Relationship Between Changes in Cerebral Blood Flow and Neuropsychiatric Symptoms in Dementia with Lewy Bodies

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Abstract

In this study, we compared cerebral blood flow（CBF）images in patients with dementia with Lewy bodies（DLB）with those in the normal control and Alzheimer's disease（AD）groups, and investigated the relationship between DLB and neuropsychiatric symptoms. The subjects in the probable DLB group were 28 outpatients who fulfilled the diagnostic criteria for DLB and underwent single-photon emission computed tomography（SPECT）. CBF was also evaluated in 32 healthy subjects and 37 patients with AD for comparison between groups, and to evaluate the presence of fluctuating cognition, visual hallucinations, parkinsonism, REM sleep behavior disorder (RBD), and depression in the DLB group. Compared with the AD group, there was a significant decrease in CBF in the medial occipital lobe in the DLB group. Compared with the DLB group, there was a significant decrease in CBF in the medial temporal lobe in the AD group. A significant decrease in CBF was also observed in the right middle temporal gyrus in the DLB group with visual hallucinations and in the right superior temporal gyrus in the DLB group with depressive symptoms. There were no significant differences in CBF with or without fluctuating cognition, parkinsonism, and RBD in DLB. Statistical imaging analysis therefore suggested that visual hallucinations and depressive symptoms were associated with specific areas of decreased CBF. Thus, it was suggested that neuropsychiatric symptoms of DLB may be associated with specific areas of brain dysfunction.

Key words : Dementia with Lewy bodies, Cerebral blood flow SPECT, Statistical imaging analysis, Visual hallucinations, Depressive symptoms, Parkinsonism

Introduction

The number of patients diagnosed with dementia continues to increase as the population ages. Dementia with Lewy bodies（DLB）is a neurodegenerative disease that was first reported in 1976 by Kosaka et al.[1] and is the second most common form of dementia, after Alzheimer's disease（AD）. An essential requirement for DLB diagnosis is a progressive cognitive decline that is of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. DLB has major symptoms such as visual hallucinations, parkinsonism, fluctuating cognition, and REM sleep behavior disorder（RBD）, and also includes sensitivity to antipsychotic agents or severe autonomic dysfunction as common clinical features.

A clinical diagnosis of DLB is made according to international clinical diagnostic criteria[2]. DLB is known to include depressive symptoms in the prodromal stage[3]; there are reports that depressive symptoms are more common in DLB patients than in AD patients, and

40% of DLB patients have major depression episodes[4)5)]. In addition to depressive symptoms, DLB presents a variety of psychiatric symptoms such as hallucinations, delusions, and agitation. Therefore, DLB causes a number of impairments in daily living[6)], leading to a decline in quality of life and an increasing burden on caregivers[7)].

Furthermore, geriatric medical care and management are required because DLB is often combined with falls, fractures, aspiration, and pneumonia[8)]. However, the appearance of psychiatric symptoms is inconsistent and their occurrence is difficult to predict. In the early stages of disease, it is especially difficult to clinically distinguish DLB patients from AD patients because of their overlapping clinical and pathological features. To differentiate DLB from other dementias, it is important to clarify the differences between DLB and AD, which is the most common type of dementia. In addition, predicting the manifestation of psychiatric symptoms in DLB is important for early psychological intervention and for the evaluation of drug treatment options.

In the diagnostic criteria of DLB, neuroimaging findings are important. Among the diagnostic criteria, dopamine transporter（DAT）scintigraphy and Meta−iodo−benzylguanidine（MIBG）myocardial scintigraphy have become indicative biomarkers that directly contribute to diagnosis. As supportive biomarkers, brain magnetic resonance imaging（MRI）/computed tomography（CT）and Single−photon emission computed tomography（SPECT）/Fluorine−18 2−fluoro−2−deoxy−D−glucose（FDG）positron emission tomography（PET）are included[2)]. However, in Japan at least, indicative biomarkers such as DAT scintigraphy and MIBG myocardial scintigraphy are expensive, and a cheaper and simpler biomarker is required.

