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Experience of negative emotions in Parkinson's disease: An fMRI investigation

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Abstract

Objective—Amygdala abnormalities have been discussed as a possible mechanism underlying reduced reactivity to negative stimuli in Parkinson's disease (PD).

Methods—The present investigation used functional magnetic resonance imaging (fMRI) in order to test this hypothesis. We compared brain activation of 17 nondepressed and nondemented PD patients with 22 healthy controls during the elicitation of negative affective states. The patients suffered from moderate motor symptoms for an average of 75 months and had stopped their antiparkinson medication 10–12 h prior to the fMRI testing. All participants were shown images which depicted disgusting, fear-relevant and neutral contents and they answered self-report scales for the assessment of disgust proneness and trait anxiety.

Results—Both groups did not differ from each other in affective state and trait ratings. In line with the self-report, the fMRI data showed similar activation (including the amygdala) in both groups during disgust and fear elicitation.

Conclusion—This fMRI investigation found no indication of diminished disgust and fear experience in PD. Significance: Previously reported affective processing deficits in PD might be due to insufficiently controlled confounding variables (medication, depression, cognitive impairment).

Keywords

Parkinson's disease; Disgust; Anxiety; Experience; fMRI

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease related to progressive degeneration of nigrostriatal dopaminergic pathways. While motor problems such as tremor, rigidity, and bradykinesia are key symptoms of this syndrome, impairments in emotional functioning additionally have been reported (for a review see Peron et al. [1]).

A variety of tests have been applied to analyze PD-related difficulties in affective processing. There are numerous studies on facial emotion recognition in PD. Surprisingly these studies produced very heterogeneous outcomes. Whereas some authors reported

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general or at least emotion-specific deficits, others observed no problems at all (for a review see Gray et al. [2]).

Other investigations focused on the experience of emotions, which were elicited by affective scenes. The findings of those studies which combined self-report with electro-cortical and startle measures were also mixed, but rather pointed to a diminished experience of aversive feelings in PD patients [3-6].

Dietz et al. [4] conducted an event-related potential (ERP) study and presented the participants with (un) pleasant and neutral images. The authors focused on the late positive potential (LPP), which is a reliable electrophysiological index of emotional perception that originates in visual cortex regions. The LPP amplitude increases with the experienced intensity of the affective stimulus. Therefore, the LPP is considered an indicator of motivated attention, in which survival-relevant stimuli draw automatic attention in order to facilitate perceptual processing [7]. The results showed that PD patients' LPP amplitude for unpleasant pictures did not differ from the neutral condition and was smaller than those of control participants. This effect was interpreted as reduced LPP modulation to aversive stimuli in the clinical group. However, patients and controls did not differ in their valence and arousal ratings for the pictures.

A discrepancy between ERP findings and explicit ratings for affective pictures had also been observed by Wieser et al. [6]. PD patients experienced arousing pictures as less intense than healthy controls, although they had displayed comparable ERP waveforms.

In experiments with the startle paradigm, the participants are presented with a sudden loud noise while looking at affective scenes (pleasant, unpleasant, and neutral). The elicited emotional state influences the strength of the startle reflex. Aversive emotional states have been shown to potentiate this reflex, whereas appetitive emotional states are inhibitors. Bowers et al. [3] reported that relative to healthy controls the startle reflex amplitude was selectively reduced in PD patients when presented with aversive pictures. As the startle reflex is mediated by the amygdala, the authors speculated that PD patients show reduced amygdala activation during the processing of threatening information.

Amygdala abnormalities are often discussed as a possible mechanism underlying PD-related emotional dysfunctions (e.g., Tessitore et al. [8]). Further, it has been proposed that frontal brain regions (e.g., orbitofrontal cortex (OFC)) show activation changes due to degeneration-based changes of striatal input. These hypotheses can be directly tested via functional magnetic resonance imaging (fMRI). To the best of our knowledge this is the first neuroimaging study to investigate neuronal and subjective responses to affective scenes in PD. We tested nondepressed, and nondemented patients, who had discontinued their Parkinson medication for 10–12 h prior to experiment. The patients were compared with healthy controls during emotion elicitation. All participants were shown images which depicted disgusting, fear-relevant and neutral contents. They were asked to rate the intensity of experienced emotions and to answer questionnaires for the assessment of affective traits (disgust proneness and trait anxiety). We expected that PD patients would show reduced activation of the amygdala, basal ganglia and prefrontal regions (e.g., OFC) during the

viewing of aversive scenes and that they would rate the pictures as less intense than the control group.

