Medicated patients were only included in the study when medication was stable for at least 2 weeks. Pharmacological treatment remained unmodified during CBT. Benzodiazepine use was not allowed throughout the entire course of the study.

Data processing and statistical analysis

Behavioral performance

Behavioral performance was addressed in terms of accuracy, defined as the proportion of correct trials from all trials, and reaction time as the time from target presentation to motor response. Incorrect trials and trials with slow reactions (> 1000 ms) were excluded. Attention network scores for the three networks were calculated by the subtraction of reaction times of the network-specific conditions: alerting = $rt_{no\ cue} - rt_{double\ cue}$, orienting = $rt_{double\ cue} - rt_{spatial\ cue}$, executive attention = $rt_{incongruent\ target} - rt_{congruent\ target}$. Changes in performance [accuracy (acc), reaction time (rt), alerting (alert), orienting (orient), executive attention (execAtt)] were calculated as T1 subtracted from T0 (i.e. acc_{diff} = acc[T0] – acc[T1], rt_{diff} = rt[T0] – rt[T1], $alert_{diff}$ = alert[T0] – alert[T1], $orient_{diff}$ = orient[T0] – orient[T1], $execAtt_{diff}$ = execAtt[T0] – execAtt[T1]).

fMRI data

Processing of fMRI data was performed using SPM 12 (Wellcome Department of Imaging Neuroscience London, UK). In addition to the standard preprocessing procedure and the movement correction step of realignment, we determined frame-wise displacement (FD) scores for all subjects (Power et al. 2012) resulting in an average FD > 0.5 mm. Average movement was FD = 0.16 (0.14) with an average % data cut of 5.9% (5.1%). To statistically correct for motion artifacts on single-subject level, movement parameters from realignment were added into the model as regressors of no interest (for further details of preprocessing and statistical analyses see Electronic Supplementary Material, ESM I).

Effective connectivity

In addition to the investigation of brain activation, connectivity between identified network regions was determined using DCM 10 as implemented in the SPM 12 software.

The choice of subject-specific coordinates was guided by group activation maxima of the 'F-test effect of interest' from GLM analyses as hypothesized in the right superior parietal lobe (SPL), the right MFG and the LC (see results), but also in the right SFG. Region-specific time courses were extracted as the first eigenvariate of all activated voxels around subject-specific maxima in these regions that were (1) within a radius of 10 mm and (2) within the same brain gyrus. In our case, four-area DCMs were specified and subdivided into 7 model families with three model variants each.

Endogenous connectivity was defined for all possible connections; modulatory input, however, was varied with

regard to its predominant bottom-up and top-down control in terms of the following 7 model families covering in total 21 models (see table ESM II). In detail, across all models, the interaction between the MFG and parietal as well as LC areas was assumed, reflecting the 'physiological' alerting network as described in earlier studies. Model families varied with regard to the predominant influence within the alerting network, i.e. whether an alerting reaction is mainly induced by stimulation from the environment. Then, the model includes a strong spatial attention-associated parietal influence on the MFG (family 1). If the alerting reaction is more likely provoked by internal stimuli, the model includes strong LC-driven bottom-up processing (family 2). If bottom-up processing is predominant but similarly driven by internal and external stimulation, bottom-up processing is described by LC and SPL input (family 3). Likewise, family 4, 5, and 6 varied regarding top-down control, i.e. predominantly by the MFG, reflecting 'physiological' alerting (family 4), predominantly by the SFG, potentially reflecting a PD-specific compensatory recruitment of additional superior frontal regions (family 5), or similarly MFG and SFG top-down control (family 6). Family 7 defines a similarly strong bottom–up and top–down control processing. In every family, individual models varied regarding the included network regions (i.e., SPL and/or LC, MFG and/or SFG, etc.).

After identification of the model with the highest evidence using Bayesian Model selection, connectivity estimates of the winning model entered statistical analyses.

