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RESEARCH ARTICLE

Emotion processing in Parkinson's disease: a blood oxygenation level-dependent functional magnetic resonance imaging study

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Abstract

Parkinson's disease is a neurodegenerative disorder caused by loss of dopamine neurons in the substantia nigra pars compacta. Tremor, rigidity, and bradykinesia are the major symptoms of the disease. These motor impairments are often accompanied by affective and emotional dysfunctions which have been largely studied over the last decade. The aim of this study was to investigate emotional processing organization in the brain of patients with Parkinson's disease and to explore whether there are differences between recognition of different types of emotions in Parkinson's disease. We examined 18 patients with Parkinson's disease (8 men, 10 women) with no history of neurological or psychiatric comorbidities. All these patients underwent identical brain blood oxygenation level-dependent functional magnetic resonance imaging for emotion evaluation. Blood oxygenation level-dependent functional magnetic resonance imaging results revealed that the occipito-temporal cortices, insula, orbitofrontal cortex, basal ganglia, and parietal cortex which are involved in emotion processing, were activated during the functional control. Additionally, positive emotions activate larger volumes of the same anatomical entities than neutral and negative emotions. Results also revealed that Parkinson's disease associated with emotional disorders are increasingly recognized as disabling as classic motor symptoms. These findings help clinical physicians to recognize the emotional dysfunction of patients with Parkinson's disease.

Key Words: *Parkinson's disease; emotion; processing; Blood oxygenation level-dependent functional magnetic resonance imaging; brain; activation; dopamine; neural regeneration*

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Introduction

Parkinson's disease (PD) is a neurodegenerative disease caused by progressive degeneration of nigrostriatal dopaminergic pathways. The major symptoms consist of motor problems including tremor, rigidity, and bradykinesia. However, affective and emotional impairments have been also reported (Peron et al., 2012). Thus, numerous studies have been conducted to elucidate PD-related impairment in affective processing (Gray and Tickle-Degnen, 2010). Surprisingly, these studies produced very different results (Gray and Tickle-Degnen, 2010). Some research groups described global emotion impairment while others reported problems in specific emotion processing. In contrast, some authors did not report any deficit (Ricciardi et al., 2017). The differences may result from confounding factors, including the stage of the disease, medication status, and comorbidities. However, it is well known that patients with PD suffer from reduced facial expressivity (hypomimia) and have difficulties in interpreting the emotional facial expressions of others, especially for non-positive emotions (Arriatti et al., 2008).

Most studies regarding emotion in PD were based on behavioral, cognitive and physiological measurements of emotion recognition (Adolphs et al., 1998; Pell and Leonard, 2005; Bowers et al., 2006; Suzuki et al., 2006; Wieser et al., 2006; Laweence et al., 2007; Clark et al., 2008; Dara et al., 2008; Lotze et al., 2009; Miller et al., 2009; Schienle et al., 2015). However, all of these studies have addressed only one aspect of emotions (Schuenle et al., 2015; Ricciardi et al., 2017). To date, few studies have investigated emotional issues in PD using fMRI (Lotze et al., 2009). To the best of our knowledge, this is the first fMRI study exploring all aspects of emotions (positive, negative, and neutral) in a homogeneous population of patients with PD. The goal of this study was to investigate emotion organization in the brain of patients with PD and to explore whether there are differences between recognition of different types of emotions.

Subjects and Methods

Patient selection

This study was conducted according to the national ethical guidelines and regulations, which are mostly compliant with the National Institute of Health standards. The approval of the local ethical committee 'Comité d'Etique Hospitalo-universitaire de Fez, Fez; Morocco' was obtained (Reference:

ECR 09/2018).

Eighteen patients with idiopathic PD including 16 patients having bilateral lesions and two patients having right-sided lesions were recruited for the study. The studied patients had no neurological or psychiatric comorbidities. The diagnosis of PD was established by a certified neurologist with advanced training in movement disorders. The diagnostic criteria were based on clinical symptoms including bradykinesia/hypokinesia and atypical movement disorders such as mix, myoclonic, task dependant, postural inaugural tremor, dopamine resistant tremor, isolated tremor at rest. Non motor symptoms are also considered. None of the patients had received deep brain stimulation before.