2. Methods

2.1. Participants

Seventeen PD patients (8 women, 9 men) and 22 healthy controls (11 women, 11 men) participated in this study. All patients had been diagnosed with idiopathic PD by neurologists of the University Hospital in Graz (Austria).

The clinical and the control groups did not differ in mean age (M_{PD} = 55.2 years (9.4)), M_{CO} = 51.8 years (9.8), $t(37) = 1.12$ ($p = 0.272$), years of education (M_{PD} = 13.4 years (3.4)), M_{CO} = 13.9 (3.9), $t(37) = 0.42$ ($p = 0.679$), and did not show signs of cognitive impairment as assessed by the Test for Early Detection of Dementia (M_{PD} = 46.2 (1.9); M_{CO} = 44.6 (3.1), $t(38) = 1.88$, $p = 0.068$). The scores of this scale [9] range between 0 and 50; a score below 35 indicates a tentative dementia diagnosis. The scores on the rating scale by Hoehn and Yahr [10] were either 2.0 (14 patients) or 3.0 (3 patients). Eleven PD patients had right body side onset of motor symptoms and 6 had left-side onset. The patients had a sum score on the Unified Parkinson's Disease Rating Scale of $M = 36.1$ (SD = 13.0) ranging between 17 and 49 [11]. This implies mild to moderate motor impairment. The symptom duration was on average $M = 75.4$ months (SD = 43.7).

With one exception all patients were treated with L-Dopa and/or a dopamine agonist (pramipexole, ropinirole). Medication was discontinued overnight for 10–12 h prior to the fMRI experiment and later continued.

Written informed consent was obtained from each participant. The study was carried out in accordance with the Declaration of Helsinki and had been approved by the Ethics Committee of the Medical University of Graz.

2.2. Questionnaires

All participants answered the following trait scales: *The Questionnaire for the Assessment of Disgust Proneness* (QADP, [12]) measures disgust propensity and describes 37 situations, which have to be judged on 5-point scales with regard to the experienced disgust (0, 'not disgusting'; 4, 'very disgusting'). The QADP has five subscales (death, spoilage, poor hygiene, oral rejection, body secretions) for the assessment of domain-specific disgust proneness. The Cronbach's alpha for the subscales varies between 0.69 and 0.87 (total scale = 0.90). The trait scale of the *State-Trait Anxiety Inventory* (STAI; [13]) measures the frequency of anxious feelings. The questionnaire consists of 20 items which are answered on 4-point scales (1 = almost never, 4 = almost ever). The Cronbach's alpha of the scale is 0.88. *The Beck Depression Inventory* (BDI, [14] consists of 21 items rated on 4-point scales. A sum score of 18 or higher indicates clinical relevance. This questionnaire was applied since depressive tendencies influence affective processing.

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2.3. Stimuli and design

In this experiment the participants were asked to view 10 disgusting (e.g. dirty toilets, maggots), 10 fear-eliciting (attacks by humans and animals) and 10 neutral pictures (e.g. nature scenes, geometric figures) from a validated set [12] with the instruction to simply experience the elicited emotions. There was no specific task. The pictures were presented in blocks of 10 pictures each taken from the same affective category. Each picture was shown for 3 s. Thus, the block duration was 30 s. In total, 9 blocks were shown as each block was repeated twice. The block sequence was pseudorandomized. This fMRI methodology represents a mixed design. We had introduced the restriction that two categories of the same type were not allowed to follow each other. Between the blocks a fixation cross was shown for 5 s. Consequently, the total experiment lasted 310 s. The short duration was chosen in order to allow the patients to stay still during scanning. This was achieved; none of the patients had to be excluded from the sample due to movement artefacts.