Statistical analyses

To address the influence of PD status on behavioral performance, brain activation and effective connectivity, both a factorial and a dimensional approach were applied. Regarding the first, we defined one-way ANOVA models with *group* as independent factor (patients vs. controls), behavioral parameters/brain activation maps/DCM estimates as dependent variable and sex and medication as nuisance variables. The following contrasts were defined in each ANOVA model: (1) *F*-tests effect of interest (EOI) reflecting the activated alerting network across all subjects and (2) group comparisons: patients > controls, and controls > patients.

The influence of the panic-related dimensional anxiety measure (i.e. ASI scores) on brain activation maps was analyzed using SPM. ANCOVA models were applied with *group* as independent factor (patients vs. controls), ASI score as covariate of interest, brain activation maps as dependent variable and sex and medication as nuisance variables. Defined contrasts were 'correlation with ASI: patients > controls' and 'correlation with ASI: controls > patients'. The influence of ASI scores on behavioral performance/DCM estimates was determined using SPSS via group-specific partial correlations correcting for sex in controls and sex and medication in patients, respectively. In a second step, correlation coefficients were compared with regard to a potential significant difference.

Correlates of treatment response were addressed applying a repeated measure ANOVA with between subject factor *group* (patients vs. controls), the within-subject factor *time* (T0 vs. T1), the nuisance variables sex and medication, and behavioral parameters/brain activation maps/DCM parameters of T0 and T1 as dependent variables.

The dimensional influence of ASI scores on brain activation before and after therapy was investigated using SPM by means of group-specific repeated measures ANCOVA models with *time* as independent factor, ASI score as covariate of interest, brain activation maps as dependent variable and sex and medication as nuisance variables. Defined contrasts were 'correlation with ASI: T0 > T1' and 'correlation with ASI: T1 > T0'. Regarding dimensional analyses on behavioral performance/effective connectivity, *group by time* interactions were addressed by group-specific partial correlations with the CBT-induced reduction of ASI_{diff} in terms of absolute values of reduced/changed ASI score [ASI(T0)-ASI(T1)] and changes in connectivity [end/mod_X_Y (T0)-end/mod_X_Y (T1)] as regressors of interest, controlling for sex in controls and sex and medication in patients, respectively. In a second step, correlation coefficients were compared regarding a potential significant difference.

In all analyses (baseline, treatment effect, behavioral performance, fMRI and effective connectivity), sex was used as nuisance variable igiven the significantly higher number of females in PD in general as well as in our sample (patients: $N_{males} = 12$, $N_{females} = 33$, $\chi^2 = 9.8$, $p = 0.002$; controls: $N_{males} = 11$, $N_{females} = 40$, $\chi^2 = 16.5$, $p = 0.000$). Results were regarded significant when passing a threshold of $p < 0.05$, FDR-corrected [34].

Results

At baseline (T0), patients scored significantly higher on the ASI, STAI and BDI instruments than controls (Table 1). In addition, ASI, BDI, STAI-S and STAI-T were positively correlated with each other in patients as well as in controls (ASI*BDI: $r_{patients} = 0.532$**, $r_{controls} = 0.639$**; ASI*STAI-T: $r_{patients} = 0.445$**, $r_{controls} = 0.327$*; ASI*STAI-S: $r_{patients} = 0.633$**, $r_{controls} = 0.468$*). BDI scores were not correlated with any study parameter (for details see ESM III).

Twenty-three patients (2 males) received stable psychopharmacotherapy, 22 patients (10 males) were unmedicated. There were no significant effects of medication on behavioral performance (see table ESM IVa). Medicated patients, however, showed stronger activation of a region in the MFG as compared to unmedicated patients (see

table ESM IVb). Effective connectivity estimates did not significantly differ between medicated and unmedicated patients. However, connectivity between the SFG and LC was more strongly negatively correlated to ASI scores in unmedicated patients as compared to medicated patients. In addition, connectivity from the MFG to the SPL more strongly negatively related to ASI scores in medicated as compared to unmedicated patients (see table ESM IVc). Therefore, medication was used as control variable in all statistical analyses.