All patients underwent clinical assessment of motor disorders using the Unified Parkinson's Disease Rating Scale (UPDRS) section V (Goetz et al., 2010). Neurological examination was performed the day before scanning. All patients were also assessed by a psychiatrist using the Beck Depression Inventory-II (BDI-II) (scale) (Beck et al., 1996) to rule out a depressive propensity which might interfere wih affective processing. All participants had normal vision.

All included patients were under L-dopa treatment. In addition, some of them simultaneously received other parkinsonian drugs trihexyphenidyl hydrochloride (n = 4), piribedil (n = 3), or a mixture of these drugs (n = 2). Medication was not discontinued prior to the fMRI session and all patients were investigated on the ON state of their dopaminergic medication cycle.

Both written and verbal informed consents were obtained from each patient. The demographic and clinical parameters of included patients are summarized in **Table 1**.

Table 1 Demographic and clinical characteristics of our PD patients

Case	Age (year)	Sex	Family history of PD	Symptom duration (year)	Hoehn and Yahr stage	Treatment
1	65	M	Yes	11	III	L-dopa + THC
2	63	F	No	2	II	L-dopa
3	60	F	Yes	6	III	L-dopa + THC
4	60	F	No	7	III	L-dopa + THC + Piribedil
5	54	F	No	1	I	L-dopa
6	83	M	No	4	II	L-dopa + THC
7	49	M	No	2	II	L-dopa + THC
8	69	F	No	1	II	L-dopa
9	56	M	No	12	III	L-dopa + Piribedil
10	65	M	No	3	II	L-dopa
11	79	F	No	3	III	L-dopa
12	63	M	Yes	4	III	L-dopa
13	62	F	No	6	III	L-dopa + Piribedil
14	50	M	No	8	III	L-dopa+ Piribedil
15	45	M	Yes	4	I	L-dopa
16	66	F	No	10	III	L-dopa + THC + Piribedil
17	56	F	No	2	II	L-dopa
18	57	F	No	8	III	L-dopa

PD: Parkinson's disease: F: female; M: male; L-dopa: levodopa; THC: trihexyphenidyle chlorhydrate.

Emotion paradigm design

Emotion stimuli were based on the international affective picture system that was developed by the Center for the Study of Emotion and Attention, University of Florida, Gainesville, FL, USA (https://csea.phhp.ufl.edu/media/requestform.html). In addition, the used pictures consisted of cultural experience adapted and validated pictures in the Moroccan context.

Twenty-seven pictures were used in our experiment. The images were presented to the participants with formal instruction to simply experience the presented emotion.

We used a block design, each block comprising three different types of pictures, positive (*e.g.*, joyful baby, happy family), negative (*e.g.*, attacks by animals, craniofacial trauma) or neutral emotions (*e.g.*, nature scenes) (**Figure 1**). Each picture was displayed for 6 seconds followed by the second and third pictures for the same duration and emotion. The single display of picture for 6 seconds was justified by avoiding habituation that starts at the ninth second of display. Thus each emotion stimulus lasted for 18 seconds (ON condition). Then rest phase (OFF condition) started when pictures vanished and lasted 18 seconds (**Figure 2**). Each block of stimulus was displayed in a pseudo-randomized order for all the included patients with PD.

The experiment was designed to last the shortest time possible to avoid potential motion artifacts during fMRI scanning sessions. In this study, the whole experiment lasted 342 seconds.

Blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI) acquisition protocol

The BOLD-fMRI protocol used was identical for all patients. All image data acquisitions were achieved in MRI Unit, Radiology and Clinical Imaging Department of the University Hospital of Fez, Morocco.

A 1.5-Tesla MRI system (Sigma, General Electric; Milwaukee, WI, USA) was used to acquire all brain BOLD-fMRI and also anatomical MRI data series.

Image acquisition was achieved using single-shot gradient-echo echo-planar imaging sequence. This MRI approach was shown to be very sensitive to T2* effect originated by increased BOLD phenomena. This reflects the level of functional activity within the cortical brain tissue (Boujraf et al., 2006, 2009, 2017; Bucher et al., 2006; Halder et al., 2007; Belaïch et al., 2015, 2016, 2017).

BOLD-fMRI acquisition parameters were set according to the following configurations: repetition time = 3000 ms, echo time = 55 ms, slice thickness = 5 mm, field of view = 240 mm. All acquired slices were set in the axial orientation.

