Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2014;37:276–285
DOI: 10.1159/000357128
Accepted: October 15, 2013
Published online: December 14, 2013

1420–8008/13/0376–0276$38.00/0
www.karger.com/dem

Original Research Article

Early Diagnosis of Alzheimer's Disease and Parkinson's Disease Associated with Dementia Using Cerebral Perfusion SPECT

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Key Words
Parkinson's disease associated with dementia · Alzheimer's disease · ^{99m}Tc-hexamethylpropyleneamine oxime perfusion SPECT

Abstract
Background: Since patterns of cognitive dysfunction in mild Parkinson's disease associated with dementia (PDD) are similar to those in mild Alzheimer's disease (AD), it is difficult to accurately differentiate between these two types of dementia in their early phases using neuropsychological tests. The purpose of the current study was to investigate differences in cerebral perfusion patterns of patients with AD and PDD at the earliest stages using single photon emission computed tomography (SPECT). ***Methods:*** We consecutively recruited 31 patients with mild PDD, 32 patients with mild probable AD and 33 age-matched healthy subjects. All subjects underwent ^{99m}Tc-hexamethylpropyleneamine oxime perfusion SPECT and completed general neuropsychological tests. ***Results:*** We found that both mild PDD and AD patients showed distinct hypoperfusion in frontal, parietal and temporal regions, compared with healthy subjects. More importantly, hypoperfusion in occipital and cerebellar regions was observed only in mild PDD. ***Conclusion:*** The observation of a significant decrease in cerebral perfusion in occipital and cerebellar regions in patients with mild PDD is likely useful to differentiate between PDD and AD at the earliest stages.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease that is clinically characterized by resting tremor, rigidity, bradykinesia and postural instability; it is pathologically characterized by a loss of neurons in the substantia nigra and by Lewy bodies [1]. Although cardinal

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DOI: 10.1159/000357128

motor symptoms predominate in the initial stages, many patients with PD also develop impairments in their cognitive functions that are sufficient to fulfill a diagnosis of dementia [2]. Patients with PD associated with dementia (PDD) mainly show executive dysfunction, disordered attention and visuospatial and constructional abilities [2, 3]. Moreover, elderly individuals with PD are at a 6-fold risk of developing dementia compared with age-matched subjects [4]. The prevalence of PDD varies from 4 to 93%, with an average prevalence of 40% [2, 5]. Previous neuropsychological studies have reported that 26% of PDD patients exhibit similar patterns of cortical cognitive impairment to those observed for patients with Alzheimer's disease (AD), the most common type of dementia characterized by deficits in memory, executive dysfunction, agnosia and apraxia [3]. Thus, it is difficult to sharply distinguish between PDD and AD using neuropsychological tests, particularly at the early stages [2]. Mild PDD is often misdiagnosed and is commonly confused with mild AD [6].

Accurate differential diagnoses of dementias have become increasingly important with the availability of current modern therapies and the promise of future novel treatments. Clinical diagnoses are often a reflection of accumulated clinical expertise and experience, but increased diagnostic precision has recently been sought from neuroimaging techniques including single photon emission computed tomography (SPECT) scanning [6]. SPECT has been used for years in patients with cognitive disorders to identify topographic patterns of brain dysfunctions in the main types of dementia [7]. The current study was designed to investigate differences in cerebral perfusion patterns of SPECT in patients with mild AD and mild PDD. A precise early diagnosis is quite valuable because it leads to proper disease management and likely prevents further disease progression.

Materials and Methods

Subjects

The current study was approved by the local ethics committee, and each patient provided written informed consent for the participation in this experiment. All subjects were prospectively recruited, and the study was conducted between July 2011 and May 2012. Finally, 31 patients with mild PDD, 32 patients with mild probable AD and 33 age-matched healthy subjects participated in this study.