Subsequent to the fMRI experiment, the participants gave affective ratings for the pictures. For each image they indicated the intensity of experienced disgust and fear (*Please indicate how intensely you experienced disgust/fear* 1 = very little, 9 = very intense).

2.4. fMRI: recording and analysis

Brain images were acquired using a 3 Tesla Siemens Tri-oTim (Siemens, Erlangen, Germany) with a 12-channel head coil. For the functional runs a total of 164 volumes were acquired by using an echo-planar imaging protocol (35 descending slices; slice thickness: 3 mm; TE = 30 ms; TR = 2300 ms; voxel size: 3.0 × 3.0 × 3.0 mm; FoV: 192; flip angle: 90°; slice orientation −25° tilted from the AC–PC line). To account for saturation effects 3 slices from the beginning of the time series were discarded.

All analyses were conducted using SPM12 (Wellcome Department of Cognitive Neurology, London). For compensating field inhomogeneity we applied a fieldmap during the pre-subtracted phase and magnitude step in SPM12. Afterwards images were motion-corrected via realignment and to account for acquisition timing subsequent we set a slice timing step. Individuals' t1 images were co-registered to the functional mean image and finally segmented into gray matter (GM) and white matter (WM). To create a study-specific template and to increase inter-subject alignment a 'Fast Diffeomorphic Registration Algorithm' (DARTEL) was executed with GM and WM images. Resulting images were further normalized to MNI-space (3 mm isotropic voxel), and smoothed with an 8 mm isotropic Gaussian kernel. Data were high pass filtered (128 s) and temporal sphericity was controlled by an AR(1) process with consecutive pre-whitening of the data.

In the first level analysis we computed *t*-contrasts for different conditions (Fear > Neutral, Disgust > Neutral, Fear > Disgust and Disgust > Fear). For a comparison of patients and controls resulting images were afterwards submitted to two sample *t*-tests comparing voxel intensities. We conducted an exploratory whole brain analysis as well as a region of interest (ROI) analysis for the amygdala, insula, dorsolateral/ ventrolateral prefrontal cortex (DLPFC, VLPFC), and basal ganglia (caudate nucleus, putamen, pallidum). The uncorrected height threshold for the analyses was set to $p < 0.005$. Voxel–peaks are reported when *p*

corrected for family-wise error (FWE) <0.05 (small volume correction). The ROI masks were taken from the Harvard-Oxford Cortical and Subcortical Structural Atlas (Center for Morphometric Analysis, MGH-East, Boston/MA, USA) and from the Juelich histological atlas [15].

We tested the following hypotheses: Relative to controls:

(a) PD patients show lower amygdala activation in the Fear and Disgust condition.

(b) PD patients show lower prefrontal activation (OFC, DLPFC, DMPFC, and VLPFC) in the Fear and Disgust condition.

Additionally, we investigated whether PD patients show generally lower activation in basal ganglia regions (putamen, pallidum, caudate nucleus) as these are the first targets of neurodegeneration.

3. Results

Self-reports

The two groups did not differ in disgust proneness, trait anxiety and depression (Table 1). The affective ratings showed that the intended emotions were elicited with sufficient intensity and specificity. In both groups, the target emotion always received higher intensity ratings than the non-target emotion (all p's < 0.001). The clinical and the control group did not differ in their affective ratings, when correcting for multiple comparisons (Bonferroni corrected significance cutoff; see Table 1).

fMRI

During the viewing of disgusting images (contrast: Disgust > Neutral) the patients showed ROI activation in the amygdala and several prefrontal regions (OFC, DLPFC, VLPFC). The whole-brain analysis revealed activation of the middle occipital gyrus (MNI coordinates x, y, z: −21, −87, 12; t = 10.16, p(FWE) < 0.001, cluster size (number of voxels) = 770). The control group recruited the amygdala, putamen, and pallidum (ROIs), and the calcarine fissure (whole brain analysis; x, y, z: −6, −84, −3, t = 8.85, p(FWE) < 0.001, cluster size = 661) during disgust-elicitation. All ROI results are depicted in Table 2.

