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ORIGINAL ARTICLE

Brain perfusion alterations in depressed patients with Parkinson's disease

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Abstract
Objective Although Parkinson's disease (PD) is frequently accompanied by depression, brain perfusion deficits in PD with depression remain unclear. This study aimed to assess alterations in regional cerebral blood flow (rCBF) in depressed PD patients using ^{99m}Tc hexamethyl-propylene-amine-oxime single-photon emission computed tomography (SPECT).
Methods Among 78 patients with PD, 35 patients were classified into the depressed PD group, while the rest (43 patients) was assigned to the nondepressed PD group based on the scores of the Geriatric Depressive Scale (GDS). All participants underwent brain SPECT imaging. The voxel-wise whole-brain analysis and region-of-interest (ROI) analysis of the limbic areas were conducted to compare rCBF between the depressed and nondepressed PD groups.
Results The depressed PD patients demonstrated higher GDS scores than nondepressed patients, whereas between-group differences in the PD severity and cognitive function were not significant. Perfusion in the left cuneus was increased, while that in the right superior temporal gyrus and right medial orbitofrontal cortex was reduced in the depressed PD patients as compared with nondepressed PD patients. In addition, the ROI analysis demonstrated rCBF decreases in the amygdala, anterior cingulate cortex, hippocampus, and parahippocampal gyrus in the depressed PD group. A positive correlation was found between the GDS scores and rCBF in the left cuneus cluster in the depressed PD patients.
Conclusion This study identified the regional pattern of brain perfusion that distinguished depressed from nondepressed PD patients. Hyperperfusion in the occipital areas and hypoperfusion in the fronto-temporo-limbic regions may be potential imaging biomarkers for depression in PD.

Keywords Parkinson's disease · Depression · Brain perfusion · SPECT · Regional cerebral blood flow

Introduction

Although Parkinson's disease (PD) is primarily characterized by several motor symptoms, including tremor, rigidity, and bradykinesia, it is frequently accompanied by other nonmotor symptoms, such as depression, anxiety, fatigue, and sleep disturbance [1]. Among these, depression is one of the most common nonmotor symptoms of PD and the prevalence of major depressive disorder was reported as 17 % in PD patients according to the meta-analysis [2]. If minor depression and dysthymia are included, the prevalence increases to 52 % in PD population, much higher than that in general population [2]. The underlying neurobiological mechanism of the close association between PD and depression is not well defined. It is possible that disabling symptoms of PD may cause distress and negative feelings. However, a number of studies have suggested that

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degeneration of the mesolimbic and mesocortical pathways may be related to depression in PD [3, 4].

To investigate the neural substrates underlying depressive symptoms in PD, only a few studies using single-photon emission computed tomography (SPECT) have examined regional cerebral blood flow (rCBF) in the PD patients with and without depression. However, the results regarding rCBF differences between the depressed and nondepressed PD patients have been inconsistent. One study revealed increased rCBF in the fronto-parietal areas of the depressed PD patients [5], whereas rCBF reduction in the frontal cortex was found in the depressed PD group of the other study [6]. Furthermore, the sample sizes of these studies were relatively small.

This study aimed to assess alterations in rCBF in depressed PD patients compared with nondepressed PD group using ^{99m}Tc hexamethyl-propylene-amine-oxime (HMPAO) SPECT. Since the whole-brain voxel-wise analysis of the SPECT images might miss rCBF differences on a regional level, we further used a region-of-interest (ROI) approach for the major limbic areas which are implicated in depression [7] by averaging all voxel values within each region. Finally, the relationships between rCBF and the severity of depression were examined.

Materials and methods

Participants

Patients who had been diagnosed as PD without history of other neurological and psychiatric disorders were recruited at Incheon St. Mary's Hospital (Incheon, South Korea). Written informed consent was obtained from all participants and the study protocol was approved by the Research Ethics Committee.