All subjects were matched for their gender, age and education level. In addition, the two dementia groups (PDD and AD) were also matched for severity of dementia using performance on the Mini-Mental State Examination (MMSE), the extended version of the Clinical Dementia Rating Scale (CDR), the CDR sum of box scores and the Global Deterioration Scale (GDS) [8–10]. To ensure that we compared only the mild forms of PDD and AD, only patients with a CDR score of 0.5 or 1, a GDS score of 3 or 4, and an MMSE score between 20 and 24 were eligible for the study. The healthy control group was matched for age, gender and education level with the patient groups. The controls did not have any history or symptoms of PD, memory impairment or other cognitive dysfunctions according to a dementia screening questionnaire, and they did not have a history of other neurological impairments including head trauma, epilepsy, stroke or brain surgery.

All subjects were examined in the Dementia Clinic and the Movement Disorder Clinic of Incheon St. Mary's Hospital. Evaluation procedures consisted of a detailed medical history, physical and neurological examination, neuropsychological assessment and brain imaging [magnetic resonance imaging and ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) SPECT]. Patients' histories of medical and neurological problems were obtained from both patients and family members and from other caregivers.

All PDD patients were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnosis criteria [11], the DSM-IV criteria for dementia and the PDD criteria suggested by Emre et al. [12]. Additionally, we only selected PD patients with decreased dopamine transporters in the posterior putamen on ^{123}I-N-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) PET. We evaluated the motor severity of patients with PD using the Hoehn-Yahr staging measure as well as the Unified Parkinson's Disease Rating Scale Part III [13, 14]. In all of the PDD patients, the onset of PD preceded the development of dementia by at least 12 months. We excluded patients with markedly fluctuating cognition

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DOI: 10.1159/000357128

with pronounced variations in attention and alertness, and/or recurrent vivid hallucinations suggesting the presence of diffuse Lewy body disease. We also excluded PD patients who were taking medications (e.g. anticholinergic agents) that have been reported to influence cognition and memory, those who had any clinical signs compatible with atypical parkinsonian disorders and those who fulfilled the DSM-IV criteria for delirium or amnesic and depressive disorders [15]. In addition, we also excluded patients with secondary causes of parkinsonism (e.g. Wilson's disease, neuroleptic drug use and psychiatric diseases) that could, in our opinion, interfere with the safe conduct of the study. Twenty-four pure AD patients met the DSM-IV criteria for AD and the NINCDS-ADRDA criteria for probable AD [16]. Our AD patients had no parkinsonian symptoms or focal neurological signs or radiological lesions that typify cerebrovascular disease. None of the patients in this study fulfilled the criteria of mixed dementia or vascular dementia according to the NINDS-AIREN criteria [17].

All statistical analyses were performed using the SPSS software version 17.0 package. Analyses of variance with post hoc analyses were used for comparison of continuous variables, and Pearson's χ^2 analyses were used for comparison of categorical variables. Values are expressed as means and standard deviations. Statistical significance was assumed at a false detection rate of less than 5% (i.e., $p < 0.05$).

Brain SPECT Imaging

Scans obtained for all patients and healthy controls were interleaved in time. Images were obtained 40 min after intravenous injection of 1,110 MBq of ^{99m}Tc-HMPAO using a dual-head gamma camera (ECAM plus; Siemens Medical, Erlangen, Germany) equipped with a low-energy, fan beam collimator. The subjects were in a supine position with their eyes open during the scan. The room was dimly lit, and noise was kept to a minimum. Images were taken by rotating the camera a total of 360° at 3-degree intervals. Images were taken at a rate of 20 s per frame. The data obtained were reconstructed in a 128 × 128 matrix with a pixel size of 3.9 × 3.9 × 3.9 mm (field of view = 240 mm, slices thickness = 7 mm) and a 20% symmetric energy window at 140 keV. Continuous transaxial tomograms of the brain were reconstructed after back-projection with a Butterworth filter (cutoff frequency of 0.4 cycles/pixel, order 5) to reduce noise. ^{99m}Tc-HMPAO images were corrected for tissue attenuation using a standard commercial correction routine (Siemens).