Regarding further potential confounding variables, analyses were performed regarding the influence of age and 'time between MR measurements in days'. Reaction time increased significantly with age. This effect was more pronounced in healthy controls than in patients (reaction time: $r_{patients} = 0.239$, $r_{controls} = 0.471$*, $Z = 1.3$, n.s.). Likewise, endogenous connectivity emerging from the MFG and going to the rSPL showed anegative correlation with age in healthy controls but not in patients (T0end_rMFG_rSPL: $r_{patients} = 0.094$, $r_{controls} = -0.391$*, $Z = 2.3$, $p < 0.05$). The factor 'time between measurements in days' did not influence any parameter, neither behavioral parameters nor brain activation or DCM estimates.

Baseline analyses

Behavioral performance

On the behavioral level, patients did not differ from healthy control subjects in any parameter (Table 1).

In addition, group-specific partial correlations between ASI and behavioral parameters were not significantly different between groups (accuracy: $r_{patients} = 0.060^{a}$, $r_{controls} = 0.081^{b}$, $Z = 0.1$, n.s.; reaction time: $r_{patients} = -0.054^{a}$, $r_{controls} = -0.308^{b}$, $Z = 1.7$, n.s.; alerting: $r_{patients} = 0.010^{a}$, $r_{controls} = -0.072^{b}$, $Z = 0.4$, n.s.; orienting: $r_{patients} = 0.254^{a}$, $r_{controls} = -.100^{b}$, $Z = 1.6$, n.s.; executive attention: $r_{patients} = 0.201^{a}$, $r_{controls} = -0.168^{b}$, $Z = 1.7$, n.s.; [a]=corrected for sex and medication, [b]=corrected for sex).

Brain activation

Across all subjects ($N = 96$), we found that the right SPL, the right SFG, bilateral LC and the right MFG were significantly activated (see Table 2a).

Group comparisons revealed a significantly reduced frontal-parietal recruitment covering regions of the right MFG and the right SPL in patients (see Table 2a and Fig. 1a). On a dimensional level, no correlation between ASI scores and brain activation was discerned.

Table 2 Analysis of group differences at T0: (a) *univariate* ANOVA with *group* as independent factor (patients vs. controls; total $N = 96$) and brain activation maps as dependent variables and (b) 2×2 repeated measures ANOVA with *group* as between-subject factor (patients vs. controls; $N = 88$), *time* as within-subject factor (T0 vs. T1) and brain activation maps as dependent variables

Contrast	*x, y, z*	*Z*	Region
(a) Univariate ANOVA (baseline)			
Effect of interest	28, −54, 54	81.7	SPL
	42, −4, 60	23.2	SFG
	−12, −16, −4	25.6	LC
	10, −24, −10	16.7	LC
	46, 8, 28	21.5	MFG
T0: controls > patients	28, 26, 32	3.8	MFG
	24, 50, 2	3.4	MFG (area Fp1)
	36, 14, 58	3.3	MFG
	28, −50, 60	3.1	SPL
T0: patients > controls			N.s
(b) 2×2 ANOVA (treatment effect)			
Main effect of group	52, 40, 8	3.1	IFG, pars triangularis
Main effect of time	–	–	N.s
Group × time interaction	56, 22, 22	3.1	MFG
	60, −38, 46	3.2	SPL

All mentioned results were considered significant when passing a threshold of $p < 0.05$, FDR-corrected for multiple comparisons. All analyses included sex and medication as nuisance variables. Coordinates are reported in MNI (Montreal Neurological Institute) space. Anatomical localization has been performed using the Anatomy toolbox as implemented in the SPM software package [66]

