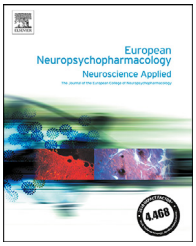
European Neuropsychopharmacology (2019) 29, 1258–1272



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Impact of dopamine and cognitive impairment on neural reactivity to facial emotion in Parkinson's disease

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Received 22 January 2019; received in revised form 4 September 2019; accepted 11 September 2019

KEYWORDS
Parkinson's disease;
fMRI;
Emotion;
Cognitive function;
Dopamine;
Facial recognition

Abstract
Emotional and cognitive impairments in Parkinson's disease (PD) are prevalent, hamper interpersonal relations and reduce quality of life. It is however unclear to what extent these domains interplay in PD-related deficits and how they are influenced by dopaminergic availability. This study examined the effect of cognitive impairment and dopaminergic medication on neural and behavioral mechanisms of facial emotion recognition in PD patients. PD patients on and off dopaminergic medication and matched healthy controls underwent an emotional face matching task during functional MRI. In addition, a comprehensive neuropsychological evaluation of cognitive function was conducted. Increased BOLD response to emotional faces was found in the visual cortex of PD patients relative to controls irrespective of cognitive function and medication status. Administration of dopaminergic medication in PD patients resulted in restored behavioral accuracy for emotional faces relative to controls and decreased retrosplenial cortex BOLD response to emotion relative to off-medication state. Furthermore, cognitive impairment in PD patients was associated with reduced behavioral accuracy for non-emotional stimuli and

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https://doi.org/10.1016/j.euroneuro.2019.09.003

predicted BOLD response to emotion in the anterior and posterior cingulate cortices, depending on medication status. Findings of aberrant visual and retrosplenial BOLD response to emotion are suggested to stem from altered attentional and/or emotion-driven modulation from subcortical and higher cortical regions. Our results indicate neural disruptions and behavioral deficits in emotion processing in PD patients that are dependent on dopaminergic availability and independent of cognitive function. Our findings highlight the importance of dopaminergic treatment not only for the motor symptoms but also the emotional disturbances in PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor dysfunction accompanied by a wide range of cognitive and psychiatric symptoms (Weintraub and Burn, 2011). Among the non-motor features, there is accumulating evidence for emotional-processing impairments. These disruptions in emotional processing were found in the subjective emotional experience, physiological arousal, production of facial expressions and recognition of facial and prosodic emotions (Péron et al., 2012). Despite past discrepancies in findings, recent studies indicated a robust deficit in PD patients in recognizing facial emotion across identification, discrimination and matching tasks (Argaud et al., 2018; Gray and Tickle-Degnen, 2010). These behavioral deficits affected all basic emotions but were suggested to be greater for negative emotions. Understanding the mechanisms of impairments in recognizing facial emotion is of clinical significance, as these were shown to hamper social interactions and reduce quality of life in PD patients (Pentland et al., 1987).

Emotion recognition requires intact cognitive abilities. These include working memory and executive functions for planning and manipulating information, visuospatial perception to identify facial features, and attention to process different sources of information at the same time. These cognitive domains are very commonly impaired in non-demented PD patients (Litvan et al., 2012). Thus, it is possible that facial emotion recognition deficits stem from a cognitive deficit. Behavioral studies confirmed the existence of specific emotional facial impairments in PD after controlling for the cognitive status of patients (Herrera et al., 2011; Pietschnig et al., 2016) or the cognitive demands of the task (Alonso-Recio et al., 2014a; Alonso-recio and Serrano, 2014b), although emotional deficits were also associated with the level of cognitive impairment (Assogna et al., 2010).

In addition to the behavioral deficits, imaging studies indicated neural disturbances in emotional face processing in PD patients, yet studies remain scarce. During matching of negative facial expressions, PD patients showed greater activity in the amygdala and the posterior fusiform gyrus compared to controls (Tessitore et al., 2002) in addition to decreased deactivation of the default mode network (Delaveau et al., 2010). During passive viewing of dynamic facial expressions, reduced neural activity was found in PD patients on medication compared to healthy controls, in diverse brain regions across emotion categories. These regions included the left ventrolateral prefrontal cortex that its decreased activity was related to the amount of dopamine transporter availability in the putamen (Lotze et al., 2009); several subcortical regions (Heller et al., 2018); and the inferior frontal, inferior parietal and supplementary motor cortices (Pohl et al., 2017). In contrast, viewing of static emotional faces did not reveal differences between PD patients off medication and controls (Schienle et al., 2015), except for some evidence for increased activity in PD patients in parietal regions (Wabnegger et al., 2015). We note that the abovementioned imaging studies did not include a comprehensive cognitive evaluation, thus cognitive abilities were not accounted for when assessing between-group neural differences. Hence, it remains to be determined to which extent neural disturbances found in PD patients during emotion processing are dependent on cognitive functions.

There is substantial support for the role of dopamine in emotion recognition (Salgado-Pineda et al., 2005), mainly by animal and human studies manipulating dopamine agonists and antagonists (Péron et al., 2012). The involvement of dopamine in emotion processing is expected since most of the brain regions implicated in emotion are targeted by the mesolimbic and mesocortical dopaminergic pathways. However, the effects of dopaminergic medication on emotion recognition in PD remain unclear with inconsistent behavioral findings (Argaud et al., 2018; Gray and Tickle-Degnen, 2010). The few imaging studies that compared PD patients on and off medication have suggested partial normalization of neural activity following dopaminergic medication (Delaveau et al., 2010; Fleury et al., 2014; Tessitore et al., 2002). In this context, it was proposed (Argaud et al., 2018) that in early disease stages when mesocorticolimbic pathways are relatively intact, dopaminergic medication results with an overdose effect on mesolimbic projections to regions such as the amygdala. In contrast, as the disease progresses, dopaminergic medication has a beneficial effect in compensating for dopaminergic depletion in the mesocorticolimbic pathways.

In the current study, we aimed to examine the effects of dopaminergic medication and cognitive impairment on facial emotion recognition in PD patients. To this end, moderate-to-advanced PD patients on and off dopaminergic medication and matched healthy controls underwent functional MRI (fMRI) scans. During the fMRI scans, subjects completed the emotional face matching task (Hariri et al., 2002). In addition, a comprehensive neuropsychological evaluation of cognitive function was conducted for all subjects. We hypothesized that PD patients would show behavioral impairments and neural disruptions during emotional processing that are independent of cognitive function and dependent on dopaminergic availability. Specifically,

Table 1 Demographic and clinical characteristics of PD patients and healthy control subjects.

Demographic and clinical variables	PD patients Mean ± SD (range) ($n = 25$)	Healthy controls Mean ± SD (range) ($n = 32$)	Statistics
Age, years	64.7 ± 8.3 (46-82)	63.3 ± 7.7 (46-83)	n.s.
Gender (male/female)	15/10	15/17	n.s.
Education, years	13.7 ± 2.6 (8-18)	14.9 ± 3.4 (11-25)	n.s.
Disease duration, years	11.9 ± 4.7 (4-26)	-	
H/Y stage ON medication	2 ± 0.5 (1-3)	-	
UPDRS-III ON medication	15.2 ± 7.5 (4-31)	-	
UPDRS-III OFF medication	30.4 ± 11.1 (8-64)	-	
LEDD	1328.2 ± 602.6 (699.5-2731)	-	

Abbreviations: H/Y, Hoehn and Yahr; LEDD, Levodopa equivalent daily dose; n.s., not significant.

administration of dopaminergic medication was expected to restore behavioral and neural emotional functioning in PD patients relative to healthy controls. Moreover, we aimed to test whether cognitive impairment has different effects on behavioral performance for emotional and non-emotional stimuli. Last, to further investigate cognition-emotion interactions in PD, we aimed to elucidate brain regions that their response to emotion is predicted by the cognitive function of patients.