SPECT Image Analysis

Image analyses were performed with Statistical Parametric Mapping 2 (SPM2) software (based on MatLab version 6.0) on an IBM PC with Windows XP operating system. SPECT data were first corrected for attenuation and scatter and then converted into the ANALYZE format. Mean pixel intensity across all slices in the imaging volume was calculated. Each pixel was then thresholded at 80% of this value to eliminate background noise and partial volume effects at the edge of the brain. Each SPECT scan was then spatially normalized by 12-parameter affine warping and sinc-linear interpolation onto a SPECT template brain from the Montreal Neurological Institute and reformatted to a 16-bit image of 79 × 95 × 68 voxels, each 2 × 2 × 2 mm in size. These images were spatially smoothed with a 16-mm full-width, half-maximum gaussian filter. Normalized regional cerebral blood flow (rCBF) values were calculated by dividing the CBF at each voxel by the global CBF obtained for each individual.

Normalized SPECT data acquired for the mild AD and mild PDD group were then compared with data from healthy controls. Group contrasts in rCBF were estimated at each voxel using a predefined general linear model available in the SPM2 software. A two-sample t test model was fitted, and a t statistic image [SPM(t)] was constructed. The AD and PDD composite t statistic image was thresholded at $t > 2.70$, corresponding to an uncorrected p value <0.005 in conjunction with a cluster filter of 100 voxels. The composite t statistic image for healthy subjects compared with AD and PDD was thresholded at $t > 2.70$, corresponding to an uncorrected p value <0.005 in conjunction with a cluster filter of 100 voxels. This combined application of a statistical threshold and a cluster filter has previously been shown to substantially reduce the rate of false-positive identification of activated pixels at any given threshold. For purposes of visualization and anatomic localization, the t score clusters were then projected onto the standard high-resolution T1-weighted MRI.

Results

Demographic and clinical information regarding the number of subjects and their mean age, length of education, duration of cognitive impairment, MMSE score, CDR score, sum of box score and GDS score by group is summarized in table 1. The AD and PDD groups were

Table 1. Demographic data and cognitive functions in the AD and PDD groups and healthy controls

Variables	AD	PDD	Controls	p value	Post hoc comparison
Subjects	32	31	33		
Men	8	5	10	>0.05	AD = PDD = controls
Mean age, years	75.78±6.52	75.03±3.67	66.94±5.40	>0.05	AD = PDD = controls
Mean education, years	3.23±3.84	3.66±3.88	11.73±4.35	0.001	AD = PDD < controls
Mean duration of dementia[1], months	14.28±6.55	15.03±8.79			
Mean duration before PDD[2], months		23.48±12.58			
Hoehn-Yahr staging		1.64±0.49			
UPDRS part III		13.73±3.06			
MMSE score	21.25±1.5	22.06±1.86	29.09±0.91	0.001	AD = PDD < controls
CDR score	0.81±0.25	0.76±0.48	ND	0.576	
SOB score	4.45±1.60	4.06±2.84	ND	0.508	
GDS score	3.59±0.76	3.23±0.92	ND	0.088	

Values are mean ± standard deviation. ND = Not done; UPDRS = Unified Parkinson's Disease Rating Scale; SOB = CDR sum of box.
[1] Duration of clinically notable cognitive impairment. [2] Duration of PD prior to the onset of mild dementia.

Table 2. Brain areas with significantly decreased rCBF in the PDD patients compared with the AD patients

k_E	t	Z	x, y, z	Brain areas
721	3.68	3.43	4, –64, –32	Right cerebellum, posterior lobe
473	3.19	3.02	6, –74, 8	Right occipital lobe, cuneus, BA 23
721	3.05	2.90	–12, –54, –14	Left cerebellum, posterior lobe
473	3.05	2.90	–2, –76, 8	Left occipital lobe, cuneus, BA 18

Height threshold: t = 2.69, uncorrected p = 0.005. Extent threshold: k = 100 voxels. k_E = Expected voxels per cluster.

similar in all demographic variables. Patients in the PDD group had a mean Hoehn-Yahr staging of 1.64 ± 0.49, a mean Unified Parkinson's Disease Rating Scale Part III score of 13.73 ± 3.06 and a mean duration of motor symptoms, prior to the diagnosis of mild PDD, of 23.48 ± 12.58 months. There were no significant differences in cognitive impairment between the AD and PDD groups.