ASI Anxiety Sensitivity Index, *MFG* middle frontal gyrus, *area Fp1* lateral frontopolar area 1, *n.s.* not significant

Effective connectivity

At T0, model comparison for the whole group favored model 2 of family 7. In this model, the SFG received input of both the SPL and the LC. Family exceedance probability was $xp = 0.74$. Group comparisons using BMS revealed that patients and controls displayed the same winning model (patients: $xp = 0.60$, controls: $xp = 0.48$), although the evidence in controls was weaker regarding the absolute value. Across all subjects, the winning model explained an average variance of 24.9% (± 17.8%) with an average connection strength of 0.61 (± 0.39). Quality parameters did not change between groups (variance: $M_{controls} = 21.4 \pm 13.2$, $M_{patients} = 29.8 \pm 22$, $T = 1.8$; connection strength: $M_{controls} = 0.59 \pm 0.38$, $M_{patients} = 0.64 \pm 0.19$, $T = 0.5$).

Connectivity strength did not differ between patients and controls. However, in patients, but not controls, higher ASI scores were correlated with weaker connectivity emerging from the SPL, the SFB and the LC heading towards the MFG. Likewise, bidirectional connectivity between the

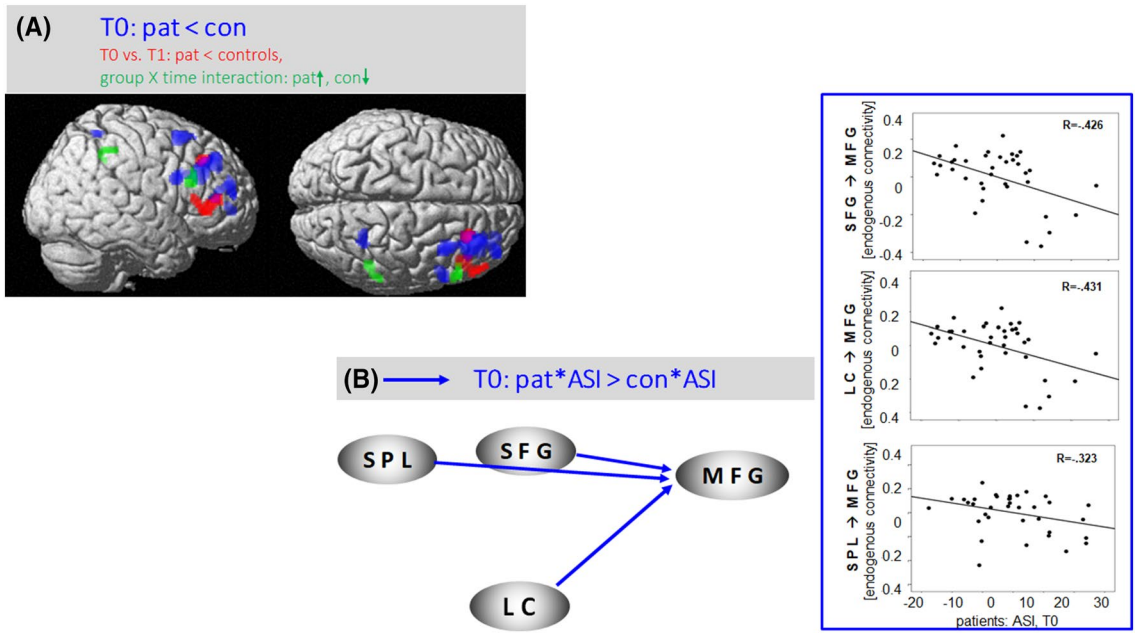

Fig. 1 Summary of significant findings at baseline: **a** shows brain activation patterns, rendered on a single subject brain surface. **b** Presents a sketch illustrating the network: circles represent the network regions, and arrows reflect network connections. Scatter plots represent the correlation between ASI scores and network connectivity. *LC* locus coeruleus, *MFG* middle frontal gyrus, *SFG* superior frontal gyrus, *SPL* superior parietal lobe