2. Experimental procedures

2.1. Subjects

The sample was composed of 37 patients (16 women, age: 64.6 ± 7.5 years) with a diagnosis of idiopathic PD based on the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria for PD (Hughes et al., 1992). All patients were in the intermediate phase associated with motor complications (Deuschl et al., 2013). Inclusion criteria were: treatment with levodopa in monotherapy or in combination with a dopamine agonist, stable medication for the previous four weeks and Hoehn and Yahr stage below III while on dopaminergic medication. Exclusion criteria were: a history of psychotic symptoms, treatment with antipsychotics, treatment with deep brain stimulation, dementia or any concomitant disease or condition affecting the cognitive state. Twelve patients were not included in the final sample due to a change in diagnosis (one patient with multiple system atrophy), severe vascular lesions, atrophy or any single time point of head motion >3 mm or 3° during the MRI scan, which yielded a final sample of 25 patients (10 women, age: 64.7 ± 8.3 years). All patients were right-handed according to the Edinburgh Handedness Inventory. Patients were measured during two randomized sessions separated by 1-4 weeks: on their regular dopaminergic medication (ON condition, i.e. on levodopa in monotherapy or combined therapy with dopamine agonists) and without their dopaminergic medication (OFF condition). The OFF condition was gradually obtained: four days before patient visit, dopamine agonists were replaced by an equivalent dose of levodopa. The levodopa was withdrawn at least 12 h before the MRI session. The order of ON and OFF medication conditions was counterbalanced across patients. Motor function and disease severity were assessed using the Unified Parkinson's Disease Rating Scale motor examination (UPDRS-III) (Fahn and Elton, 1987) and the Hoehn and Yahr rating scale. The UPDRS-III was evaluated immediately before each MRI session. In addition, a matched group of 41 healthy controls (22 women, age: 63.9 ± 8.1 years) was recruited. Nine control subjects were not included in the final sample due to the presence of moderate neuropsychiatric symptoms, severe vascular lesions, atrophy or any single time point of head motion >3 mm or 3° during the MRI scan, which yielded a final sample of 32 control subjects (17 women, age: 63.3 ± 7.7 years). The main demographic and clinical characteristics of the subjects are summarized in Table 1. PD patients and control subjects were matched for age, gender and education. The study was approved by the Ethical Committee of the General University Hospital in Prague, Czech Republic. All participants provided written informed consent prior to inclusion in the study in compliance with the Declaration of Helsinki and all methods were performed in accordance with the relevant guidelines and regulations. Results from different imaging data sets of this sample were previously published (Dan et al., 2017).

2.2. Cognitive evaluation

PD patients and healthy controls underwent cognitive assessment by a neurologist experienced in movement disorders and a neuropsychologist during a preliminary visit held approximately two weeks before the first MRI session of each subject, prior to inclusion in the study. Cognitive evaluation of patients was conducted on their regular dopaminergic medication. A neuropsychological battery to measure cognitive function in PD was administered as recommended by Litvan et al. (2012) (level II- comprehensive assessment). In the comprehensive assessment, two neurophysiological tests were used for each of the following five domains: (1) attention and working memory: Trail Making Test, part A (Bezdicek et al., 2012) and Digit Span Backwards from the Wechsler Adult Intelligence Scale, third revision (WAIS-III) (Wechsler, 1997); (2) executive function: Tower of London (Michalec et al., 2014) and semantic verbal fluency (Nikolai et al., 2015); (3) language: Boston Naming Test, Czech version (Tombaugh and Hubley, 1997; Zemanová et al., 2016) and WAIS-III Similarities (Wechsler, 1997); (4) short term memory: Rey Auditory Verbal Learning Test, delayed recall (Bezdicek et al., 2014) and Brief Visuospatial Memory Test, revised, delayed recall (Benedict et al., 1996); (5) visuospatial function: CLOX (Royall et al., 1998) and Judgment of Line Orientation (Woodard et al., 1998). The score on each test was transformed into a z-score using the Rankit formula (Solomon and Sawilowsky, 2009). The z-scores for all ten tests were summarized for each subject to create a cognitive summary score, with a higher score indicating a better cognitive function. This cognitive summary score was further used in the analyses. Group-differences between PD patients and healthy controls in each cognitive task and in the cognitive summary score were evaluated by using two-sample two-tailed t tests. Associations between cognitive and motor functions (UPDRS-III, disease duration) were computed using Pearson's correlation.

2.3. MRI data acquisition

Magnetic resonance images were acquired with a 3T MR scanner (Magnetom Skyra, Siemens, Germany). Wakefulness was monitored during the whole scan using an MRI compatible camera. Functional images were acquired using T_2^*-weighted gradient-echo echo-planar imaging (GE-EPI) sequence with TR=2 s, TE=30 ms, image matrix=64 × 64, field of view=192 × 192 mm, flip angle=90°, resolution=3 × 3 × 3 mm, interslice gap=0.45 mm. Anatomical images were acquired using a sagittal T1-weighted MP-RAGE sequence with TR=2.2 s, TE=2.43 ms, resolution=1 × 1 × 1 mm; and a T2-weighted 2D sequence with TR=3.2 s, TE=9 ms, resolution=0.9 × 0.9 × 3 mm. T1-weighted images were acquired for coregistration and normalization of the functional images and T2-weighted images were acquired for diagnostic purpose to rule out significant atrophy or any other pathological brain changes.

2.4. Experimental paradigm: the emotional face matching task

Emotional function was studied using the emotional face matching task of Hariri et al. (2002). This block-design paradigm consisted of four blocks of an emotional face processing task interleaved with five blocks of a sensorimotor control task. During the emotion blocks, a target face was presented at the top of the screen and subjects were instructed to select one of two faces presented at the bottom which showed the same emotional expression as the target face (fearful or angry). During the sensorimotor blocks, a target ellipse was presented at the top of the screen and subjects were instructed to select one of two ellipses presented at the bottom which was at the same orientation as the target ellipse. Facial stimuli were derived from Ekman's Pictures of Facial Affect (POFA) (Ekman and Friesen, 2003). Each block consisted of six trials, each presented for 4 s, and started with an instruction ('match the emotion in the face' or 'match the orientation of the shape') presented for 2 s. Each emotion block had three trials of anger as the target emotion and three trials of fear as the target emotion. Each emotion trial consisted of faces of the same sex and the identity of all three faces was different. Each emotion block had an equal mix of the sex of the actors. Subjects responded by pressing one of two possible buttons with their right hand and subject accuracy and reaction time were collected for each trial. Note that this task was previously used in PD patients, however past analyses were restricted to the amygdala (Tessitore et al., 2002) or to deactivations (Delaveau et al., 2010), and did not consider cognitive function.