Most interestingly, SPECT analysis showed significant hypoperfusion in the PDD patients compared with the AD patients in the posterior lobe of the cerebellum and in the cuneus in both occipital lobes [Brodmann area (BA) 18 and BA 23] (fig. 1a; table 2). However, significant hyperperfusion was not observed in any regions in the PDD patients compared with the AD patients.

In addition, hypoperfusion was observed bilaterally in the AD patients in the inferior frontal gyri (BA 45, BA 47), the medial frontal gyri (BA 25), the inferior temporal gyri (BA 20), the inferior parietal lobes (BA 40), the cingulate gyri (BA 32), and the posterior cerebellum with respect to the healthy subjects (fig. 1b; table 3). Hypoperfusion was also observed in AD in the left postcentral gyrus (BA 3) and the right precentral gyrus (BA 4).

On the other hand, the PDD patients showed hypoperfusion bilaterally in the posterior cingulate gyri (BA 31), the middle frontal gyri (BA 6), the medial frontal gyri (BA 6, BA 25), the insula (BA 13), the posterior cerebellum, the cuneus in the occipital lobes (BA 18) and the

Dement Geriatr Cogn Disord 2014;37:276–285
DOI: 10.1159/000357128

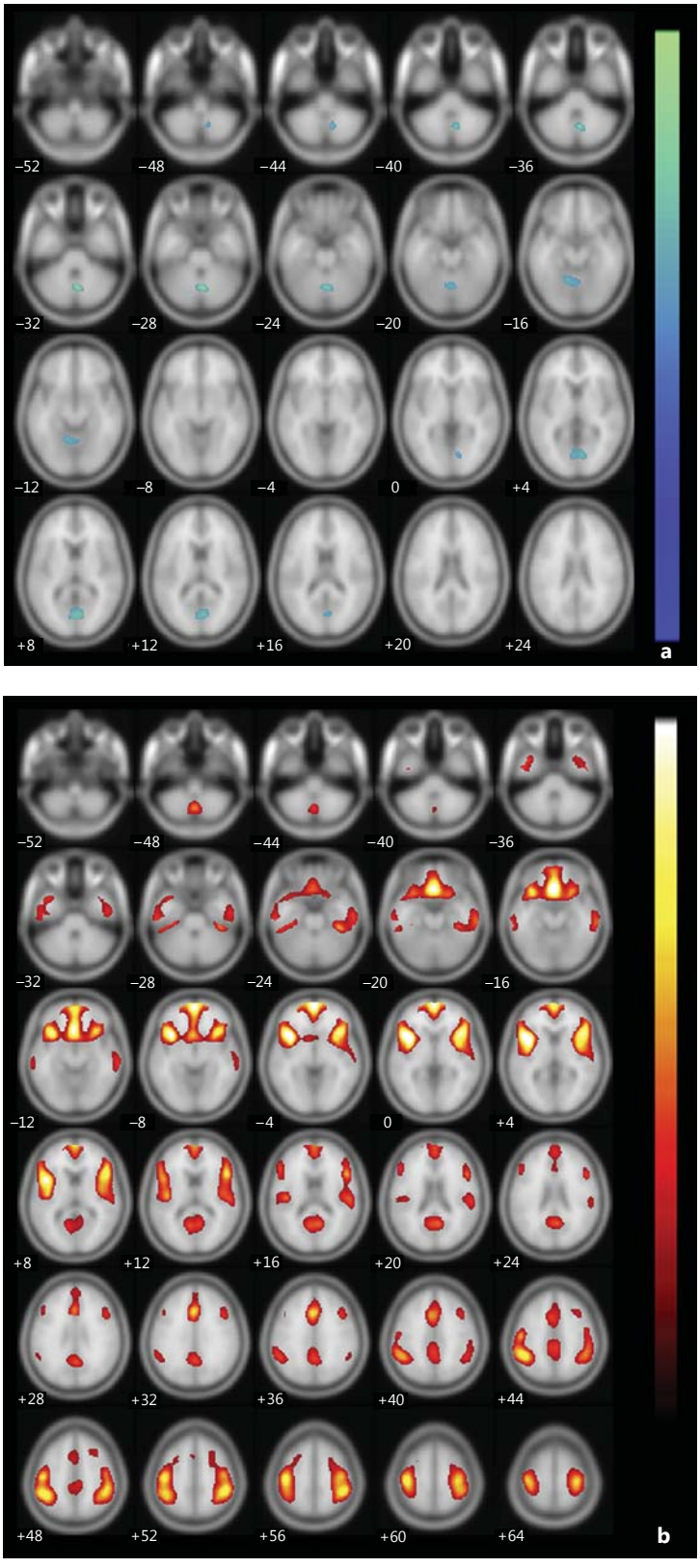

Fig. 1. a Fusion of SPM2 results to transaxial MR images. The PDD patients compared with the AD patients showed decreased perfusion in the posterior lobe of both cerebellums and in the cuneus in both occipital lobes. **b** Group differences in mild AD compared with healthy control. The patients with mild AD showed decreased perfusion in the inferior frontal gyri, the medial frontal gyri, the inferior parietal lobes, the cingulate gyri, the inferior temporal gyri, and the posterior cerebellum.

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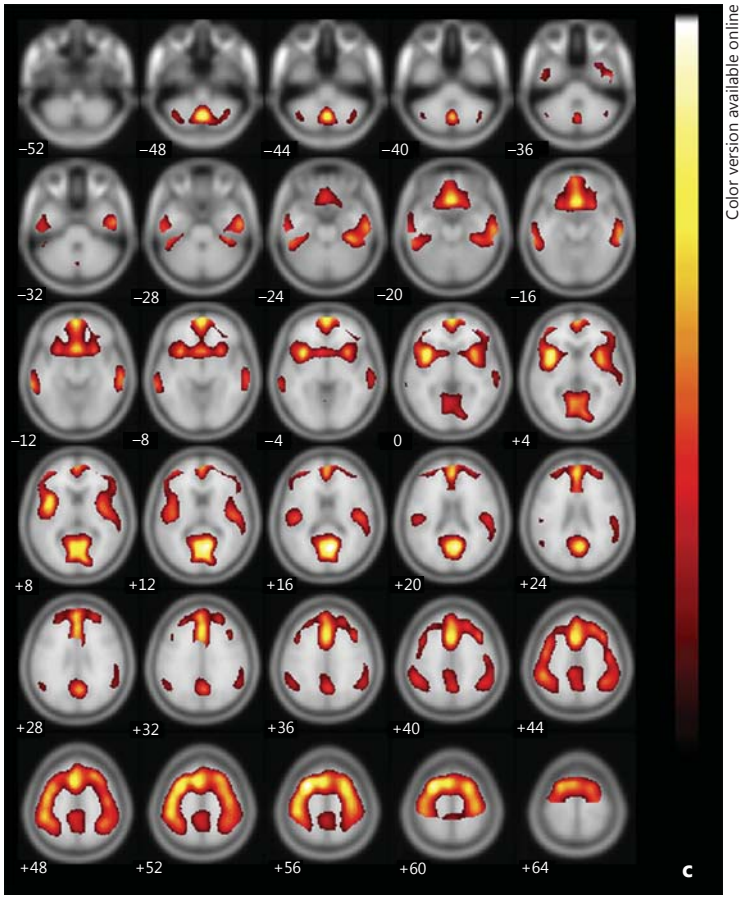

Fig. 1. c Group differences in mild PDD compared with healthy control. The patients with mild PDD showed bilaterally decreased perfusion in the posterior cingulate gyri, the middle frontal gyri, the medial frontal gyri, the insula, the posterior cerebellum, the cuneus of the occipital lobes, and the inferior temporal gyri.

inferior temporal gyri (BA 20) with respect to healthy subjects (fig. 1c; table 3). However, significant hyperperfusion was not observed in any regions in patients with early AD or early PDD compared with healthy controls.