In the fear condition (Fear > Neutral) the controls activated the amygdala, whereas the patients displayed no statistically significant ROI activation (Fig. 1). For this contrast, the patients showed activation of the middle temporal gyrus (x, y, z: 48, −72, 3, t = 9.81, p(FWE) < 0.001, cluster size = 314) as revealed by the whole brain analysis.

The group comparison indicated one significant difference for Fear > Neutral. The controls showed stronger pallidum recruitment than the patients. The contrasts Disgust > Neutral as well as Fear > Disgust and Disgust > Fear indicated no statistically significant group differences, neither on the whole-brain level nor for the ROIs. (The control group had shown marginally stronger pallidum activation (p = 0.10) than controls for Disgust > Neutral).

4. Discussion

This fMRI investigation found no indication of diminished disgust and fear experience in patients suffering from moderate PD symptoms. The selected pictures had induced the target emotions with sufficient intensity and specificity in patients as well as in controls. Both groups did not differ in their affective ratings. Similar findings have been reported by Dietz et al. [16]. The participants of this study (PD patients and healthy controls) had been presented with affective pictures while changes of pupil size as an indicator of sympathetic arousal were recorded. Neither the subjective ratings of the images (valence, arousal) nor the pupillary responses differed between the groups. In the same vein, Vicente et al. [17] found that PD patients at different stages of the disease reported comparable emotional experience to film excerpts for the elicitation of happiness, anger, fear, sadness, and disgust as controls. Previous studies which had identified diminished responses to aversive visual stimuli in PD patients had also often observed higher apathy and/or depression scores compared to controls (e.g., Wieser et al. [6]). Thus, confounding effects of these variables cannot be excluded.

In line with the comparable ratings of patients and controls in the present study, the brain activation during the picture viewing did also not differ between patients and controls. The whole brain approach indicated enhanced visual cortex activation when the participants looked at affective relative to neutral pictures. This effect has been interpreted in the theoretical framework of ‘motivated attention’: more extensive visual system activation facilitates perceptual processing of survival-relevant information [7]. No group differences were observed.

The PD group displayed additional activation of the amygdala and several prefrontal regions (OFC, DLPFC, and VLPFC) in the disgust condition. This activation pattern has previously been described for healthy subjects (e.g., Schienle et al. [12]). The mentioned areas are involved in the assignment of affective value (amygdala, OFC) and are recruited during attempts of emotion regulation (DLPFC, VLPFC). The control group showed activation of the amygdala and basal ganglia regions (putamen, pallidum) for the contrast Disgust > Neutral. Striatum activation has repeatedly been identified during disgust processing (e.g. Calder et al. [18]).

The group contrasting for the Disgust condition revealed no significant effect for the selected ROIs. Thus, on the subjective level as well as on the neuronal level PD patients and controls did not differ from each other.

In the fear condition (contrast: Fear > Neutral) the control participants showed the expected amygdala activation, whereas no supra-threshold activation was detected in the clinical group. However, the group difference was statistically non-significant, which also was true for the emotion-specific contrasts Fear > Disgust and Disgust > Fear, respectively.

It would be interesting to conduct a follow-up study with our clinical sample in order to find out, whether deviations in amygdala responding will occur with increasing symptom duration and severity. The only group difference for the fear condition concerned greater pallidum activation in controls relative to patients. Previous research could not identify a

specific role of this brain region for fear processing. It is more likely that the lowered activation is related to reduced grey matter volume. The basal ganglia are one of the first targets of neurodegeneration in PD (e.g., Alexander, [19]). In a morphometric study with the same sample, we had detected reduced pallidum volume in the patients, whereas limbic structures such as the amygdala had not been affected [20]. As the patients of the present study had also shown marginally reduced pallidum activation relative to controls for the contrast Disgust > Neutral, this suggests that this effect is not tied to a specific emotion.