The acquisition of a single volume of brain was achieved within 3 seconds. The full BOLD-fMRI acquisition protocol allows acquiring 114 brain volumes within 342 seconds. The anatomical MRI data were also acquired.

Data post-processing and image generation

The BOLD-fMRI image data were processed using the Statistical Parametric Mapping package version 12 (SPM12, 2012; http://www.fil.ion.ucl.ac.uk/spm; Wellcome Depart-

Figure 1 Blood oxygenation level-dependent functional magnetic resonance imaging paradigm components showing the main emotional tasks (positive, negative, and neutral).
Each emotional task was repeated three times with unique images, *e.g.* each picture was displayed once.

Figure 2 Block design paradigm showing the arrangement of the emotional tasks (positive, negative, and neutral).
Each emotional task was repeated three times with unique images, *e.g.* each picture was displayed once.

ment of Cognitive Neurology, London, UK). The statistical model used by SPM12 was general linear model approach. All brain MRI image volumes acquired were used in the post-processing steps.

The post-processing steps with SPM12 included realignment, co-registration, and spatial normalization in the Montreal Neurological Institute template (Boujraf et al., 2006, 2009, 2017; Bucher et al., 2006; Halder et al., 2007; Belaïch et al., 2015, 2016, 2017).

Indeed, the gradient-echo EPI image data underwent realignment using a rigid-body transformation to the first volume of the time series for each patient. Subsequently, the image data were spatially smoothed using a Gaussian filter Full width at half maximum (FWHM 8 × 8 × 8 mm) and then spatially normalized (Boujraf et al., 2006, 2009, 2017; Bucher et al., 2006; Halder et al., 2007; Belaïch et al., 2015, 2016, 2017).

All cerebral activations were rendered onto brain slices of T1-weighted MRI image or on the surface of the standard brain of Montreal Neurological Institute, Montreal, Quebec, Canada. The task was designed according to the boxcar pattern and convolved with the functional hemodynamic response recorded in the brain. The brain areas that were significantly activated were decided. Each voxel element was statistically processed using SPM12 (Boujraf et al., 2006, 2009, 2017; Bucher et al., 2006; Halder et al., 2007; Belaïch et al., 2015, 2016, 2017). A *P*-value less than 0.01 was considered statistically significant. The calculated BOLD activation maps were overlaid on anatomical images.

Quantitative evaluation of individual activation maps

Each calculated activation map of individual patients was evaluated and scored to reflect the activation level originated by each emotion (namely positive, negative, and neutral).

Statistical analysis

One-way analysis of variance was used for comparison of quantitative data between paired emotion categories (namely positive versus negative, positive versus neutral, and negative versus neutral). A value of $P < 0.05$ was considered to be statistically significant.

Results

Clinical assessment results

This study included 18 patients, consisting of 10 women and 8 men, with a mean age of 61 (45–86) years. All patients were right-handed. They had been in school for at least 5 years and three of them had a high level of education. Three patients had a history of arterial hypertension, two patients underwent operation for prostatic adenoma, and four had a history of familial PD. The mean duration of the disease was 5.4 years (range 11 months–12 years). The staging of PD for these patients was based on the Hoehn and Yahr scale. Two of our patients were classified as stage I, six of them as stage II, and ten as stage III (Hoehn and Yahr, 1967). **Table 1** summarizes the demographic and clinical profile of the included patients with PD.

fMRI assessment results

Different brain structures (in particular the occipito-temporal cortices, insula, orbitofrontal cortex, basal ganglia, and parietal cortex) involved in the organization of emotions were activated during the functional control. In addition, the activation level depended on the emotion type of stimuli. Thus, positive emotion was shown to activate larger volumes of the anatomical entities involved in the emotional processing in all patients. However, the importance of activation decreased significantly in the negative emotion compared with the positive emotion (**Figure 3**).