Discussion

To the best of our knowledge, no study has yet explored potential differences in cerebral perfusion patterns in patients with PDD and AD at the earliest stages. This study compared changes in rCBF between groups of patients with mild AD and mild PDD and healthy subjects. We found decreases in rCBF in frontal, parietal and temporal regions in both mild AD and mild PDD patients compared with healthy subjects. Most interestingly, decreases in rCBF were observed in occipital and cerebellar regions in patients with mild PDD compared with mild AD patients. Although it is difficult to sharply distinguish between mild PDD and mild AD in general, we suggest that identifying such decreases in rCBF in occipital regions and in the cerebellum could be a crucial differential diagnostic method for these diseases in their early phases.

Comparisons of mild AD patients with healthy subjects revealed statistically significant decreases in blood flow bilaterally in regions of the parietal, frontal and temporal lobes. This finding is consistent with previous SPECT studies showing parietal, frontal and temporal deficits and is in broad agreement with studies showing characteristic parieto-temporal

Table 3. Brain areas with significantly decreased rCBF in the AD patients and PDD patients compared with the healthy subjects

k_E	t	Z	x, y, z	Brain areas
Comparison between AD patients and healthy subjects				
49,544	9.82	6.96	–42, 12, 2	Left frontal lobe, inferior frontal gyrus, BA 45
49,544	9.69	6.91	–2, 24, –16	Left frontal lobe, medial frontal gyrus, BA 25
49,544	8.70	6.48	2, 24, –16	Right frontal lobe, medial frontal gyrus, BA 25
49,544	7.68	5.99	42, 20, 0	Right frontal lobe, inferior frontal gyrus, BA 47
49,544	7.01	5.63	–44, –48, 46	Left parietal lobe, inferior parietal lobule, BA 40
49,544	6.93	5.59	–42, –22, 58	Left parietal lobe, postcentral gyrus, BA 3
49,544	6.93	5.58	46, –42, 56	Right parietal lobe, inferior parietal lobule, BA 40
49,544	6.34	5.24	–2, 20, 34	Left frontal lobe, cingulate gyrus, BA 32
49,544	5.84	4.94	40, –18, 56	Right parietal lobe, precentral gyrus, BA 4
638	5.50	4.75	6, –64, –40	Right cerebellum, posterior lobe
49,544	5.46	4.72	–4, 20, 32	Right limbic lobe, cingulate gyrus, BA 32
49,544	5.06	4.42	62, –26, –18	Right temporal lobe, inferior temporal gyrus, BA 20
49,544	4.55	4.06	–60, –22, –20	Left temporal lobe, inferior temporal gyrus, BA 20
638	3.04	2.87	–4, –66, –42	Left cerebellum, posterior lobe
Comparison between PDD patients and healthy subjects				
46,388	8.28	6.34	6, –66, 16	Right limbic lobe, posterior cingulate gyrus, BA 31
46,388	8.28	6.34	–4, –68, 16	Left limbic lobe, posterior cingulate gyrus, BA 31
46,388	8.08	6.24	–26, 10, 58	Left frontal lobe, middle frontal gyrus, BA 6
46,388	7.43	5.91	–40, 4, 6	Left insula, BA 13
1,685	7.37	5.87	4, –64, –42	Right cerebellum, posterior lobe
1,685	7.37	5.87	–6, –66, –42	Left cerebellum, posterior lobe
46,388	7.10	5.72	–4, 16, 44	Left frontal lobe, medial frontal gyrus, BA 6
46,388	6.92	5.62	–2, 24, –18	Left frontal lobe, medial frontal gyrus, BA 25
46,388	6.92	5.62	2, 26, –16	Right frontal lobe, medial frontal gyrus, BA 25
46,388	6.51	5.38	26, 14, –6	Right frontal lobe, middle frontal gyrus, BA 6
46,388	6.32	5.27	–6, –70, 18	Left occipital lobe, cuneus
46,388	5.84	4.97	38, 6, 6	Right insula, BA 13
46,388	5.39	4.67	–62, –30, –16	Right temporal lobe, inferior temporal gyrus, BA 20
1,972	5.07	4.45	–58, –24, –20	Left temporal lobe, inferior temporal gyrus, BA 20
46,388	4.47	4.02	6, –76, 22	Right occipital lobe, cuneus, BA 18