Table 3 Partial correlations between anxiety sensitivity and DCM estimates

	Baseline			Treatment effects		
	Patients [*r*]	Controls [*r*]	Zr_{pat} vs. r_{con}	Patients [*r*]	Controls [*r*]	Zr_{pat} vs. r_{con}
end_SPL_SFG	−0.064[a]	0.057[b]	0.5	0.219[a]	−0.265[b]	1.7
end_SPL_MFG	−0.323[a]*	0.103[b]	1.9*	0.173[a]	−0.199[b]	1.6
end_SFG_SPL	0.238[a]	0.092[b]	0.6	0.156[a]	−0.072[b]	1.0
end_SFG_MFG	−0.426[a] *	0.032[b]	2.1*	0.193[a]	−0.117[b]	1.3
end_SFG_LC	0.050[a]	−0.101[b]	0.6	0.036[a]	−0.332[b]	1.6
end_MFG_SPL	−0.003[a]	0.185[b]	0.8	0.362[a]*	−0.062[b]	1.9*
end_MFG_SFG	0.033[a]	−0.039[b]	0.1	0.120[a]	−0.084[b]	0.9
end_MFG_LC	0.043[a]	−0.061[b]	0.4	0.109[a]	−0.290[b]	1.6
end_LC_SFG	−.005[a]	−0.092[b]	0.41	0.112[a]	−0.254[b]	1–5
end_LC_MFG	−0.431[a]*	0.010[b]	2.0*	0.203[a]	−0.084[b]	1.2
mod_SPL_SFG	0.386[a]*	−0.081[b]	2.1*	−0.081[a]	0.108[b]	0.8
mod_SPL_MFG	0.181[a]	−0.245[b]	1.7	0.045[a]	0.067[b]	0.1
mod_SFG_SPL	0.381[a]*	0.126[b]	1.2	−0.131[a]	−098[b]	0.1
mod_SFG_LC	0.294[a]	−0.131[b]	1.7	0.200[a]	0.131[b]	0.3
mod_MFG_SPL	0.302[a]	0.130[b]	0.8	−0.072[a]	0.128[b]	0.8
mod_LC_SFG	0.280[a]	−0.180[b]	1.7	−0.035[a]	−0.045[b]	0.1

Anxiety sensitivity measured with Anxiety Sensitivity Index (*ASI*), *LC* locus coeruleus, *MFG* middle frontal gyrus, *SFG* superior frontal gyrus, *SPL* superior parietal lobe, *end* endogenous connectivity, *mod* modulatory input, *SD* standard deviation

[a]Corrected for sex and medication

[b]Corrected for sex

*$p < 0.05$, FDR-corrected for multiple comparisons

SFG and SPL was positively correlated with ASI in patients but not controls (see Table 3; Fig. 1b).

Analyses of treatment effects

Anxiety sensitivity decreased significantly with psychotherapy in patients, whereas there was no significant change in controls (see Table 1).

Behavioral performance

Regarding group by time interactions no significant effects of therapy were detected, neither on behavioral parameters (see Table 1) nor on correlations between differences in behavioral parameters and differences in ASI (accuracy: $r_{patients} = 0.360^{a}$, $r_{controls} = 0.127^{a}$, $Z = 1.2$, n.s.; reaction time: $r_{patients} = -0.028^{a}$, $r_{controls} = -0.263^{b}$, $Z = 1.1$, n.s.; alerting: $r_{patients} = -0.009^{a}$, $r_{controls} = 0.025^{b}$, $Z = 0.2$, n.s.; orienting: $r_{patients} = 0.280^{a}$, $r_{controls} = -0.103^{b}$, $Z = 1.9$, n.s.; executive attention: $r_{patients} = 0.337^{a}$, $r_{controls} = 0.166^{b}$, $Z = 0.9$, n.s.;[a]corrected for sex and medication, [b]corrected for sex).