The severity of PD symptoms was evaluated with the Hoehn–Yahr Scale [8]. The Korean Mini-Mental State Examination (MMSE) was used to assess global cognitive function [9]. The total score ranges from 0 to 30, with a higher score indicating a better cognitive performance. The cut-off score of 18 was suggested for screening of dementia [10]. Depressive symptoms were examined using the Korean version of the Geriatric Depressive Scale (GDS) [11]. The total score ranges from 0 to 30 and a higher score represents greater depressive symptoms. The cut-off score of 14 was suggested for screening of depression [11]. Participants were divided into the depressed and nondepressed PD groups based on the cut-off score of the GDS.

Image acquisition

All participants were scanned 40 min after intravenous injection of 1110 MBq of HMPAO using a dual-head gamma camera (ECAM plus; Siemens Medical, Erlangen, Germany). The participants were rested in a supine position with their eyes open in a low-light and low-noise environment during the scan. All images were attenuation corrected and reconstructed in a 128 × 128 matrix with a voxel size of 3.9 × 3.9 × 3.9 mm (field of view 240 mm) using filtered back projection.

Image processing and analysis

Statistical Parametric Mapping 8 (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) was used for image processing and statistical modelling. All images were spatially normalized to the SPM SPECT template (Montreal Neurological Institute, McGill University, Montreal, Canada) and resliced with a voxel size of 2 × 2 × 2 mm^3. The SPM binary brain mask was applied to remove extracerebral signal. The images were smoothed with a 16 mm full-width half-maximum isotropic Gaussian kernel.

A voxel-wise two-sample t test was conducted to examine differences in rCBF between the two groups with age and gender as nuisance covariates. Global counts were normalized to 50 mL/100 g/min with proportional scaling, and relative threshold masking of 0.8 was applied. The statistical threshold was set at uncorrected $p < 0.001$ at voxel level with an extent threshold of 100 voxels. Normalized rCBF values were extracted from each significant cluster using MarsBar toolbox version 0.44 (http://marsbar.sourceforge.net) [12].

For the ROI analysis, four bilateral ROIs in the limbic system were selected based on the previous review of neuroimaging studies in depression [7]: the amygdala, anterior cingulate cortex, hippocampus, and parahippocampal gyrus. The WFU PickAtlas toolbox version 3.0.5 (http://fmri.wfubmc.edu/software/pickatlas) [13] was used to create binary masks for these ROIs using the Automated Anatomical Labeling atlas [14]. Normalized rCBF value of each ROI was extracted using MarsBar toolbox [12].

Statistical analysis

Differences in continuous variables between two groups were examined with independent t tests or Mann–Whitney U tests. Chi-square test was used to compare the ratio of gender.

To assess correlations between rCBF and depressive symptoms, multiple linear regressions were performed in

the depressed PD group with normalized rCBF value from each cluster as an independent variable and the GDS score as a dependent variable, while adjusting for age and gender. For each ROI, difference in the normalized rCBF between the two groups was assessed using multiple linear regression with age and gender as covariates of no interest.

A two-tailed p value of less than 0.05 without correction for multiple comparison was considered statistically significant, since the correlation and ROI analyses were based on specific hypotheses. All analyses were conducted with Stata version 13.1 (StataCorp., College Station, TX, USA).

Results

A total of 78 patients with PD were included in this study. Among them, 35 patients were classified into the depressed PD group, while the rest (43 patients) was assigned to the nondepressed PD group based on the GDS scores. No patients were on antidepressant medication at the time of the assessments. Demographic and clinical characteristics of the participants were presented in Table 1. Although the two groups did not differ in age ($p = 0.54$), the duration of PD symptoms ($p = 0.21$), the duration of PD treatment ($p = 0.47$), the Hoehn–Yahr score ($p = 0.19$), the levodopa equivalent dose ($p = 0.33$), and the MMSE score ($p = 0.11$), these two groups had statistically different gender distributions, with more women in the depressed PD group ($p < 0.001$). The mean GDS score of the depressed PD group (mean 22.9 ± 4.1, range 17–30) was higher than that of the nondepressed PD group (mean 4.5 ± 2.6, range 0–10, $p < 0.001$).