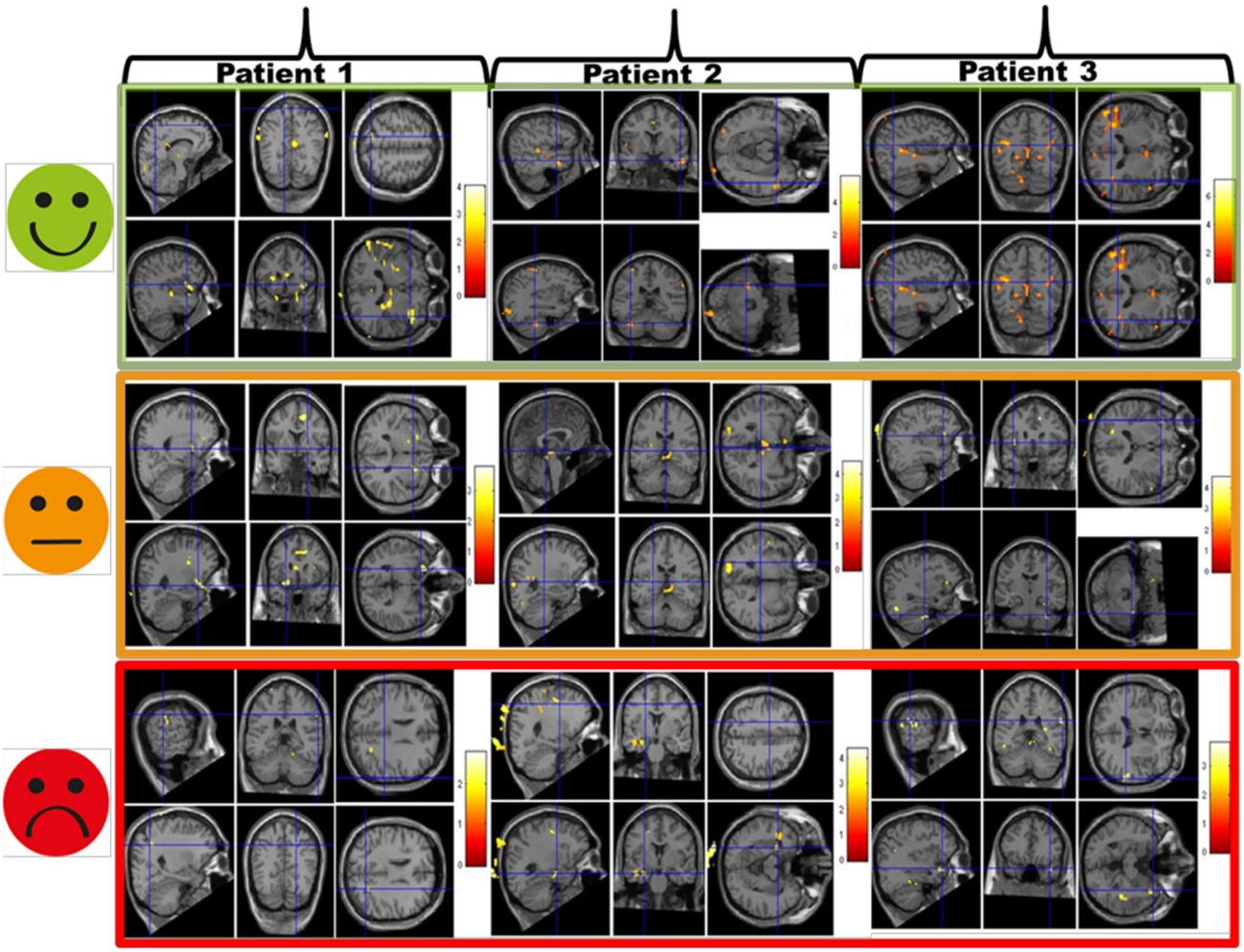

Figure 3 Blood oxygenation level-dependent activations in three Parkinson's disease patients showing that positive emotion activates larger volumes of the brain networks involved in emotional processing, compared to neutral and negative emotions.
Green, orange and red faces to the left indicate activations in response to positive emotions (brain slices inside the green frame), neutral stimuli (orange frame) and negative emotions (red frame) respectively. A color scale is inserted next to each set of images to indicate the intensity of activations (black, no activation; yellow, highest activation).