Brain activation

In controls, a stronger activation of the right IFG was observed across both time points as compared to patients. In addition, a *group by time* interaction analysis revealed an increase of MFG and SPL activation with time in patients but not in controls (Table 2b and Fig. 2a). On the dimensional level, no significant correlations were observed.

Effective connectivity

Model comparison at T1 again favored model 2 of family 7, with an exceedance probability of $xp = 0.73$ (controls: $xp = 0.71$, patients: $xp = 0.48$). A *group by time* interaction analysis revealed an increase of MFG connectivity to the SPL in patients but not in controls ($F_{timeXgroup} = 5.3^{*}$ $\eta^2 = 0.06$; see Fig. 2b). In addition, reduction in ASI scores after treatment was positively correlated to connectivity emerging from the MFG and going to the SPL in patients but not in controls (see Table 3b and Fig. 2b).

Discussion

In this study, we investigated alerting processing in PD aiming to clarify whether alerting processing in patients with PD differed from that in healthy volunteers, and if so, whether it was related to anxiety sensitivity. In addition, it was analyzed whether altered alerting processing in PD could be modified or even normalized by a cognitive-behavioral psychotherapeutic intervention (CBT).

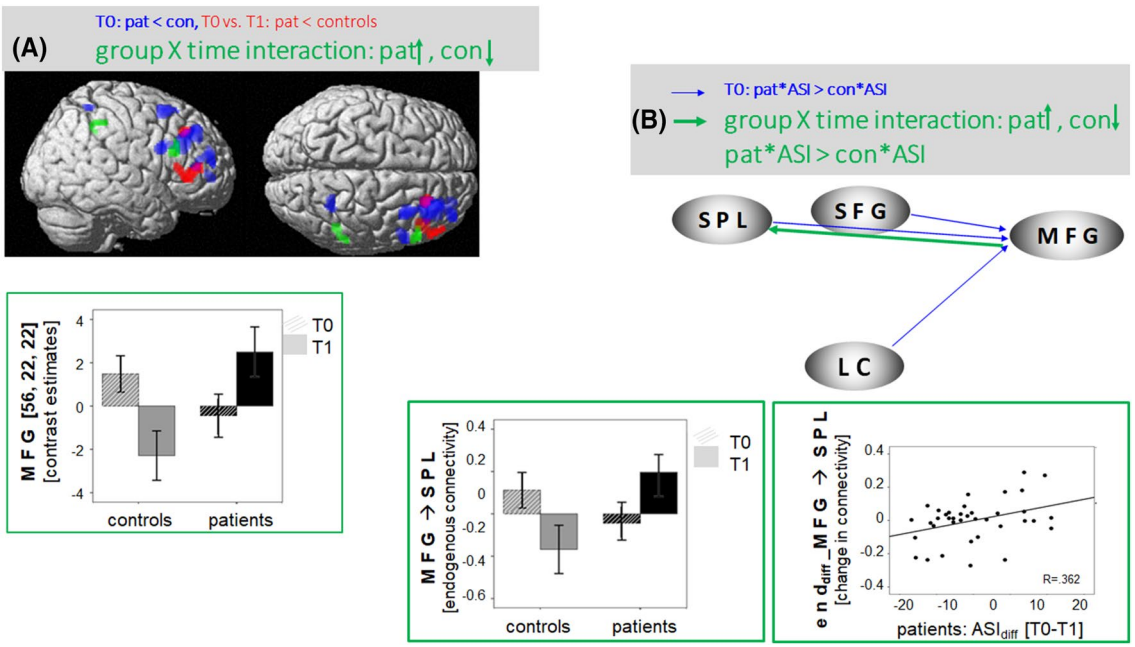

Fig. 2 Summary of significant findings regarding the effect of cognitive-behavioral psychotherapy (CBT): **a** shows brain activation patterns following a group X time interaction. **b** Presents arrows indicating the connections of significant group by time interactions. Scatterplot show the correlation between increase in connectivity strength and ASI reduction. Please note that ASI scores are the mean-corrected not absolute values of ASI scores. *LC* locus coeruleus, *MFG* middle frontal gyrus, *SFG* superior frontal gyrus, *SPL* superior parietal lobe