Results from the voxel-wise SPM analysis were summarized in Table 2 and Fig. 1. The depressed PD group showed increased rCBF in the left cuneus ($t = 3.55$, cluster size 129 voxels). In contrast, significantly lower rCBF was found in the right superior temporal gyrus ($t = -3.71$, cluster size 298 voxels) and right medial orbitofrontal cortex ($t = -3.57$, cluster size 139 voxels). In addition, the ROI analysis demonstrated decreases of rCBF in the amygdala ($t = -2.09$, $p = 0.04$), anterior cingulate cortex ($t = -2.52$, $p = 0.01$), hippocampus ($t = -2.21$, $p = 0.03$), and parahippocampal gyrus ($t = -2.54$, $p = 0.01$) in the depressed PD group (Table 3).

Regression analysis revealed the positive correlation between the GDS scores and the rCBF in the left cuneus cluster in the depressed PD group after adjusting for age and gender ($\beta = 0.96$, $p = 0.006$).

Discussion

The current brain perfusion SPECT study investigated differences in rCBF between the depressed and nondepressed PD patients. Correlations between rCBF and the severity of depressive symptoms were also examined in the depressed PD group. We found increased rCBF in the cuneus and perfusion reduction in the superior temporal gyrus, medial orbitofrontal cortex, and four limbic ROIs, including the anterior cingulate cortex, amygdala, hippocampus, and parahippocampal gyrus, in the depressed PD group. In addition, the rCBF in the cuneus cluster was positively associated with depressive symptoms in the depressed PD patients.

The voxel-wise image analysis revealed that the depressed PD group relative to the nondepressed group showed higher rCBF in the cuneus and occipital areas which were associated with their greater depressive symptoms. In line with these results, the previous study using PET demonstrated the dysphoria-related topographic pattern of glucose metabolism in PD patients, which was characterized by metabolic increases in the medial occipital areas and the decrease in the frontal lobe [15]. Increased glucose metabolism in the cuneus and surrounding areas has also been implicated in geriatric depression of PD patients [16, 17]. Furthermore, the

Table 1 Demographic and clinical characteristics of the participants

Characteristics	Depressed PD ($n = 35$)	Nondepressed PD ($n = 43$)	Test
Age (years)	68.9 ± 9.2	67.7 ± 7.6	$t = 0.61$, $p = 0.54$
Gender (male/female)	9/26	29/14	$\chi^2 = 13.45$, $p < 0.001$
Duration of PD symptoms (years)	2.8 ± 3.2[a]	4.0 ± 4.5[b]	$t = -1.26$, $p = 0.21$
Duration of PD treatment (years)	1.9 ± 2.8	2.3 ± 2.0	$t = -0.72$, $p = 0.47$
Hoehn–Yahr score	2.2 ± 0.7[a]	2.0 ± 0.9[c]	$z = 1.3$, $p = 0.19$
Levodopa equivalent dose (mg/day)	434.9 ± 284.1[d]	375.3 ± 251.2[e]	$t = 0.96$, $p = 0.33$
MMSE	26.2 ± 2.1	27.0 ± 2.1	$t = -1.62$, $p = 0.11$
GDS	22.9 ± 4.1	4.5 ± 2.6	$t = 24.04$, $p < 0.001$

GDS Geriatric Depression Scale, *MMSE* Mini-Mental State Examination, *PD* Parkinson's disease

[a] $n = 32$, [b] $n = 42$, [c] $n = 38$, [d] $n = 34$, [e] $n = 41$

Table 2 Brain areas with significant differences in regional cerebral blood flow

Region	Cluster size (voxels)	*t*	Coordinates[a] (*x*, *y*, *z*)
Depressed PD > nondepressed PD			
Left cuneus	129	3.55	−22, −72, 36
Depressed PD < nondepressed PD			
Right superior temporal gyrus	298	−3.71	52, 2, −10
Right medial orbitofrontal cortex	139	−3.57	2, 28, −22

PD Parkinson's disease

[a] Coordinates are given in millimeter and refer to the Montreal Neurological Institute coordinate system