SPECT is a functional brain imaging study that is comparatively inexpensive to perform. Cerebral blood flow（CBF）is determined by the synaptic density and activity of each brain region when there are no structural abnormalities in the cerebral blood vessels[9)]. Because sites with reduced cerebral nerve cell function are depicted as sites with reduced blood flow, a differential diagnosis of dementia can be performed using differences in the characteristic patterns of blood−flow−reduced sites for each disease. The characteristic CBF reduction in DLB is seen as hypoperfusion in the occipital lobe, including the primary visual cortex. In AD, the CBF decrease begins in the posterior cingulate gy-

rus and precuneus before spreading to the parietal lobe, temporal lobe, and frontal lobe as the disease progresses. However, the primary sensory/motor cortex, occipital visual cortex, thalamus, basal ganglia, and cerebellum are not easily damaged in AD, and the blood flow in these regions is relatively maintained. This is an important diagnostic point. A meta−analysis reported that the sensitivity and specificity of SPECT in distinguishing between DLB and AD is 70.2% and 76.2%, respectively（DLB：hypoperfusion in the occipital or bilateral parietal lobes；AD：hypoperfusion in the unilateral or bilateral temporal/parietal lobes)[10)]. However, although many studies have compared CBF between dementia diseases such as DLB and AD, there are limited studies comparing CBF in relation to differences in symptoms. Many studies have reported the relationship between visual hallucinations and CBF, including systematic reviews that conclude that visual hallucinations are related to hypoperfusion and hypometabolism in the occipital lobe[11)]. However, few studies have compared the relationship between CBF and other neuropsychiatric symptoms of DLB.

In this study, we aimed to accurately distinguish between DLB and AD patients by directly comparing CBF of patients with DLB to that of patients with AD and measuring the difference. Furthermore, by comparing the relationship between neuropsychiatric symptoms and CBF of DLB, we aimed to clarify imaging−related factors related to neuropsychiatric symptoms of DLB.

Subjects and methods

We recruited patients with DLB or AD who underwent consultation at the Department of Psychiatry of Fukuoka University Hospital from 2011 to 2017. Patients with DLB fulfilled the diagnostic criteria for probable DLB[2)] and patients with AD fulfilled the National Institute of Neurologic, Communicative Disorders and Stroke AD and Related Disorders Association（NINCDS−ADRDA）diagnostic criteria for probable AD[12)] were included. All patients received a medical history interview and neurological examinations by geriatric psychiatry specialist or dementia specialist and were examined using mini−mental state examinations（MMSE）and SPECT. Their diagnoses were made by the consensus of a panel composed of psychiatrists, neurologists, and a nuclear medicine specialist. We excluded subjects who were taking acetylcholinesterase inhibitors, had his-

tories of psychiatric diseases, or had obvious cerebrovascular lesions in MRI or CT scans. Patients with vascular stenosis or stroke were excluded because their asymmetric cerebral perfusion profile may have outweighed the degenerative process and confounded the results. The study participants and their legal representative gave written consent for their participation in this study. In total, 28 DLB patients and 37 AD patients were selected.

Geriatric psychiatric specialist or dementia specialist identified neuropsychiatric symptoms such as fluctuating cognition, visual hallucinations, parkinsonism, RBD, and depression in patients with DLB. To compare with the DLB group for MMSE and CBF, we selected 32 age-matched normal controls（NC）from a normal database in the National Center of Neurology and Psychiatry. This study was approved by the Institutional Review Board of Fukuoka University (Ethical review number 2018M028).

All participants with DLB and AD received SPECT with Tc−99m ethylcysteinate dimer（Tc−99m ECD）. The SPECT scan started 5 min after the administration of 600 MBq of Tc−99m ECD, and data were collected for 20 min using a 3−head gamma camera（PRIZM 3000 IRIX, Philips）. The SPECT images were reconstructed using the filtered back projection（FBP）method using a Butterworth filter（order 8, cut−off level 0.22 cycles/pixel）. Attenuation correction was performed using Chang's method. Image analysis was performed using statistical parametric mapping（SPM）12 software（Functional Imaging Laboratory, Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, UK）running in MATLAB R2015a（The MathWorks, Natick, MA, USA）.