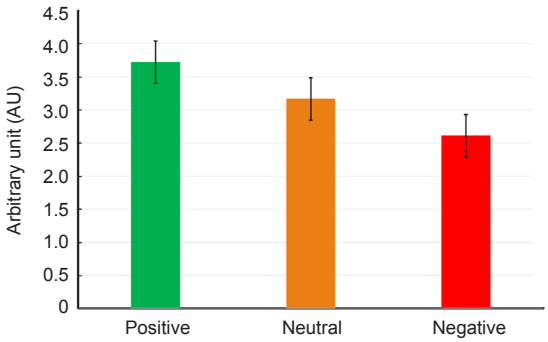

Figure 4 Whole brain blood oxygenation level-dependent activation elicited by positive, negative, and neutral emotions in the group of patients studied.
The bars represent activation scores, and the error bars represent the standard error.

The global activation induced by the positive, negative, and neutral emotions was quantitatively evaluated (**Figure 4**). In PD patients, positive emotion had the largest activation area and negative emotion had the smallest activation area (**Figure 4**).

Statistical analysis

Global brain activation level in each motion category (positive, negative, and neutral) was statistically analyzed using analysis of variance. Positive and negative emotions produced significantly different effects on global brain activation level. Quantitative statistical analysis results demonstrated significant difference in the brain activation level associated with positive versus negative emotions ($P < 0.05$). However, there was no significant difference in the brain activation level between negative and neutral emotions ($P > 0.05$).

Discussion

PD is a neurodegenerative disorder characterized by depletion of dopaminergic neurons in specific brain anatomic entity called substantia nigra. This degenerative process of the nigrostriatal dopaminergic pathway instigates the impairment of the basal ganglia-thalamo-cortical circuit functions, including the motor and prefrontal cortex functions (Alexander et al., 1990). Besides motor symptoms, PD patients exhibit cognitive dysfunction (Jankovic, 2008; Hsu

et al., 2012) and a deficit in emotional processing (Assogna et al., 2008; Gray and Tickle-Degnen, 2010).

The basal ganglia are crucial structures for emotion recognition. Stroke (Fromm et al., 1985; Pogarell and Oertel, 1999) or other neurodegenerative diseases, such as Huntington's disease (Robotham et al., 2011) damage the basal ganglia, leading to marked deficits in emotion recognition. Mauss and Robinson (2009) reported that the state of emotion in PD involves a series of brain circuits rather than specific isolated brain regions. Moreover, the cortical and subcortical brain structures are involved together in emotional processing through cortical-thalamic-striatal cognitive loops (Owen et al., 1998). The limbic system represents the most important basal ganglia-thalamo-cortical circuits, which has a crucial role in emotional and motivational processes (Butters et al., 1973; Afifi, 2003). BOLD-fMRI studies have revealed an increased activation of orbitofrontal cortex and anterior cingulated cortex when volunteers are experiencing to recognize emotions using facial expressions (Dolan et al., 1996; Blair et al., 1999). Besides, impairment of emotional identification has been demonstrated in patients with orbitofrontal cortex and/or anterior cingulate cortex lesions using facial expressions (Hornak et al., 2003).

Several assessment methods such as BOLD-fMRI, positron emission tomography, PET scan, and electroencephalography were used to analyze interconnected neuronal activities in various brain regions to detect the activation yielded by emotional processing in the brain. Baumgartner et al. (2006) reported that electroencephalography activity in the left hemisphere was increased under happy conditions compared to negative emotional conditions. Hinrichs and Machleidt (1992) demonstrated a changed degree of coherence in the alpha frequency band on electroencephalography, principally with a larger coherence in happiness compared to sadness.

A recent meta-analysis regarding fMRI of emotional processing has suggested that basic emotions are implemented by different neural circuits, and each type of emotion activates preferentially a specific brain region (Fusar-Poli et al., 2009). Happy and fearful faces activate bilateral amygdala, sad faces activate the right amygdala only, and disgusting faces seem to activate essentially the anterior insula (Phan et al., 2002).

Numerous studies have found emotion recognition deficits in patients with PD (Jacobs et al., 1995; Benke et al., 1998; Breitenstein et al., 1998; St. Clair et al., 1998). Breitenstein et al. (1998) reported that compared to healthy controls, patients with PD performed poorer in commenting the emotional content of speech or sketches (Scott et al., 1984) and in recognizing emotional displays, in particular in prosodic recognition tasks involving anger and fear. PD patients showed reduced recognition of sadness, anger, and disgust facial expressions (St.Clair et al., 1998; Baggio et al., 2012).