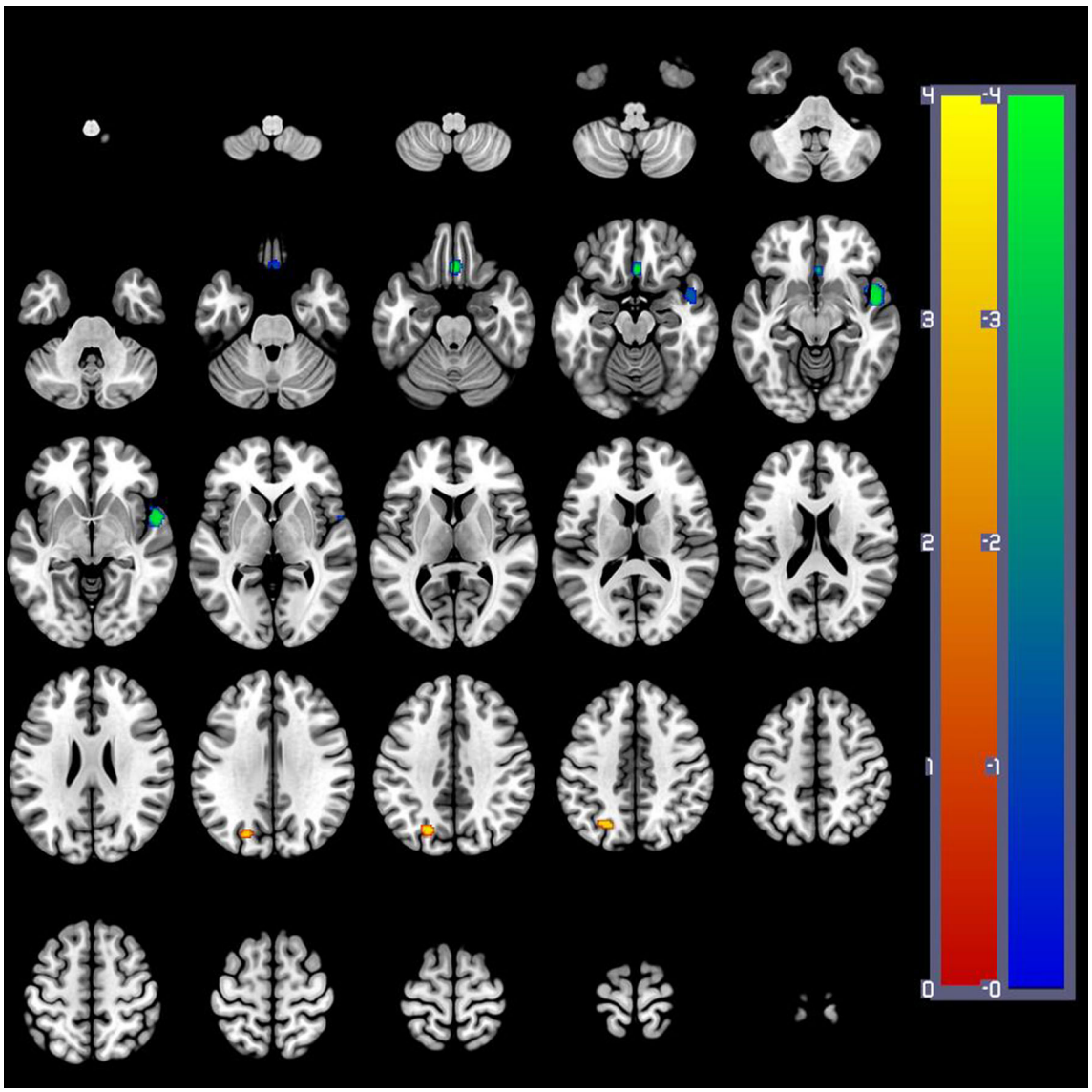

Fig. 1 Differences in rCBF in the depressed PD group as compared with the nondepressed PD group. Images are shown in neurological convention and *color bars* represent voxel-level *t* values. Increases and decreases in rCBF appear in *red-yellow* and *blue-green color*, respectively. *PD* Parkinson's disease, *rCBF* regional cerebral blood flow

behavioral experiment study of healthy volunteers revealed that sustained anxiety was associated with increased rCBF in various regions, including the parieto-occipital cortex [18]. The underlying mechanism of higher rCBF of the cuneus in the depressed PD patients remains unclear. As one possible explanation, the reductions of γ-aminobutyric acid (GABA) concentrations [19] and GABAergic neurons [20] were found in the occipital cortex of patients with