2.5. Behavioral performance analyses

Subject accuracy (% of correct responses) and reaction time were calculated separately for emotion (faces) and sensorimotor (shapes) blocks. Statistical analyses were conducted with SPSS v.23 (SPSS Inc., Chicago, IL). First, to test our hypothesis of behavioral impairment in emotional processing in PD patients and its relation to cognitive function and dopaminergic availability, the associations between cognitive function and behavioral processing of facial stimuli (accuracy and reaction time) were determined using Pearson's correlation, followed by three separate one-way ANOVA models implemented by a GLM (PD-OFF vs. controls; PD-ON vs. controls; PD-OFF vs. PD-ON) with performance for faces as the dependent variable and group or medication status as the independent variable. Cognitive function was not included as a covariate in the models since it was not associated with the dependent variable (see results).

Second, an exploratory analysis was performed to test whether cognitive impairment has different effects on behavioral performance for emotional and non-emotional stimuli. Differences in performance between PD patients and controls were tested by two-way mixed ANCOVA models implemented by a GLM with group (PD, control) as a between-subject factor, condition (faces, shapes) as a within-subject factor and the cognitive summary score as a covariate. Differences in performance between PD patients OFF and ON medication states were tested by a two-way repeated measures ANCOVA model implemented by a GLM with medication status (OFF, ON) and condition (faces, shapes) as within-subject factors and the cognitive summary score as a covariate. ANCOVA analyses were done as recommended by Schneider et al. (2015) for classification designs. Third, correlation analyses were done to test for an association between behavior and motor function. Finally, guided by results of the above analyses, a bootstrapped mediation analysis was conducted using the SPSS PROCESS macro (Hayes, 2013) to test whether cognitive function mediates the association between motor function and accuracy of matching non-emotional stimuli. Path coefficients were estimated using unstandardized regression coefficients of multiple regression analyses, and the significance of the indirect effect was tested using bootstrapped 95% confidence intervals, with 10,000 resamples.

2.6. Functional MRI data analysis

2.6.1. Between-group differences in BOLD response to emotional faces

Standard initial preprocessing of functional MRI data used SPM8 software. Functional images were spatially realigned, coregistered to T1 anatomical images, normalized to MNI space and resampled at an isotropic voxel size of 2 mm. The normalized images were smoothed with an isotropic 8 mm full-width-at-half-maximum Gaussian kernel. First level and second level analysis were conducted in SPM8. Single subject activation maps were computed with the general linear model (GLM) on the blood oxygenation level dependent (BOLD) contrast signals. One regressor for each condition (emotion and sensorimotor) was defined using a boxcar response function. For the emotion regressor, boxcar values were equal to 1.0 during face blocks and 0.0 during shape blocks. For the sensorimotor regressor, boxcar values were equal to 0.0 during face blocks and 1.0 during shape blocks. Each regressor was convolved with SPM's canonical hemodynamic response function combined with its time derivative (Supplemental Figure S1). The inclusion of the time derivative of the hemodynamic response function allows to control for variations between subjects and voxels in the delay of the hemodynamic function, i.e. its peak response. For each subject, contrast maps of the beta values of the convolved regressor for emotional stimuli subtracted by the beta values of the convolved regressor for the sensorimotor stimuli were obtained (i.e. the contrast "faces>shapes"). These contrast maps were then used for group comparisons. Supplemental Figure S2 shows examples of individual subjects' BOLD responses associated with the convolved regressors for the contrast faces>shapes. Three separate one-way ANCOVA models were implemented by a GLM to test for between-group differences (PD-OFF vs. controls; PD-ON vs. controls; PD-OFF vs. PD-ON – using a repeated measures model), all models including the cognitive summary scores as a covariate. A statistical threshold of uncorrected voxel-level $p<0.01$, FWE cluster-extent corrected at $p<0.05$ for multiple comparisons was used. MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/) (Rorden et al., 2007) was used for visualization of the results. To further examine the effect of cognitive function on neural differences in emotional processing, the results of the above ANCOVA models were compared to corresponding ANOVA models without the cognitive function covariate.

Table 2 Results of the neuropsychological evaluation of subjects as a function of cognitive domain.

Cognitive domain and tasks	PD patients Mean ± SD (range) ($N = 25$)	Healthy controls Mean ± SD (range) ($N = 32$)	Statistics
Attention and working memory			
Trail Making Test, part A (TMT-A)	53.7 ± 22.8 (31-130)	35.3 ± 9.1 (20-58)	$t = 3.73$, $p = 0.0007$
Digit Span Backwards (DS back)	6.1 ± 2.2 (2-11)	6.6 ± 2.3 (4-12)	n.s.
Executive function			
Tower of London (ToL)	22.7 ± 5.3 (11-31)	26.1 ± 4.1 (16-34)	$t = 2.59$, $p = 0.012$
Semantic verbal fluency: animals + clothes + shopping (COWAT)	61.7 ± 10.3 (37-81)	65.6 ± 11.9 (38-93)	$t = 2.64$, $p = 0.012$
Language			
Boston Naming Test, Czech version (BNT-60)	53.5 ± 3.8 (45-60)	54.4 ± 6.5 (27-60)	n.s.
Wechsler Adult Intelligence Scale, third revision, similarities (WAIS-III Sim)	24.8 ± 6.1 (6-32)	23.5 ± 5.8 (11-32)	n.s.
Short term memory			
Rey Auditory Verbal Learning Test, Delayed Recall (RAVLT-DR.)	7.0 ± 3.3 (0-14)	8.9 ± 2.4 (2-13)	$t = 2.34$, $p = 0.023$
Brief Visuospatial Memory Test, Revised, Delayed Recall (BVMT-R-DR..)	8.3 ± 2.9 (0-12)	10.2 ± 1.7 (5-12)	$t = 2.81$, $p = 0.007$
Visuospatial function			
Royall's CLOX (CLOX I)	12.6 ± 2.4 (5-15)	13.2 ± 1.1 (11-15)	n.s.
Judgment of Line Orientation (JoL)	24.4 ± 5.6 (3-30)	24.5 ± 3.9 (11-29)	n.s.
Cognitive summary score	50.7 ± 15.2 (19.0-78.2)	61.6 ± 13.1 (34.6-81.5)	$t = 2.87$, $p = 0.006$

The raw scores (before transformation into a z-score) are provided for all tests. n.s., not significant.

2.6.2. Associations between cognitive function and BOLD response to emotion in PD patients

Two separate regression models were used to test for neural clusters that their BOLD response to emotional faces was predicted by cognitive function in PD-OFF and PD-ON patients. The cognitive summary score was used as a measure of cognitive function. A whole-brain analysis was done using the contrast maps of the beta values of the emotional stimuli (faces) subtracted by the sensorimotor stimuli (shapes), i.e. the contrast "faces>shapes". A statistical threshold of uncorrected voxel-level $p<0.01$, FWE cluster-extent corrected at $p < 0.05$ for multiple comparisons was used. MRIcroGL (Rorden et al., 2007) was used for visualization of the results.

3. Results

3.1. Cognitive function of subjects

The results of the neuropsychological evaluation of PD patients and controls as a function of cognitive domain are summarized in Table 2. PD patients had significantly lower performance relative to controls in tests of visual attention, executive function and short-term memory. No significant between-group differences were noted for language or visuospatial function, implying intact functions in PD patients. The cognitive summary score comprising all cognitive domains differed significantly between the groups, with overall reduced cognitive function in PD patients [$t(55)=2.87$, $p = 0.006$]. Notably, a better cognitive function was associated with a better motor function (UPDRS-III scores) during OFF medication state [$r(23)=-0.42$, $p = 0.038$], but not associated with the disease duration.

3.2. Behavioral performance

The results of the behavioral performance of the task are summarized in Table 3. Due to a technical problem, behavioral data were missing for one patient and seven controls.