Altered alerting processing in PD/anxiety sensitivity

In line with earlier studies [12] and in high consensus with a recent publication regarding the localization of activation [35], both patients and control subjects activated the LC, the SPL, the MFG and the SFG. However, against our hypothesis of a hyperactive alerting system in PD, results revealed diminished activation within the alerting network in patients. In detail, at T0 patients showed reduced recruitment of the MFG and IFG. Within the alerting network, this set of regions is particularly involved in executive aspects of attentional processing. Thus, decreased activation as presently observed might be directly related to deficits in top-down control. This interpretation is supported by the present connectivity analyses showing that in patients connectivity emerging from the SFG, the SPL and the LC and aiming at the MFG decreased along with increasing anxiety sensitivity, hinting towards a patient-specific decoupling or disintegration of the MFG in the alerting network.

Fronto-parietal pathways in the alerting context predominantly cover the SPL and the MFG [36], reflecting (parietal) bottom–up and (frontal) top-down processing of stimuli emerging from the environment and being strong enough to catch attention. In PD patients, altered activity within fronto-parietal pathways has been reported in terms of reduced prefrontal [37, 38] and parietal volume [39, 40], reduced prefrontal [41, 42] and parietal blood perfusion [43, 44] as well as reduced brain activation at rest [45, 46] and while performing a task [47–49]. Against this background, the present finding of patients with PD showing a decreased recruitment of the MFG in the alerting condition as compared to healthy controls strongly supports the notion of a failure of the MFG, i.e. prefrontal areas, to exert a functional top-down control in PD.

Interestingly, patients showed an enhanced controlling influence of the SFG, SPL and LC on the MFG while performing the ANT. This was, furthermore, reflected by the SFG-driven winning model of effective connectivity analyses. This enhanced connectivity emerging from the SFG in PD might reflect the need for compensatory attention processing in terms of focusing on relevant while ignoring irrelevant stimuli to counteract an increased bottom-up signaling of particularly internal stimuli [16]. The LC has been suggested to constitute the primary center of arousal, alerting and panic response based on its key function in the noradrenergic system. Physiologically, the LC-driven noradrenergic system confers intrinsic alertness and functions as an 'attentional filter' to enable goal-relevant information processing by recruiting cortical regions associated with task performance [35, 50]. In states of anxiety, this noradrenergic attentional alerting system is particularly active [15]. Studies in anxiety disorders and specifically in PD revealed higher baseline noradrenaline secretion and increased reactivity to noradrenergic challenge [51, 52].

Effects of CBT on alerting processing in PD

After the six-weeks course of CBT, overall IFG and right MFG activation remained reduced in patients as compared to controls. However, within the patient group recruitment of inferior frontal and parietal regions increased after treatment. In addition, in patients but not in controls after treatment an increase in MFG connectivity to the SPL was observed, accompanied by a positive correlation of reduced ASI scores with increased connectivity emerging from the MFG and going to the SPL, hinting towards a recovery of top-down control as induced by CBT. Thus, successful psychotherapy as reflected by decreased anxiety sensitivity seemed to normalize altered bottom-up/top-down alerting processing by re-establishing a sufficient physiological top-down control.

