Longitudinal cerebral perfusion changes in Parkinson's disease with subjective cognitive impairment

Abstract

Background and Purpose: Although subjective cognitive impairment (SCI) is often accompanied by Parkinson's disease (PD) and may predict the development of mild cognitive impairment (MCI) or dementia, longitudinal brain perfusion changes in PD with SCI remain to be elucidated. The current prospective study examined cerebral perfusion changes in PD with SCI using technetium-99m hexamethylpropylene amine oxime single photon emission computed tomography (SPECT). Methods: Among 53 PD patients at the baseline, 30 patients were classified into the PD with SCI group and 23 patients were assigned to the PD without SCI group. The mean follow-up interval was 2.3 ± 0.9 years. The Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Global Deterioration Scale (GDS) were used to assess objective impairment of cognitive function. Brain SPECT images were acquired at the baseline and follow-up. Results: Differences between the two groups were not significant for demographic variables, PD severity, and cognitive function both at the baseline and follow-up. At the baseline, the PD with SCI group showed decreased perfusion in the left angular gyrus compared to the PD without SCI group. In the longitudinal analysis, the PD with SCI patients demonstrated widespread perfusion reductions primarily in temporo-parieto-occipital areas and cerebellum, bilaterally. Relative to the PD without SCI group, the excessive decrease of perfusion was found in the left middle frontal gyrus of the PD with SCI patients. Conclusions: Our findings suggest that perfusion deficits in the middle frontal area may play an important role in the pathophysiology of SCI in PD.
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**Conclusions:** Our findings suggest that perfusion deficits in the middle frontal area may play an important role in the pathophysiology of SCI in PD.

**Key Words**

Parkinson’s disease, Subjective cognitive impairment, Cerebral perfusion
Introduction

Parkinson's disease (PD) has been widely known as a movement disorder, but recently, other non-motor, troublesome symptoms of PD, such as cognitive difficulties, have begun to receive attention.\(^1\) Cognitive impairment is known to frequently accompany the characteristic motor deficits of PD, generally in the late stages of the illness. A longitudinal study of PD patients reported that at baseline, dementia was diagnosed in about 26% of the participants, of which, after 8 years, increased to about 80%.\(^2\) In addition, PD patients have an almost sixfold increased risk of developing dementia compared to the general population.\(^3\)

Subjective cognitive impairment (SCI) is defined as subjective complaints of cognitive declines with normal levels of cognitive performance on objective measures.\(^4\) Several lines of research have shown that SCI may predict the development of mild cognitive impairment (MCI) or dementia in PD patients\(^5,6\) as well as in the healthy elderly.\(^7\) Despite the potential of imaging techniques in providing valuable insight for early detection and development of management strategies, to our knowledge, only a few in vivo neuroimaging studies have investigated neural correlations of SCI in PD. Previous magnetic resonance imaging (MRI) studies in PD with SCI demonstrated reduced gray matter density in the medial frontal, angular, and anterior cingulate cortex when compared to PD without SCI\(^8\) and cortical thinning in the frontal, parietal, and parahippocampal areas compared with healthy controls.\(^9\) In addition, the single photon emission computed tomography (SPECT) study found that PD patients with SCI showed hypoperfusion in the frontal, inferior temporal, and anterior cingulate cortex, and thalamus compared to those without SCI.\(^10\) Since these studies adopted a cross-sectional design, there is a compelling need to elucidate longitudinal brain changes.
The current prospective SPECT study intended to examine perfusion changes in PD with SCI in comparison with those in PD without SCI. SPECT with $^{99m}$Tc-hexamethylpropyleneamine oxime (HMPAO) is widely available and may be advantageous in detecting subtle cognitive decline related to PD with SCI.\textsuperscript{10} Notwithstanding the insufficient number of studies in this area to draw a specific hypothesis, evidence from literature in PD with MCI may be useful to anticipate brain perfusion changes specific to the progression of SCI in PD. In neuroimaging studies, frontal regions of PD patients with MCI consistently showed cortical atrophy,\textsuperscript{11,12} decreased functional connectivity,\textsuperscript{13} and hypometabolism.\textsuperscript{14} Furthermore, executive dysfunction is the most common neuropsychological deficit in PD with MCI.\textsuperscript{15,16} Finally, the frontal cortex is also consistently implicated in the imaging studies of PD with SCI.\textsuperscript{8-10} We, therefore, hypothesized that excessive decreases in regional cerebral blood flow (rCBF) would be prominent in the frontal areas of PD patients with SCI as compared to those without SCI at the follow-up.
Methods