As a short-coming of our study we have to mention the small sample size. However, the homogeneity of the clinical sample is a clear asset. We analyzed data from nondepressed patients without cognitive impairment, who had discontinued their medication for the experiment. Previous inconsistent results on affective processing deficits in PD might be due to the fact that these possibly confounding variables were not sufficiently controlled. Our findings suggest that affective experience in PD with moderate symptom severity is not blunted even with longer disease duration.

In the future, more sophisticated and ecologically valid fMRI designs (e.g., Bellace et al. [21]) should be used with multisensory presentations (e.g. visual, acoustic) combined with the analysis of different processes such as identification, experience, and memory of affective stimuli in PD.

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HIGHLIGHTS

- First neuroimaging study on disgust and fear experiences in Parkinson's disease.
- Patients were nondemented, nondepressed and nonmedicated during the experiment.
- Despite long disease duration no indication of diminished brain activation and emotion experience.

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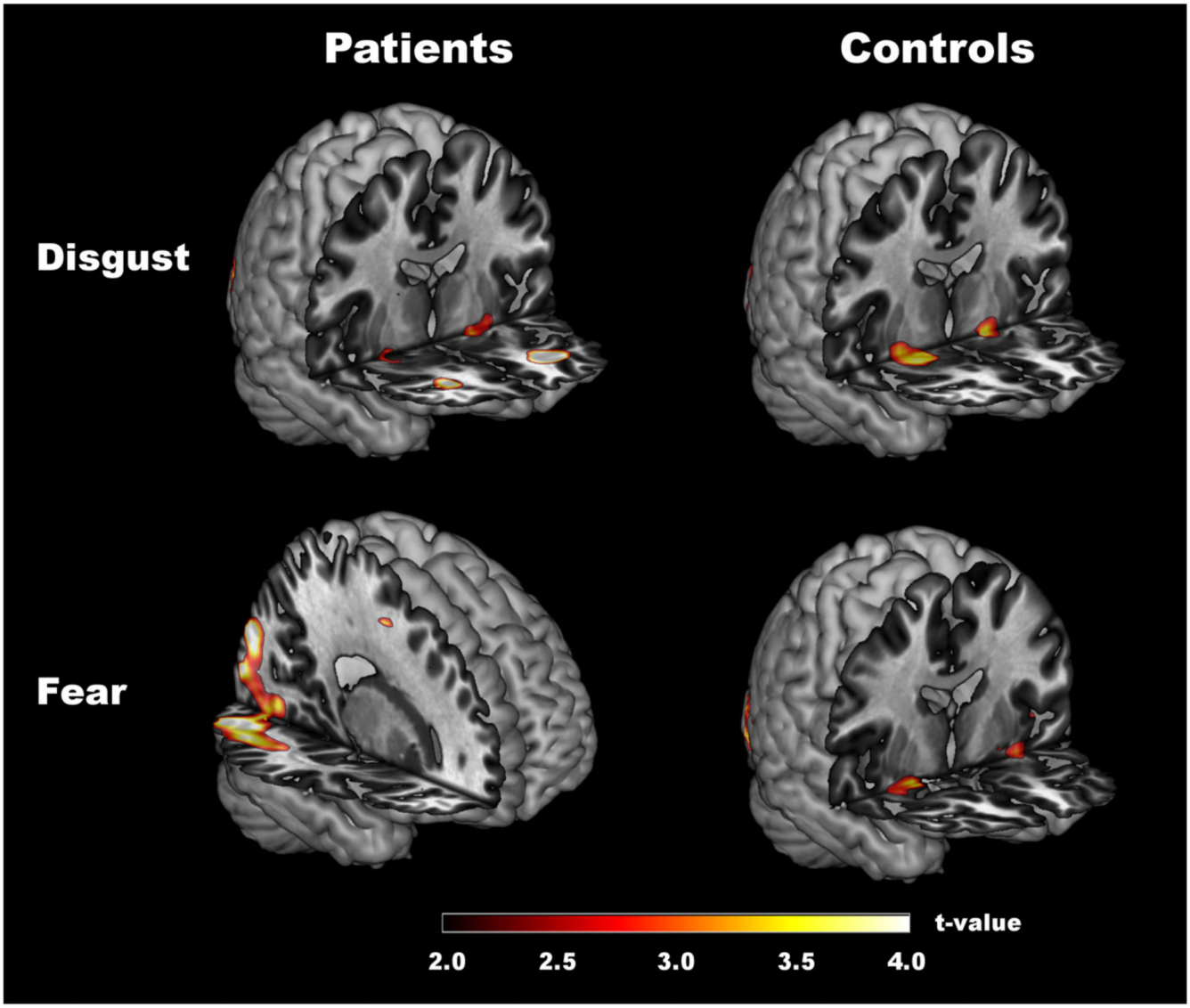