3.2.1. Reaction time

Reaction time for emotional facial stimuli was not associated with cognitive function and did not differ between the groups.

3.2.1.1. Effect of cognitive function. In the exploratory ANCOVA analysis, a main effect of condition was found across all groups, indicating smaller reaction times for shapes compared to faces, as expected [PD-OFF vs. control: $F(1,47)=152.88$, $p = 2.2 \cdot 10^{-16}$; PD-ON vs. control: $F(1,47)=172.86$, $p = 2.3 \cdot 10^{-17}$; PD-OFF vs. PD-ON: $F(1,23)=97.17$, $p = 10^{-9}$]. There were no main effects of cognitive function, group, group-by-condition interaction or condition-by-cognitive function interaction.

3.2.1.2. Association between reaction time and motor function. Reaction time was not associated with motor function (UPDRS-III) or with the disease duration.

3.2.2. Accuracy

3.2.2.1. Emotional faces. Accuracy of matching emotional facial stimuli was not associated with cognitive function of subjects [PD-OFF: $r(22)=0.05$, $p = 0.81$; PD-ON: $r(22)=0.03$, $p = 0.88$; controls: $r(23)=0.02$, $p = 0.92$]. Reduced accuracy for facial stimuli was found for PD patients OFF medication compared to healthy controls [$F(1,47)=4.69$, $p = 0.035$] and to ON medication state

Table 3 Subject accuracy (% of correct responses) and reaction time for emotional faces and sensorimotor stimuli (shapes).

	Healthy controls Mean ± SD ($N=25$)	PD-ON Mean ± SD ($N=24$)	PD-OFF Mean ± SD ($N=24$)	Statistics
Accuracy for faces (%)	79±13.2	74.82±12.91	69.96±15.92	OFF vs. ON: $F(1,23)=5.99$, $p=0.022$ OFF vs. control: $F(1,47)=4.69$, $p=0.035$
Accuracy for shapes (%)	89.46±16.9	84.58±20.7	86.11±15.96	n.s.
Reaction time for faces (sec)	2.44±0.3	2.54±0.37	2.55±0.32	n.s.
Reaction time for shapes (sec)	1.53±0.48	1.52±0.5	1.59±0.6	n.s.

n.s., not significant.

[$F(1,23)=5.99$, $p=0.022$]. No differences in accuracy for facial stimuli were found between PD patients ON medication and healthy controls.

3.2.2.2. Effect of cognitive function. In the exploratory ANCOVA analysis, a main effect of condition was found across all groups, indicating greater accuracy for shapes compared to faces, as expected [PD-OFF vs. control: $F(1,47)=19.20$, $p=6.6{\cdot}10^{-5}$; PD-ON vs. control: $F(1,47)=9.72$, $p=0.003$; PD-OFF vs. PD-ON: $F(1,23)=10.44$, $p=0.004$]. A significant effect of the cognitive function covariate on accuracy was found when comparing patients and controls [PD-OFF vs. control: $F(1,46)=4.82$, $p=0.033$; PD-ON vs. control: $F(1,46)=4.58$, $p=0.038$]. In addition, a marginal significant condition-by-cognition interaction was found [PD-OFF vs. control: $F(1,46)=3.85$, $p=0.056$; PD-ON vs. control: $F(1,46)=3.84$, $p=0.056$; PD-OFF vs. PD-ON: $F(1,22)=3.97$, $p=0.059$]. To further examine the interaction between the cognitive function covariate and the condition (faces, shapes), a regression analysis was done. Fig. 1 presents the relationship between the cognitive function and the different levels of the within-subject condition factor: shapes (top) and faces (bottom). The left panel shows the results for PD-OFF vs. controls, and the right panel for PD-ON vs. controls. A significant association was found between cognitive function and accuracy for shapes (Fig. 1A and B) whereas no association was found between cognitive function and accuracy for faces (Fig. 1C and D). There were no main effect of group or group-by-condition interaction.

3.2.2.3. Association between accuracy and motor function. Accuracy of matching non-emotional stimuli (shapes) was associated with motor function (UPDRS-III scores) in PD patients OFF medication [$r(22)=-0.54$, $p=0.005$] but not with the disease duration. No associations with motor function or disease duration were found for the emotional stimuli.

3.2.2.4. Mediation analysis. Following the direct effects of motor and cognitive function on accuracy of matching non-emotional stimuli in PD patients OFF medication, mediation analysis was performed to examine whether cognitive function mediates the effect of motor function on accuracy for non-emotional stimuli. This mediation model was based on previous findings suggesting that motor function is one of the predictors of cognitive impairment in PD (Schrag et al., 2017). The indirect effect was assessed using bootstrapped confidence intervals and was found not significant (standardized indirect effect=−0.14, SE(boot)=0.08, 95% CI=[−0.31, 0.008]), indicating no mediation (Supplemental Figure S3).

3.3. Between-group differences in BOLD response to emotional faces

Results for the contrast faces>shapes are presented for each group separately in Fig. 2A-C.

3.3.1. PD-OFF compared to healthy controls

PD patients OFF medication showed increased BOLD response to negative emotional faces compared to healthy controls in the bilateral calcarine sulci and lingual gyri, while controlling for cognitive function (cluster size: 3822 voxels; MNI: [18 −82 2]; $p=7.4{\cdot}10^{-7}$, FWE cluster corrected for multiple comparisons) (Fig. 2D). Note that these between-group differences were found to a greater extent in the right hemisphere. The same between-group differences were found without controlling for cognitive function (Supplemental Figure S4).

3.3.2. PD-ON compared to healthy controls

PD patients ON medication showed increased BOLD response to negative emotional faces compared to healthy controls in the bilateral calcarine sulci and lingual gyri, while controlling for cognitive function (cluster size: 1558 voxels; MNI: [18 −82 4]; $p=0.002$, FWE cluster corrected for multiple comparisons) (Fig. 2E). Note that these between-group differences were found to a greater extent in the right hemisphere. The same between-group differences were found without controlling for cognitive function (Supplemental Figure S4).

3.3.3. PD-ON compared to PD-OFF

PD patients OFF medication showed increased BOLD response to negative emotional faces compared to PD patients ON medication in the bilateral posterior cingulate/retrosplenial cortex (cluster size: 718 voxels; MNI: [−6 −46 14]; $p=0.040$, FWE cluster corrected for multiple comparisons) (Fig. 3). The same between-group differences were found without controlling for cognitive function (Supplemental Figure S5).