Participants
Patients with PD were recruited at Incheon St. Mary's Hospital (Incheon, South Korea). Due to the lack of general consensus on the diagnostic criteria of SCI, it was defined as self-reported memory complaints, in spite of normal cognitive performance in formal neuropsychological tests. Patients were classified into PD with SCI group or PD without SCI group based on clinical diagnosis by a board-certified neurologist. PD was diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria for PD. Fluorinated N-3-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane positron emission tomography ($^{18}$F-FP-CIT PET) was also used for the diagnosis of PD. Exclusion criteria were the patients who had (i) past or present neuropsychiatric disorders including stroke, head trauma, epilepsy, depression, or brain surgery; (ii) significant medical comorbidities such as diabetes mellitus, hypertension, or hypercholesterolemia; (iii) cerebrovascular lesions on magnetic resonance imaging; (iv) any other detectable cause of memory deficit; and (v) lifelong memory complaints. Patients who were taking any psychotropic medications were also excluded. Written informed consent was obtained from all study participants and the study protocol was approved by the Research Ethics Committee.

Clinical Assessment
Physical and neurological examinations were performed by a board-certified neurologist. The severity of PD symptoms was assessed with the Hoehn-Yahr Scale. The Clinical Dementia Rating (CDR) and Global Deterioration Scale (GDS) were used to evaluate overall
severity of dementia. Global cognitive function was measured with the Mini-Mental State Examination (MMSE). 20

**Image Acquisition and Processing**

Brain SPECT scans were conducted at the baseline and follow-up. All patients were intravenously injected with 1110 MBq of HMPAO in a dark and quiet room. After approximately 40 minutes, perfusion images were acquired with a dual-head gamma camera (NM640, GE Healthcare, Milwaukee, WI, USA) equipped with a low-energy, fan-beam collimator. 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 = 240mm) using filtered back projection.

We used the Statistical Parametric Mapping 12 (SPM; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) for the image processing and statistical modeling. All images were spatially normalized to the SPM SPECT template (Montreal Neurological Institute, McGill University, Montreal, Canada), resliced with a voxel size of 2 × 2 × 2 mm³, and then smoothed with a 16 mm full-width half-maximum isotropic Gaussian kernel.

**Statistical Analysis**

Differences in continuous demographic or clinical variables were assessed with independent t-test or Mann-Whitney U test, while those in gender ratio were evaluated with the chi-square
test. A two-tailed $p$ value of less than 0.05 was considered statistically significant. All analyses were conducted with Stata version 13.1 (StataCorp., College Station, TX, USA).

A series of SPM statistical analyses were conducted with age and gender as nuisance covariates. A two-sample t-test was used to investigate differences in rCBF between the two groups at the baseline. A relative threshold masking of 0.8 was applied and global counts were normalized to 50 mL/100 g/min with proportional scaling. The statistical threshold was set at uncorrected $p < 0.001$ at voxel level with an extent threshold of 100 voxels.

Paired t-test was performed to examine perfusion differences between the baseline and follow-up in PDSMI group. Reference cluster normalization instead of SPM default normalization was used since it provides a significant increase of statistical power in neurodegenerative diseases.\textsuperscript{21} In brief, an analysis with the default normalization was performed to find rCBF increases in the follow-up using a threshold of $t > 2.0$.\textsuperscript{22} The mean rCBF value in the significant area was extracted from each image using MarsBar toolbox version 0.44 (http://marsbar.sourceforge.net/) and used as a scaling factor for the subsequent analysis to analyze rCBF decreases in the follow-up images. The statistical threshold was set at uncorrected $p < 0.001$ at voxel level with an extent threshold of 100 voxels.

The flexible factorial design was used to assess the interaction effect of group by time. The perfusion increases specific to the PD with SCI group were determined by the contrast of $[(\text{PD with SCI at the baseline} < \text{PD with SCI at the follow-up}) > (\text{PD without SCI at the baseline} < \text{PD without SCI at the follow-up})]$, whereas the decreases were revealed by the contrast of $[(\text{PD with SCI at the baseline} > \text{PD with SCI at the follow-up}) > (\text{PD without SCI at the baseline} > \text{PD without SCI at the follow-up})]$. The reference cluster normalization was
applied and the statistical threshold was set at uncorrected $p < 0.005$ at voxel level with an extent threshold of 50 voxels.
Results

Demographic and clinical characteristics of the participants are presented in Table 1. A total of 53 PD patients were recruited at baseline. Among them, 30 patients were classified into the PD with SCI group. At follow-up, 20 PD with SCI patients and 14 PD without SCI patients participated in the study. The mean follow-up interval was 2.3 ± 0.9 years. Both at the baseline and follow-up, no participant showed a significant cognitive decline in the objective measures including the MMSE, CDR, and GDS. In addition, differences between the two groups were not significant for age, gender, duration of PD symptoms, Hoehn-Yahr score, levodopa equivalent dose, MMSE, CDR, and GDS at the baseline and follow-up (all \( p > 0.05 \)).