Height threshold: t = 2.70, uncorrected p = 0.005. Extent threshold: k = 100 voxels. k_E = Expected voxels per cluster.

changes associated with AD [18, 19]. Comparisons of mild PDD patients with healthy subjects showed a significant decrease in adjusted rCBF in the cerebellar dentate nucleus and in occipital, parietal, frontal, and temporal regions with little asymmetry, but no significant regions of decreased rCBF were found in the basal ganglia. Previous studies have reported that PD patients without concurrent dementia show hypoperfusion of rCBF in parietal, frontal, occipital and cerebellar regions. This hypoperfusion is worse in patients with PDD compared with patients presenting with PD without dementia [5, 20–22]. Our results were in accordance with these previous studies. We might not find a decrease in the expected alteration of rCBF such as hyperperfusion or hypoperfusion in the basal ganglia in this study, likely because alterations of rCBF in the basal ganglia have typically been shown in patients with advanced PD [20, 23, 24].

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DOI: 10.1159/000357128

In contrast, we did find reduced rCBF in mild PDD patients compared with mild AD patients in bilateral occipital and cerebellar regions in the current study. These occipital and cerebellar regions, which are not typically thought to influence cognitive decline, showed significant decreases in rCBF in mild PDD compared with mild AD. This cerebellar hypoperfusion may be due to the involvement of cerebello-thalamo-cortical circuits, particularly those originating or terminating in the vermis/paravermis region of the cerebellum, which are affected by PD. The cerebellum is an important component in motor control and is known to influence cerebral-cortical activity via cerebello-thalamo-cortical circuits [25, 26]. These cerebello-thalamo-cortical circuits have been implicated in somatosensory integration and information updating [26, 27]. The cerebellum is also involved in the coordination of movement, and changes in perfusion/metabolism in the cerebellum in PD have been reported [23, 28]. A recent meta-analysis study demonstrated that several quantitative PET studies revealed significant cerebellar hypoperfusion or hypometabolism in PD, but other studies reported no significant changes in the cerebellum in PD [29]. Thus, the authors suggested that the cerebellum probably is unchanged in PD or at least displays less decrease [29]. However, results from several previous studies regarding perfusion/metabolism in the cerebellum in PD have been contradictory [30]; namely, cerebellar blood flow and metabolism in PD have been reported to be increased, decreased, or unchanged [21–23, 31–33]. Therefore, the role of the cerebellum in PD pathophysiology is not well understood. Significant reductions in rCBF in occipital regions in mild PDD, but not mild AD, are in keeping with previous studies which have reported occipital hypofunction in PD [5, 20, 34, 35]. Occipital hypofunction may be associated with impairments in saccadic eye movements, hemispatial neglect, or a combination of the two [5, 20, 35].

This study is limited by the fact that individual patient analysis and quantitative evaluation were not performed. Further research with additional analyses is required in order to confirm the findings of this study. Another limitation of this study was the use of PDD diagnostic criteria that have not yet been validated, and differentiating between PDD and dementia with Lewy bodies on the basis of clinical criteria is difficult. Furthermore, we were unable to carry out any neuropathological investigations to confirm the presence of Lewy body pathology and Alzheimer pathology since the patients are still living [36]. However, we attempted to reduce these confounders by including those patients who fulfilled two sets of diagnostic criteria and had decreased dopamine transporter uptake in the striatum on FP-CIT PET, although this selection procedure might have been an obstacle to the patients having a prior clinical suspicion of PDD.

In conclusion, we propose that the presence of hypoperfusion in these areas might be a useful clinical marker of early PDD, particularly relative to mild AD. Further large-scale, longitudinal studies are needed to clarify differences in rCBF in the two diseases and to investigate whether this hypoperfusion, either at baseline or over time, predicts the progression of PDD or AD.

Acknowledgements

This work was supported by the Global Frontier R&D Program on Human-Centered Interaction for Coexistence and the National Research Foundation of Korea grant funded by the Korean Government (MEST; 2012M3A6A3055707).

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DOI: 10.1159/000357128

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