With regard to recognition of emotional facial expression, a recent meta-analysis evaluating behavioral studies found that individuals with PD exhibited more severe impairment than healthy individuals in the recognition of negative emotions (anger, disgust, fear, and sadness) and individuals with PD exhibited more severe impairment in the recognition of negative emotions than in the recognition of positive emotions (happiness, surprise) (Gray and Tickle-Degnen, 2010). This problem is likely related to disturbances in the limbic loop, and in particular in the connections of the basal ganglia to the orbitofrontal cortex and anterior cingulated cortex.

Interestingly, a relationship was demonstrated between the expression of facial emotions by both PD patients and healthy volunteers and the ability to recognize facial emotions expressed by others (Ariatti et al., 2008). The capability of recognizing the emotions expressed by others is based on the processes that internally stimulate the identical emotional state in each individual (Scott et al., 1984; Heberlein and Atkinson., 2009; Baggio et al., 2012). This is called the simulation or goal directed model of emotion recognition which depends on the mirror neurons located in F5 brain area within the pars opercularis of the inferior frontal gyrus (Rizzolatti and Arbib, 1998).

In our study, we demonstrated that brain activation is weaker in negative emotion. Wieser et al. (2006) found that PD patients rated negative pictures as less arousing than did healthy controls, but they had no such problem in accurately rating positive and neutral pictures. Alonso-Recio et al. (2014) found also that patients with higher disease severity performed worse than healthy controls in the recognition of emotional facial expressions, however, such result was not found in patients with lower disease severity.

PD patients' deficits in the recognition of negative emotions may be related to faulty communication between the amygdala and prefrontal cortex due to low levels of dopamine (Lin et al., 2016). As supported by the present study, in PD patients, there is a reduction in the brain complexity during emotional processing initiated by a decrease of neural connectivity and the existence of functional disconnections between cortical areas (Adolphs et al., 1996; Lawrence et al., 2006; Kober et al., 2008; Cronin-Golomb, 2010; Lin et al., 2016).

In addition, dopamine levels have been shown to be correlated with patients' performance when recognizing facial emotions (Sprengelmeyer et al., 2003; Lawrence et al., 2007). Motor performances and cognitive functions worsen over time in PD patients because of dopaminergic neurodegeneration.

Our study showed that positive emotion activates large volumes of the anatomical entities involved in the emotional processing in PD patients. However, the negative emotions activate the least area of brain regions in the same PD patients. As the disease progresses, the recognition of negative emotions is impaired and then followed impairment to the recognition of positive emotions (Lawrence et al., 2007). These facts are supported by physiological data. It is well known that prefrontal dopamine influences cognitive functions (Arnsten et al., 2005; Cools and D'Esposito, 2011). Interestingly, dopamine uptake has been reported to be increased in prefrontal regions (Rakshi et al., 1999; Kaasimnen et al., 2000; Cools et al., 2002) in early PD. However, later in the disease, PET scanning revealed marked decrease in prefrontal dopamine and in D2-type dopamine receptors (Kaasinen et al., 2000; Rakshi et al., 2001; Yip et al., 2003). Based on this, we could speculate that preservation of rec-

ognition of positive emotion in our PD patients is related to the presence of dopamine reserve in the prefrontal cortex. However, the heterogeneity and the small sample of our population might be a limitation that should be considered. Future clinical and *in vivo* molecular imaging studies (*e.g.*, PET/SPECT) of patients with early PD may resolve this question.

Finally, Yip et al. (2003) found that compared to unilateral PD patients, bilateral PD patients showed greater deficits in the emotion recognition task regardless of the stimulus modality.

Conclusion

Emotion is an essential tool for social communication between individuals. Because of dopaminergic degeneration, emotion is affected in PD similar to motor function. Thus, clinicians should be aware of this fact to identify the emotional impairment in PD patients and to direct specific treatment for the patients, such as computerized cognitive rehabilitation (Yuvaraj et al., 2016).

Our study demonstrated a specific impairment of negative emotional processing in PD patients. This result could be explained by our demographic data since all patients were relatively in the early stage of the disease. Nevertheless, we believe that prospective studies using clinical/fMRI emotional tests and involving larger number of PD patients would be the best way to confirm this hypothesis.

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Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients or guardians have given their consent for the patients' images and other clinical information to be reported in the journal. The patients or guardians understand that the patients' names and initials will not be published and due efforts will be made to conceal their identity.*
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