While no imaging study so far has investigated the impact of CBT on neural alerting processing, two PET studies [53, 54], one SPECT study [55], and four fMRI studies [56–59] have reported modulation of brain physiology by CBT in PD focusing on either resting-state activity or on brain response during fear conditioning or agoraphobic symptom provocation. PET/SPECT studies revealed mostly increases in frontal brain regions such as the IFG and the medial prefrontal cortex conferred by CBT [60]. For instance, Sakai et al. observed a reduction of symptoms in 11 PD patients along with increased glucose utilization in the bilateral medial prefrontal cortices [54], which fits well with the present results of an increase in middle frontal activation after CBT as well as an increased MFG top-down control along with decreases in anxiety sensitivity. However, the findings by Prasko et al. [53] in 12 patients with PD are more inconsistent with decreased utilization in the right inferior temporal, superior and inferior frontal gyrus, but increased utilization in the left IFG in the CBT group ($N=6$). The latter finding is corroborated by the SPECT study, which discerned an increased regional cerebral blood flow (rCBF) in the left IFG after CBT in 14 patients with PD [55]. In fMRI studies applying fear conditioning paradigms [56, 58, 59] mostly decreased IFG activation, increased hippocampal activation, and decreased connectivity between the hippocampus and the IFG were observed after CBT treatment [60]. For instance, Kircher et al. reported an initially increased IFG activation, which normalized, i.e. decreased after CBT along with a significant reduction of agoraphobic symptoms in 42 patients with PD [56]. Given the different foci of these studies, with fear conditioning paradigms relating IFG activation to increased threat expectancy or attention to threat normalizing after CBT rather than IFG at resting state or during an alerting condition, results are not directly comparable to the

present ones, but also point to a modulation of top-down processes by CBT.

Limitations

It could be argued that the scanning environment is a phobic cue per se. However, in the present study no patient aborted the fMRI measurement and only two patients initially recruited for the study refused to undergo fMRI scanning. This is in line with a previous fMRI study in PD/A patients, who—while showing significantly elevated distress and moderately impaired data quality—did not drop-out more frequently than controls [61]. Thus, while in general large-scale fMRI studies in PD/AG patients are feasible, it has to be acknowledged that the MRI setting may enhance stress reactions. Along these lines, it has to be noted that the presently observed effects could be due to the fact that PD subjects might per se be more aroused in the scanner environment and treatment effects might thus be a consequence of habituation due to the repetition of the scanning rather than treatment itself. However, since behavioral performance, i.e. accuracy, reaction time, alerting, orienting and executive attention, did not differ between patients and healthy controls, this aspect does not seem to constitute a major confounding factor. Patients were partly medicated with mostly SSRIs/SNRIs, which might have influenced the present results in terms of a treatment x disease interaction effect at baseline, since e.g. chronic SSRI administration has been shown to alter prefrontal and paralimbic responses in anxiety disorders [62] and to decrease firing rate of LC noradrenergic neurons [63]. Although we statistically controlled for medication, this caveat also applies to the observed effects of CBT, although patients were stable on pharmacotherapy for at least 2 weeks before inclusion into the study and pharmacological treatment remained unmodified during CBT. However, stability for 2 weeks might still have been too short to conclusively rule out confounding effects of antidepressant medication, particularly since the average length of time participants were on medication was not accounted for and the clinical effect of antidepressants is expected to manifest not earlier than after 2 weeks. Clinically, given partial comorbidity with depression and other anxiety disorders, the present result cannot exclusively be attributed to PD and warrant replication in a pure PD sample and extension to other anxiety/affective disorders.

Conclusion

In sum, the present findings point to a pathological disintegration of the MFG in the alerting network in PD mirroring an insufficient top-down control by the MFG, which seemed to be partly reversible by a cognitive-behavioral psychotherapeutic intervention. These findings contribute to a deeper insight into risk factors and treatment mechanisms of PD relating to the alerting system and—in combination with machine-learning approaches predicting treatment response at a single-subject level [64]—might allow for more targeted, i.e. personalized and thereby more effective preventive and therapeutic interventions [65].

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interests.

Informed consent Written informed consent was obtained from all participants. The study was approved by the local ethics committee at Wuerzburg University, Germany, and carried out in accordance with the declaration of Helsinki.

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