The results from the SPM analysis are demonstrated in Table 2. At the baseline, the PD with SCI group showed decreased perfusion in the left angular gyrus (\( t = 4.36 \), voxel-level \( p < 0.001 \), cluster size = 200 voxels) compared to the PD without SCI group (Fig. 1). In comparison between the baseline and follow-up within the PD with SCI group, widespread reductions in rCBF were found in the bilateral cerebellum and temporo-parieto-occipital areas including right middle temporal gyrus, left lateral occipital cortex, and right precuneus at the follow-up (Fig. 2). In addition, we identified excessive perfusion decrease specific to PD with SCI patients in the left middle frontal gyrus compared to PD without SCI patients (\( t = 3.25 \), voxel-level \( p = 0.001 \), cluster size = 52 voxels) (Fig. 3).
Discussion

The current study investigated the longitudinal changes of cerebral perfusion in PD patients with SCI using HMPAO SPECT. First, we compared the differences between PD patients with SCI and those without SCI at baseline. Then, changes in rCBF in the PD with SCI group were examined at follow-up. Finally, we examined the group-by-time interaction in order to test for the difference in perfusion changes between the two groups.

At baseline, the PD with SCI group showed rCBF decreases in the left angular gyrus when compared with the PD without SCI group. This is in line with the previous positron emission tomography (PET) study that revealed reduced parieto-temporal glucose metabolism among healthy subjects with SCI.\(^{23}\) Moreover, the structural MRI study indicated significant reductions in gray matter density in the angular gyrus for PD with SCI compared to those without SCI.\(^{8}\) The angular gyrus has a strong connection with the parahippocampal gyrus\(^ {24}\) and is closely involved in attention and memory retrieval.\(^ {25}\) Abnormalities in this area may contribute to the subjective feeling of memory decline.

At follow-up, the PD with SCI group demonstrated widespread rCBF reductions in the temporal, parietal and occipital cortical regions and the cerebellum compared to the baseline measurements. In consistent with these results, hypoperfusion has been found primarily in the parieto-occipital areas in studies of PD.\(^ {26-28}\) Additionally, a meta-analysis of PD suggested that cerebellar perfusion may be unchanged or slightly decreased.\(^ {26}\) In support of this view, hypoperfusion\(^ {29}\) and hypometabolism\(^ {30}\) were found in the cerebellum of PD patients. Increasing evidence indicates certain roles of the cerebellum in the pathophysiology of PD.\(^ {31}\)
The progressive perfusion decrease found in this study may reflect pathological changes induced by dopaminergic degeneration.\textsuperscript{31}

When the longitudinal perfusion changes of the PD without SCI group were taken out from those of the PD with SCI group, an excessive decrease in rCBF was found in the middle frontal gyrus. Similar to this result, the previous cross-sectional SPECT study in PD with SCI reported reduced rCBF in the medial frontal regions.\textsuperscript{10} Moreover, PD patients with MCI\textsuperscript{14} also showed decreased glucose metabolism\textsuperscript{14,32} and cortical atrophy\textsuperscript{11,12} in the middle frontal cortex. Our findings may suggest different brain changes related to cognitive impairment between healthy population and PD patients. In the progression to dementia, neuropathological changes generally start in the memory-related hippocampal and entorhinal cortex, spread into the parieto-temporal areas and finally affect the frontal cortices.\textsuperscript{33,34} However, neurological deficits in the prefrontal regions may occur in the earlier stages of cognitive decline in PD.\textsuperscript{35} The prefrontal cortex is known to interact with both the hippocampus regarding memory processes\textsuperscript{36} and the caudate nucleus for decision making and establishing associations between events,\textsuperscript{37} indicating its importance in executive function. Therefore, functional alterations in the prefrontal regions in the course of SCI in PD may account for the subjective neuropsychological symptoms such as deficits in memory retrieval, attention, and executive function.