Fig. 1.

Brain activation of PD patients and controls while viewing disgusting and fear-eliciting pictures (contrasts: Disgust > Neutral, Fear > Neutral).

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Table 1

Self-report data on affective states and traits.

	PD	CG	*t*	*p*
Affective traits				
QADP	1.92 (0.44)	1.99 (0.53)	0.46	0.650
Death	1.14 (0.99)	0.94 (0.69)	0.74	0.460
Spoilage/decay	1.56 (0.62)	1.91 (0.60)	1.81	0.079
Body secretions	2.36 (0.54)	2.39 (0.80)	0.12	0.902
Poor hygiene	2.05 (0.58)	2.40 (0.62)	1.78	0.083
Oral rejection	1.91 (0.44)	1.99 (0.53)	0.64	0.528
BDI	9.35 (7.77)	6.55 (4.39)	1.43	0.162
STAI	39.24 (11.7)	32.73 (9.02)	1.96	0.057
Affective states (intensity ratings)				
Disgust pictures				
Disgust	5.90 (1.16)	5.56 (1.87)	0.63	0.531
Fear	2.82 (1.62)	2.26 (1.42)	1.14	0.262
Fear pictures				
Disgust	2.64 (1.33)	2.22 (1.27)	1.01	0.321
Fear	6.93 (1.32)	5.43 (2.39)	2.27	0.029
Neutral pictures				
Disgust	1.33 (0.43)	1.29 (0.54)	0.25	0.807
Fear	1.76 (1.22)	1.35 (0.78)	1.15	0.221

QADP: Questionnaire for the Assessment of Disgust Proneness; BDI: Beck Depression Inventory; STAI: State Trait Anxiety Inventory (trait scale).

Table 2

ROI activation during the viewing of affective scenes.

	hem.	*x*	*y*	*z*	*t*	*p*(FWE)	Cluster size
Patients: Disgust > Neutral							
Amygdala	L	−21	−6	−12	3.49	0.025	15
Amygdala	R	27	−6	−12	3.18	0.017	3
DLPFC	R	51	42	15	6.69	0.005	214
DMPFC	R	6	54	45	4.33	0.047	113
OFC	L	−24	36	−12	8.38	<0.001	176
OFC	R	27	33	−9	5.02	0.035	47
VLPFC	L	−24	36	−12	8.38	<0.001	166
VLPFC	R	51	39	15	8.09	<0.001	555
Patients: Fear>Neutral							
No significant ROI activation							
Controls: Disgust > Neutral							
Amygdala	L	−18	−6	−12	4.02	0.006	13
Amygdala	R	21	−3	−18	4.48	0.002	26
Pallidum	L	−27	−12	−6	3.01	0.047	10
Putamen	R	27	−6	−9	3.59	0.039	71
Controls: Fear > Neutral							
Amygdala	L	−27	−9	−12	3.07	0.036	5
Amygdala	R	21	−3	−15	3.21	0.029	14
Group comparison Controls > Patients: Fear > Neutral							
Pallidum	R	18	3	−3	4.26	0.002	32

hem. = hemisphere; MNI coordinates, *p*(FWE) corrected for family-wise error.