Table 3 Results of ROI Analysis

ROI	Normalized rCBF		Test
	Depressed PD	Nondepressed PD	
Amygdala	73.7 ± 3.3	75.4 ± 3.1	$t = -2.09$, $p = 0.04$
Anterior cingulate cortex	75.6 ± 4.6	77.8 ± 4.9	$t = -2.52$, $p = 0.01$
Hippocampus	74.8 ± 2.7	75.8 ± 2.2	$t = -2.21$, $p = 0.03$
Parahippocampal gyrus	68.5 ± 3.1	69.9 ± 2.3	$t = -2.54$, $p = 0.01$

PD Parkinson's disease, *rCBF* regional cerebral blood flow, *ROI* region of interest

depression. Inverse correlations between the GABA levels and rCBF in the brain have also been suggested by the previous literature [21, 22]. Further studies are warranted to examine structural, functional, or metabolic changes in the occipital area and potential visual impairments in PD with depression, since both subjective visual deficits [23] and changes of visual evoked potential [24, 25] were observed in patients with major depression.

On the other hand, decreased rCBF in the superior temporal and medial orbitofrontal cortices was found in the depressed PD patients. These results correspond with the findings of the previous neuroimaging studies in major depression that have consistently reported both functional and structural alterations in these areas [26–28]. The superior temporal gyrus in combination with the fronto-limbic areas (orbitofrontal cortex, amygdala, and anterior cingulate cortex) has been known to be involved in emotional processing and social cognition [29, 30]. Functional neuroimaging studies demonstrated that patients with major depression exhibited abnormal functional connectivity [31] and decreased activation at rest or to sad stimuli in this region [26]. Furthermore, regional volume of superior temporal gyrus was negatively associated with severity of depressive symptoms [28]. The rCBF decrease in the medial orbitofrontal area is in line with the previous studies that revealed hypometabolism in the same region in depressed PD patients when compared with nondepressed PD patients [15, 32]. Interestingly, the orbitofrontal cortex, which has reciprocal connections with both the ventral tegmental area and dorsal raphe, may play important roles in the pathophysiology of depression with PD [33, 34]. Although still speculative, the degeneration of dopaminergic system may cause the functional deficits in orbitofrontal cortex, which, in turn, may affect serotonergic system and cause depressive symptoms.

The ROI analysis of this study revealed lower rCBF in the limbic system including the anterior cingulate cortex, amygdala, hippocampus, and parahippocampal gyrus of the depressed PD patients. Lower rCBF in the anterior cingulate cortex was also suggested from the previous report [35]. However, rCBF alterations in the amygdala, hippocampus, and parahippocampal gyrus have not been suggested in the previous studies of depressed PD patients [5, 35, 36]. In addition, perfusion studies of major depression have also demonstrated inconsistent results regarding the activation of the limbic regions [37–40]. Our results suggest that depression with PD may be characterized by coherent decreases of rCBF in the major limbic areas.

Potential limitations of this study include a group difference in gender ratio, although gender was covaried out in the statistical analyses. The epidemiological and other studies of PD showed controversial results whether there is a gender difference in the prevalence of comorbid depression. [41, 42], while gender difference in major depression has been well documented [43]. However, there is still a possibility that neural correlates of depression in PD may be different between genders, and therefore, further studies are warranted to investigate this issue. The reliance on the self-report questionnaires for the assessment of depressive symptoms is another weakness of this study due to the potential response bias. Complementary use of structured clinical interviews would be helpful in future research.

In summary, this study identified the regional pattern of brain perfusion that distinguished depressed from nondepressed PD patients. Hyperperfusion in the occipital area and hypoperfusion in the fronto-temporo-limbic regions may be potential imaging biomarkers for depression in PD. However, although the mean rCBF values of the ROIs significantly differed between depresssed and nondepressed PD groups, the perfusion ranges considerably overlapped between the two groups. Therefore, our findings should be confirmed and validated in prospective studies with a larger cohort for the development of reliable and robust biomarkers for depression in PD.

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Compliance with ethical standards

Conflict of interest The authors declare no financial conflicts of interest.

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