Potential limitations of this study include that the patients with SCI were dichotomously classified according to clinical diagnosis. Levels of SCI could not be assessed on a continuous scale due to the lack of validated tools and therefore correlations between rCBF and symptom severity could not be examined. Secondly, the follow-up period was relatively too short to observe a progression from SCI to MCI or dementia. Despite these limitations,
the current longitudinal SPECT study provided insight into rCBF changes in PD patients with SCI and suggested that perfusion deficits in the middle frontal gyrus can be detected in a preclinical stage of both MCI and dementia. Future studies in larger samples are warranted to investigate whether perfusion decrease in the prefrontal regions can serve as a reliable and valid biomarker for SCI in PD.
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Conflicts of Interest

The authors declare no financial conflicts of interest.

Acknowledgements

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<table>
<thead>
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<th>Characteristics</th>
<th>Baseline</th>
<th>Follow-up</th>
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<tr>
<td>PDSCI</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>64.2±10.1</td>
<td>66.0±11.2</td>
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<td>Gender (male/female)</td>
<td>13/17</td>
<td>11/12</td>
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<td>Duration of PD symptoms (year)</td>
<td>3.0±2.5</td>
<td>2.3±1.8</td>
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<td>Hoehn–Yahr score</td>
<td>2 (1.0-2.0)</td>
<td>2 (1.0-2.0)</td>
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<td>Levodopa equivalent dose (mg/day)</td>
<td>340.6±162.9</td>
<td>289.7±240.3</td>
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<td>MMSE</td>
<td>27.8±1.4</td>
<td>27.1±2.7</td>
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<tr>
<td>CDR</td>
<td>0.5 (0-0.5)</td>
<td>0 (0-0.5)</td>
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<td>GDS</td>
<td>2.0 (2.0-3.0)</td>
<td>2.0 (1.0-2.0)</td>
<td>0.06</td>
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</table>

Table 1. Demographic and clinical characteristics of the participants

* Data are presented in mean±standard deviation or median (interquartile range).
† Independent t-test or Wilcoxon-Mann-Whitney test for continuous variables and chi-square test for gender.
Table 2. Brain areas with significant differences in regional cerebral blood flow

<table>
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<tr>
<th>Region</th>
<th>t</th>
<th>Voxel-level p</th>
<th>Cluster size (voxels)</th>
<th>Coordinates* (x, y, z)</th>
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<td><strong>PDSCI (B) &gt; PD (B)</strong></td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>L angular gyrus</td>
<td>4.36</td>
<td>&lt; 0.001</td>
<td>200</td>
<td>-46, -56, 26</td>
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<tr>
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<tr>
<td>R middle temporal gyrus</td>
<td>7.10</td>
<td>&lt; 0.001</td>
<td>708</td>
<td>58, -48, 6</td>
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<tr>
<td>L inferior occipital gyrus</td>
<td>6.10</td>
<td>&lt; 0.001</td>
<td>239</td>
<td>-38, -70, 8</td>
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<td>R fusiform gyrus</td>
<td>5.89</td>
<td>&lt; 0.001</td>
<td>280</td>
<td>36, -26, -22</td>
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<tr>
<td>R precuneus</td>
<td>5.76</td>
<td>&lt; 0.001</td>
<td>2497</td>
<td>6, -64, 48</td>
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<tr>
<td>R lingual gyrus</td>
<td>5.73</td>
<td>&lt; 0.001</td>
<td>522</td>
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<td>L cerebellum</td>
<td>5.15</td>
<td>&lt; 0.001</td>
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<td>-28, -72, -48</td>
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<tr>
<td>R cerebellum</td>
<td>4.38</td>
<td>&lt; 0.001</td>
<td>307</td>
<td>18, -84, -38</td>
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<tr>
<td>R calcarine cortex</td>
<td>4.22</td>
<td>&lt; 0.001</td>
<td>179</td>
<td>20, -88, 2</td>
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<tr>
<td>L fusiform cortex</td>
<td>4.09</td>
<td>&lt; 0.001</td>
<td>142</td>
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<tr>
<td>L middle frontal gyrus</td>
<td>3.25</td>
<td>0.001</td>
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<td>-38, 40, 6</td>
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<tr>
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*Coordinates are given in mm and refer to the Montreal Neurological Institute coordinate system

Fig. 1. Decrease in cerebral perfusion in the PD with SCI group compared with the PD without SCI group. The color bar represents voxel-level t-values. PD: Parkinson's disease, SCI: subjective cognitive impairment.
Fig. 2. Decreases in brain perfusion at the follow-up in the PD with SCI group compared with the baseline. The images are shown in neurological convention and the color bar represents voxel-level t-values.
PD: Parkinson's disease, SCI: subjective cognitive impairment.
Fig. 3. Excessive decrease in cerebral perfusion specific to the PD with SCI group compared with the PD without SCI group. The color bar represents voxel-level t-values. PD: Parkinson's disease, SCI: subjective cognitive impairment.