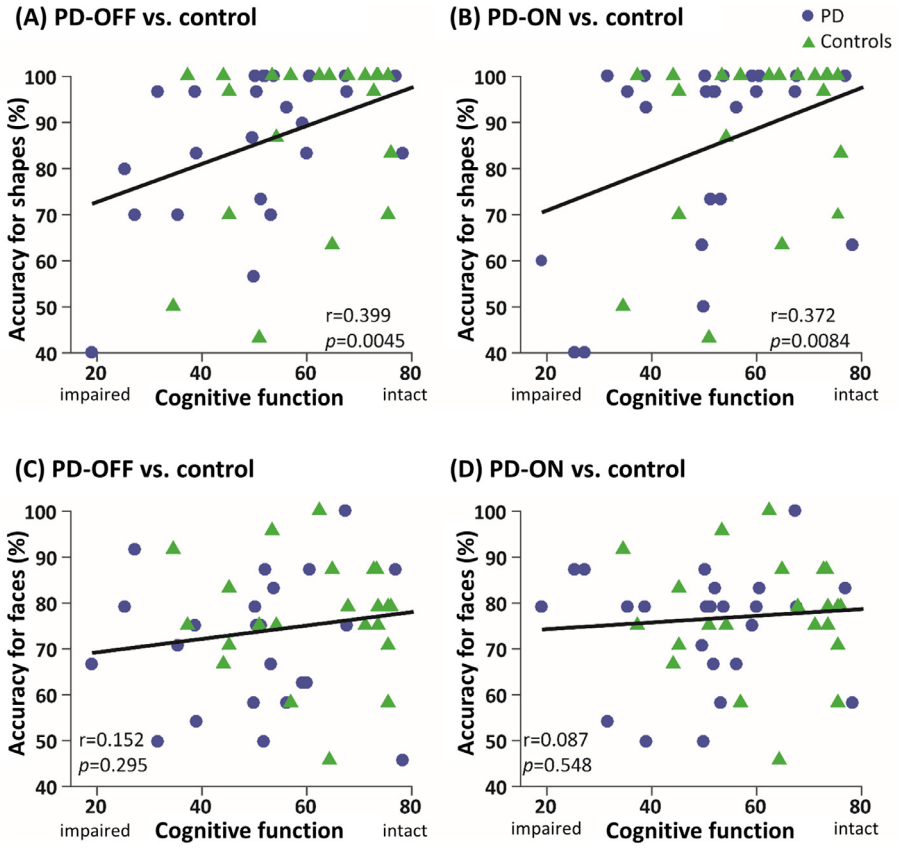

Fig. 1 Relationships between cognitive function and accuracy of matching emotional and non-emotional stimuli. Top row: Accuracy (% of correct responses) of matching shapes as a function of the cognitive score for **(A)** PD-OFF vs. controls, and for **(B)** PD-ON vs. controls. Bottom row: Accuracy (% of correct responses) of matching emotional faces as a function of the cognitive score for **(C)** PD-OFF vs. controls, and for **(D)** PD-ON vs. controls. Data for PD patients are marked by blue circles and controls by green triangles. The cognitive score was computed as the summary of the z-scores on the ten tests of cognitive function included in the neuropsychological battery (see Methods for more details and specific tests used), with a higher score indicating a better cognitive function. Pearson's correlation coefficients and *p* values are indicated. While there was no association between cognitive function and accuracy for emotional faces, a significant association was found between cognitive function and accuracy for non-emotional stimuli, i.e. shapes (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

3.4. Associations between cognitive function and BOLD response to emotion in PD patients

3.4.1. PD-ON

A better cognitive function in PD patients ON medication predicted increased BOLD response to negative emotional faces in the bilateral posterior cingulate cortex (cluster size: 1339 voxels; MNI: [2 −20 30]; $p = 0.0027$, FWE cluster corrected for multiple comparisons) (Fig. 4A). Post-hoc analysis was conducted to determine whether this region is part of the default mode network. This was done by: (i) examining if this region was deactivated in response to faces compared to shapes in subjects (PD patients and controls); (ii) comparing the region to the mask of the default mode network provided by CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012), that was obtained by ICA analysis on a dataset of 497 healthy controls from the Human Connectome Project. For all subject groups, this cluster did not show deactivation for emotional faces compared to shapes across subjects and was outside the default mode network mask.

3.4.2. PD-OFF

A better cognitive function in PD patients OFF medication marginally predicted increased BOLD response to negative emotional faces in the bilateral anterior cingulate cortex (cluster size: 731 voxels; MNI: [8 32 18]; $p = 0.057$, FWE cluster corrected for multiple comparisons) (Fig. 4B). Post-hoc analysis was conducted to determine whether this region is part of the default mode network, as described above. For all subject groups, this cluster was outside the default mode network and did not show deactivation for emotional faces compared to shapes across subjects.

4. Discussion

In the present study, we demonstrated behavioral and neural disturbances in PD patients in recognizing negative facial emotion that were irrespective of cognitive function. Increased BOLD response for emotional faces in the visual cortex was found in PD patients relative to controls during both dopaminergic medication states, not accounted

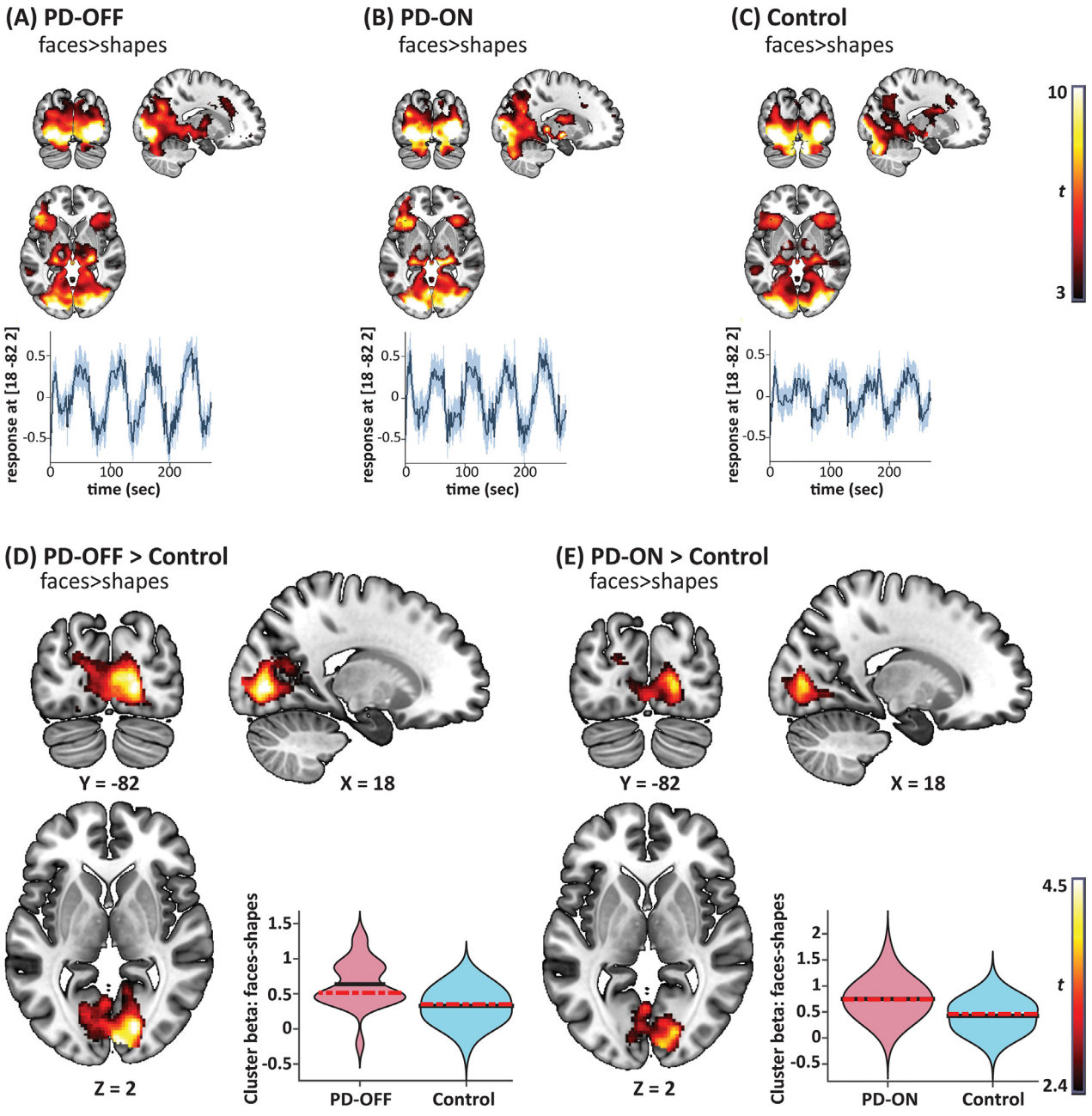

Fig. 2 Differences between PD patients and controls in BOLD response to emotional faces. BOLD activation maps for the contrast faces>shapes while controlling for cognitive function, and time series of the BOLD responses (average and confidence intervals) are shown for **(A)** PD patients OFF dopaminergic medication, **(B)** PD patients ON dopaminergic medication and **(C)** healthy controls, at [18 −82 2] MNI. **(D,E)** PD patients showed increased BOLD response to emotional faces relative to healthy controls in the bilateral calcarine sulci and lingual gyri, while **(D)** OFF and **(E)** ON dopaminergic medication. Coordinates are presented in MNI space and *t* values are indicated by the color bar. Cluster sizes: 3822 voxels for PD-OFF>control and 1558 voxels for PD-ON>control. The violin plots present the cluster beta values of the emotional stimuli (faces) subtracted by the sensorimotor stimuli (shapes) for each subject group. The median is indicated by a dashed red line and the mean by a solid black line. Between-group differences were tested using one-way ANCOVA models implemented by a GLM controlling for cognitive function. Uncorrected voxel-level $p < 0.01$, FWE cluster-extent corrected for multiple comparisons at $p < 0.05$.

by cognitive function. Administration of dopaminergic medication in PD patients resulted in restored behavioral accuracy for emotional faces relative to controls and decreased posterior cingulate/retrosplenial cortex BOLD response to emotion relative to OFF medication state. Furthermore, cognitive function in PD patients was associated with accuracy of matching non-emotional stimuli and predicted BOLD response to emotion in the anterior and posterior cingulate cortices, depending on medication status.

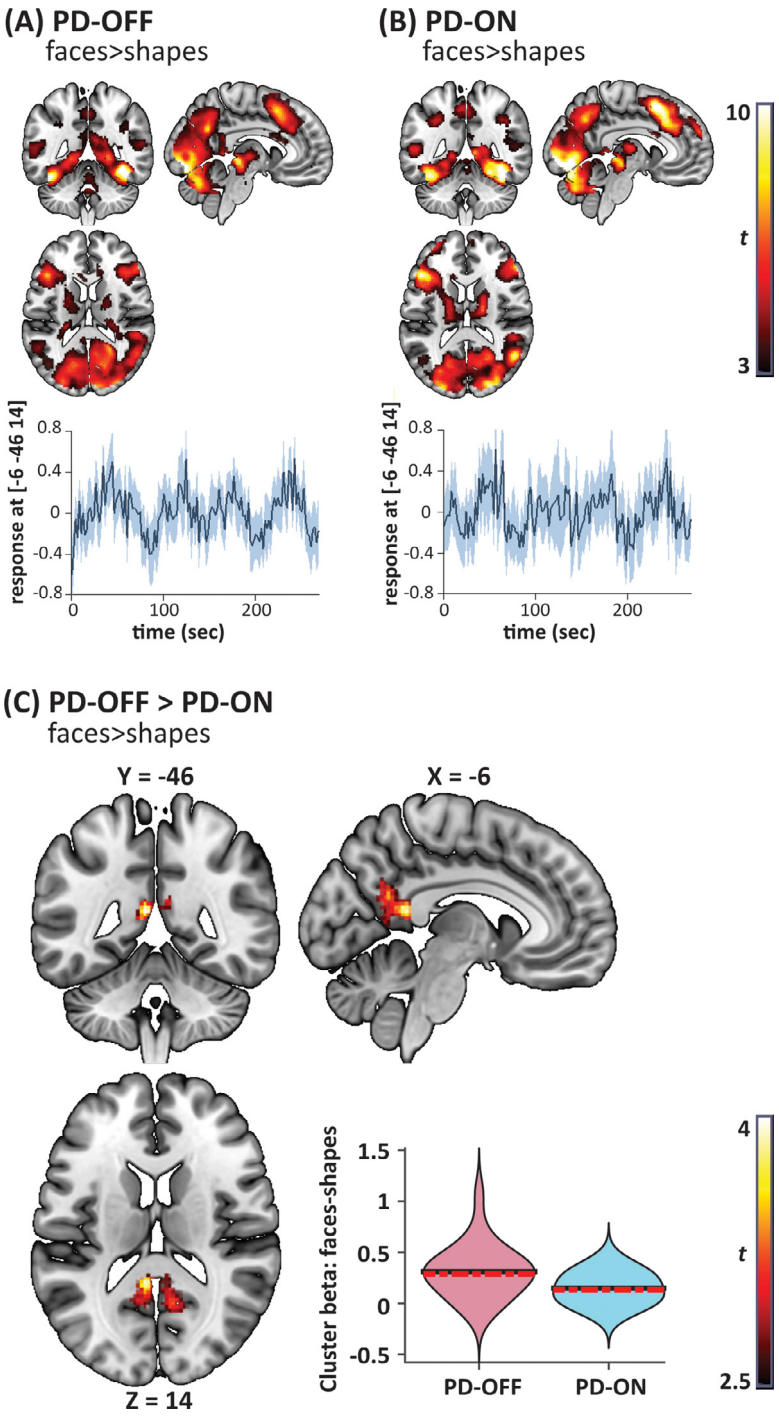

Fig. 3 Differences between PD patients OFF and ON dopaminergic medication in BOLD response to emotional faces. BOLD activation maps for the contrast faces>shapes while controlling for cognitive function, and time series of the BOLD responses (average and confidence intervals) are shown for **(A)** PD patients OFF and **(B)** ON dopaminergic medication, at [−6 −46 14] MNI. Note that the same activation maps are presented in Fig. 2A and B at a different location. **(C)** PD patients OFF relative to ON medication showed increased BOLD response to emotional faces in the bilateral posterior cingulate/retrosplenial cortex. Coordinates are presented in MNI space and *t* values are indicated by the color bar. Cluster size: 718 voxels. The violin plots present the cluster beta values of the emotional stimuli (faces) subtracted by the sensorimotor stimuli (shapes) for each subject group. The median is indicated by a dashed red line and the mean by a solid black line. Between-group differences were tested using a one-way repeated measures ANCOVA model implemented by a GLM controlling for cognitive function. Uncorrected voxel-level $p < 0.01$, FWE cluster-extent corrected for multiple comparisons at $p < 0.05$.

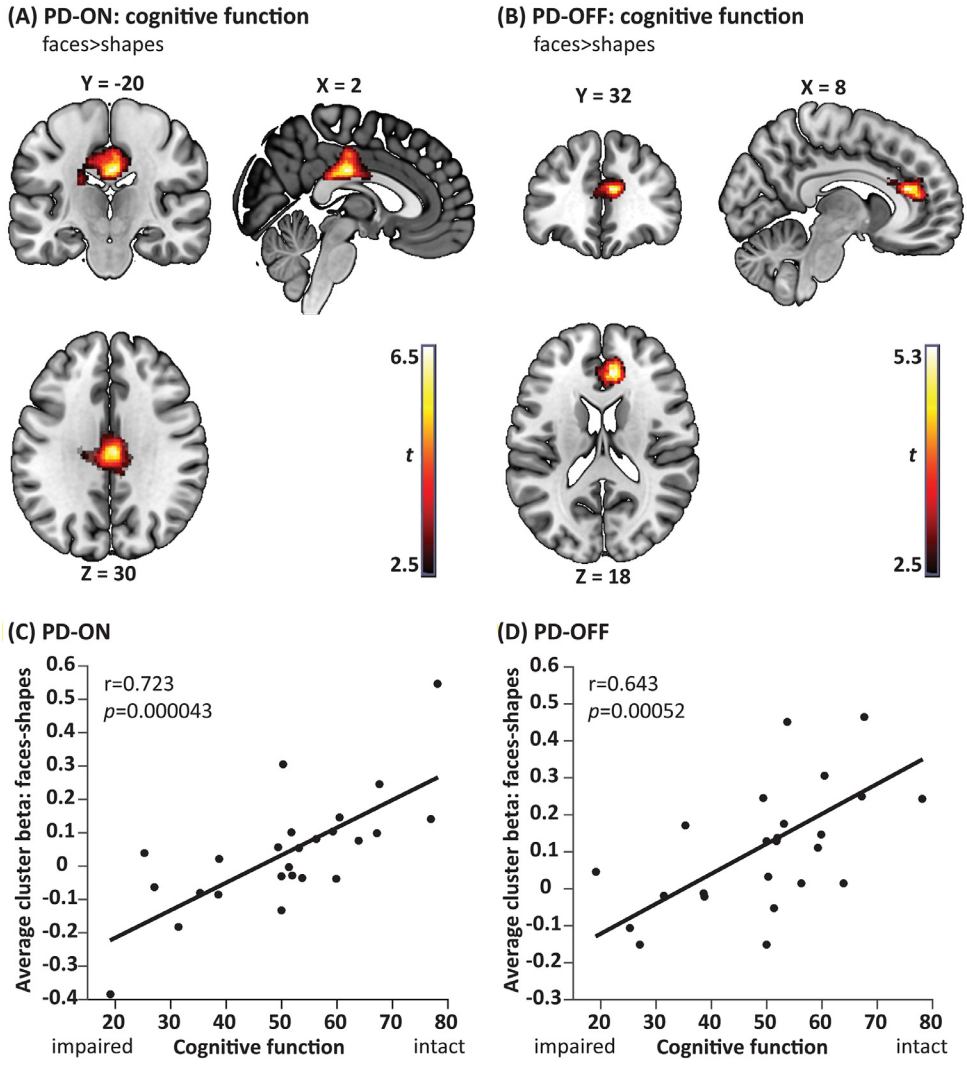

Fig. 4 Associations between cognitive function and BOLD response to emotion in PD patients. A better cognitive function in PD patients predicted increased BOLD response to emotional faces **(A)** in the bilateral posterior cingulate cortex during ON medication state and **(B)** in the bilateral anterior cingulate cortex during OFF medication state. Coordinates are presented in MNI space and *t* values are indicated by the color bar. At the bottom row, the average cluster beta values of the emotional stimuli (faces) subtracted by the sensorimotor stimuli (shapes) (*y* axis) are plotted against the cognitive function score (*x* axis) for PD patients **(C)** ON and **(D)** OFF dopaminergic medication. Pearson's correlation coefficients and *p* values are shown. A statistical threshold of uncorrected voxel-level $p < 0.01$, FWE cluster-extent corrected for multiple comparisons at $p < 0.05$ was used.

Reduced accuracy of matching emotional faces was found in PD patients OFF medication compared to healthy controls. This performance was normalized with dopaminergic medication. Notably, accuracy of matching emotional stimuli was not associated with cognitive function. The results are consistent with the proposed role of dopamine in emotion recognition (Salgado-Pineda et al., 2005). However, there have been previous conflicting findings regarding the influence of dopaminergic medication on behavior in emotional face processing. In their meta-analysis, Gray et al. (2010) found a larger impairment effect size for PD patients in hypodopaminergic state compared to that derived from patients in a dopamine-replete state, although the difference between effect sizes was not significant. A behavioral study comparing different patients ON and OFF medication, found a deficit regardless of medication status that was greater among unmedicated patients (Sprengelmeyer et al., 2003).

Increased BOLD response in the visual cortex, specifically the calcarine sulci and the lingual gyri, was found in PD patients compared to healthy controls during negative emotional face matching. Importantly, these BOLD changes in PD patients during emotion processing were not dependent on cognitive function. Moreover, increased visual cortex BOLD response in patients was found for both medication states. However, we note that there was some qualitative evidence for a greater deviation in the BOLD response to emotion in PD patients during the OFF medication state, as indicated by a larger cluster showing between-group differences in the visual cortex. Increased BOLD response during emotional face perception was previously found in the fusiform gyrus of PD patients compared to controls (Cardoso et al., 2010),

in agreement with our results. Notably, the visual and emotional systems are extensively interconnected. Emotional face processing implicates a distributed brain network, from early occipital areas to regions in temporal, parietal and cingulate cortices involved in social, cognitive or somatic processing (Vuilleumier and Pourtois, 2007). Specifically, the primary and associative visual cortices were shown to robustly increase their activity according to the emotional content of stimuli, for faces among other types of visual stimuli (Kober et al., 2008; Schindler and Kissler, 2016; Vuilleumier and Pourtois, 2007). The modulation of visual cortex activity by emotional content may correspond to a principal regulatory role of emotion signals, but also to effects of attention. It has been demonstrated that emotion and attention have parallel and distinct influences on face processing in the visual cortex (Schindler and Kissler, 2016). Emotional content was thought to mediate visual processing through subcortical regions, mainly the amygdala and pulvinar (Pessoa and Adolphs, 2010; Tamietto and De Gelder, 2010). It was shown that these limbic regions have direct anatomical connections to the primary visual cortex and suggested that their projections enhance activity in the visual cortex when viewing emotional stimuli. Attention was thought to modulate visual processing by top-down signals from fronto-parietal areas (Ungerleider, 2000). Notably, these frontal and limbic regions are strongly innervated by dopaminergic projections that are damaged in PD patients (Björklund and Dunnett, 2007). In this context, animal studies have demonstrated changes in neural activity in the visual cortex due to dopaminergic influences (Noudoost and Moore, 2011; Zaldivar et al., 2018, 2014). These studies showed that the dopaminergic modulation of neural activity in the visual cortex is not dependent on the local expression of dopaminergic receptors but rather on long-range interactions from regions expressing dopaminergic receptors, such as the prefrontal cortex. Thus, we postulate that the increased visual BOLD response in PD patients during emotional face perception may result from altered top-down attentional modulation from higher prefrontal cortical areas and/or emotion-driven modulation from subcortical areas, due to the damage of dopaminergic pathways in the disease.

It is important to note that since fMRI is an indirect measure of neural activity, the effects of dopamine on the hemodynamic response function and its relation to neural activity should be considered (Ekstrom, 2010). For example, in nonhuman primates, the injection of dopamine resulted in increased neural activity and increased cerebral blood flow but decreased BOLD response in the visual cortex (Zaldivar et al., 2014). This dissociation between the changes in the neural and BOLD responses under the administration of dopamine indicates that caution should be taken when interpreting the greater BOLD response to emotion found in PD patients relative to controls. Thus, conclusions should not be drawn regarding the specific direction of the altered neural reactivity in patients (i.e. increased or decreased), but rather on its presence.

Another possible explanation for the aberrant visual cortex activity in PD patients is the dysfunction of the visual system frequently reported in PD (Weil et al., 2016). Multiple stages of the visual system may be affected by the disease, from the retina to higher visual cortical regions. Dopamine is an important neurotransmitter in the retina (Armstrong, 2017) and retinal dopaminergic deficiency has been demonstrated in PD patients (Archibald et al., 2009). Moreover, independent patterns of damage were reported within the parvo-, konio- and magnocellular pathways in PD (Silva et al., 2005). In the visual cortex, functional abnormalities were shown in PD patients, including reduced metabolism (Eberling et al., 1994) in addition to hypoperfusion, the latter associated with visual hallucinations (Matsui et al., 2006). Hypoperfusion of the visual cortex was suggested to result from diminished dopaminergic neurons in the retina, or alternatively, from the pathological damage to the striatum, due to its structural and functional connections with visual associative areas (Denny-Brown et al., 1975; Kemp and Powell, 1970). However, the aforementioned deficits of the visual system are expected to impair processing of emotional and non-emotional stimuli in a similar manner. Thus, we argue that it is less likely that the increased visual cortical BOLD response to emotion vs. non-emotional stimuli in PD patients in the current study results from a general dysfunction of the visual system, but rather it is plausibly related to an imbalanced modulation of the visual cortex by emotional and attentional processes.

Administration of dopaminergic medication in PD patients altered the BOLD response to emotion in the posterior cingulate/retrosplenial cortex with increased BOLD response during the OFF medication state. The posterior cingulate/retrosplenial cortex was previously indicated as one of the cortical regions most consistently activated by emotionally salient stimuli, independent of the emotion category (Kober et al., 2008; Maddock, 1999). Moreover, in a meta-analysis on studies of emotion, it was shown to be consistently co-activated with the primary visual cortex during emotional tasks (Kober et al., 2008). This co-activation suggested that the posterior cingulate/retrosplenial cortex acts as a "relay-station" from the visual cortex, due to its direct connections with the dorsomedial prefrontal cortex and with subcortical regions such as the ventral striatum, insula and hippocampus. In contrast to the visual cortex that is poorly innervated by dopamine, the posterior cingulate cortex is innervated by dopaminergic projections (Berger et al., 1991). Thus, during the OFF medication state, the posterior cingulate/retrosplenial cortex that has a predominant role in emotional processing is less innervated by dopamine, in addition to a wide-spread reduced dopaminergic innervation of frontal and limbic regions.

It is noteworthy that administration of dopaminergic medication in PD patients did not result in wide-spread differences in BOLD reactivity to emotion. This is in possible contrast to previous findings in healthy subjects, such as in Alavash et al. (2018). However, a less wide-spread effect of dopaminergic administration in PD patients compared to healthy subjects may be expected since the dopaminergic pathways of these patients are damaged and likely to be only partially restored or compensated under the administration of dopamine. Moreover, our patients were in the moderate to advanced stage of the disease, implying severe damage to dopaminergic pathways. In this context, we found similar differences between PD patients and controls regardless of the dopaminergic medication status of patients, suggesting a greater effect of the disease than of the medication state. In addition, the effect of dopamine

was specifically examined in this study for the reactivity to visual emotional faces. The effects of dopamine on other tasks, such as auditory cognitive ones as examined in the study of Alavash et al., or on resting-state functional connectivity in PD (Esposito et al., 2013; Evangelisti et al., 2019) are also likely to differ. We further hypothesize that if this study was repeated in healthy subjects, greater differences were found between medication states, including in limbic and prefrontal regions. This may be interesting to examine in a following study.

Cognitive function of PD patients predicted BOLD response to emotion in the anterior and posterior cingulate cortices, during OFF and ON medication states, respectively. A better cognitive function was associated with increased BOLD response to emotional faces compared to the sensorimotor control condition. Cognitive decline in PD was previously associated with deficits in the anterior and posterior cingulate gyri, including atrophy (Pagonabarraga et al., 2013; Zarei et al., 2013), hypoperfusion (Lin et al., 2016), hypometabolism (Vander Borght et al., 1997) and reduced regional monoaminergic capacity (Klein et al., 2010). Moreover, the posterior cingulate cortex was associated with cognitive function in several other brain diseases. For example, in Alzheimer's disease hypometabolism and neural degeneration in the posterior cingulate predicted cognitive decline (Minoshima et al., 1997; Yoshiura et al., 2002), while hyperactivity of the posterior cingulate predicted cognitive deficits in schizophrenia (Whitfield-Gabrieli et al., 2009). Importantly, our findings add on previous findings by demonstrating associations between the cingulate cortices and cognitive function that were specific for emotion-related processing. We suggest that our results are in accordance with the central role of the cingulate cortex, particularly its anterior part, in the interface between emotion and cognition (Bush et al., 2000). With regard to the behavioral performance, cognitive function was associated with accuracy for non-emotional stimuli, namely shapes, and not for emotional stimuli. This was indicated despite impaired accuracy for emotional stimuli, and not shapes, in PD patients OFF medication. This agrees with our neural findings of abnormal BOLD response to emotion in PD patients that was not accounted by cognitive abilities. Taken together, these results may support the notion that emotion processing in PD patients is partially independent from cognitive function and requires different mechanisms, thus may be differentially impaired.

Several methodological issues require consideration. The relatively modest sample size may limit the generalizability of the findings and studies with greater number of subjects are needed to strengthen the results. Furthermore, studies applying non-facial emotional stimuli are needed to determine whether our findings are specific for recognizing facial emotion or generalize to other types of stimuli. In addition, the possible impact of visual low-level features such as the contrast of the images, should also be explored by future research. Last, cognitive evaluation of PD patients was done during the ON medication state. Possible effects of medication depletion on cognitive function cannot be ruled out, and may possibly reduce the accuracy of accounting for cognitive function during OFF medication state.

5. Conclusions

Our findings argue for independent processes underlying emotional and cognitive impairments in PD. Specifically, we illustrated deficits in behavior and aberrant BOLD responses to emotion in PD patients irrespective of their cognitive function. Moreover, these impairments were dependent on dopaminergic availability, with restored behavioral emotional performance and altered BOLD response during administration of dopaminergic medication. We suggest that the aberrant visual and retrosplenial cortical reactivity to emotion in PD patients arise from altered attentional and/or emotion-driven modulation from subcortical and higher cortical regions. Our findings highlight the importance of dopaminergic treatment not only for the motor symptoms but also the emotional disturbances in PD.

Role of funding sources

This work was supported by the Czech Science Foundation (GACR 16-13323S) and a Czech-Israel cooperative research grant issued by the Israel Ministry of Science (3-9814) and the Czech Ministry of Education (LH13256 VES13-KontaktII). Additional support was provided by Charles University in Prague (PRVOUK-P26/LF1/4). The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Declaration of Competing Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Rotem Dan: Data curation, Formal analysis, Investigation, Resources, Writing - original draft. **Filip Růžička:** Investigation, Resources. **Ondrej Bezdicek:** Investigation, Resources. **Jan Roth:** Conceptualization. **Evžen Růžička:** Conceptualization. **Josef Vymazal:** Conceptualization. **Gadi Goelman:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **Robert Jech:** Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing - review & editing.

Acknowledgment

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.09.003.

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