All participants with segmentation errors were excluded by visual inspection. All of the images were spatially normalized into the MNI standard template （Montreal Neurological Institute, McGill University, Montreal, Canada）prior to statistical analysis. Spatially normalized images were smoothed by convolution using an isotopic Gaussian kernel with a 12 mm full width at half maximum. Statistical comparisons within subjects were performed on a voxel−by−voxel basis using two−way ANOVA（full factorial analysis on SPM12), generating SPM（t）maps. The resulting maps of F−statistics and t−statistics were created using a height threshold at $p < 0.01$（F test）and $p < 0.001$（f test）, uncorrected for multiple comparisons. The extent threshold of 400 voxels was also used when considering whether the cluster was significant. The two−tailed paired t test was used to compare clinical features at the initial examination with those at the second examination in each of the two groups, while the two−tailed non−paired t test was used to compare the clinical and demographic characteristics between the two groups.

Results

Demographic and cognitive findings of all participants with DLB, AD, and NC are shown in Table 1. MMSE scores were significantly lower in the DLB and AD groups than in the NC group.

The demographic summary and neuropsychiatric symptoms of DLB are shown in Table 2. The age at onset was 70.9 ± 6.1 years（range 60−81), and the mean length of education was 12.3 ± 3.2 years（range 1−20). The percentages of core symptoms were 67.9% for fluctuating cognition, 60.7% for visual hallucinations, 82.1% for parkinsonism, and 35.7% for RBD. 25.0% of DLB group had 3 core symptoms that are fluctuating cognition, visual hallucinations, and parkinsonism. 21.4% of DLB group had 2 core symptoms that are fluc-

Table 1 Demographic features of study participants

	DLB	NC	AD
N	28	32	37
Sex（F/M）	19/9	20/12	29/8
Age, mean±SD（range）, y	72.3±6.5（62−82）	72.6±3.4（68−78）	73.0±8.6（54−85）
MMSE score, mean±SD（range）	24.1±4.7*（13−30）	29.8±0.4（29−30）	21.3±4.5*（12−28）

*$p < 0.05$：Tukey−Kramer test compared with NC（two−sided）.
DLB, dementia with Lewy bodies；NC, normal controls；AD, Alzheimer's disease；MMSE, mini−mental state examination；SPECT, single−photon emission computed tomography.

tuating cognition and parkinsonism. Depressive symptoms were as frequent as 64.3%.

Next, we showed changes in CBF obtained by SPECT image analysis. When comparing between NC and DLB, significant hypoperfusion was observed in a wide range of cerebral cortex areas in the DLB (Fig. 1).

Comparing AD and DLB groups, there was significant hypoperfusion in the medial occipital lobe in the DLB compared with AD (Fig. 2a). In addition, the AD group had significant hypoperfusion around the hippocampus and in the posterior cingulate gyrus and precuneus compared with DLB (Fig. 2b).

Next, we measured changes in CBF in the DLB group with or without fluctuating cognition, visual hallucinations, parkinsonism, RBD, or depressive symptoms. A significant hypoperfusion was observed in the right middle temporal gyrus in the group with visual hallucinations compared with the group without visual hallucinations (Fig. 3). In addition, when comparing CBF with and without depressive symptoms, there was a significant hypoperfusion in the right superior temporal gyrus in the group with depressive symptoms (Fig. 4). There were no significant differences in CBF with or without fluctuating cognition, parkinsonism, and RBD in DLB, however.

Table 2 Demographic summary of DLB subjects (n＝28)

|	
Age at disease onset, mean±SD (range), y	70.9±6.1 (60–81)
Education, mean±SD (range), y	12.3±3.2 (1–20)
Fluctuating cognition, %	67.9
Visual hallucination, %	60.7
Parkinsonism, %	82.1
REM sleep behavior disorder, %	35.7
Depression, %	64.3
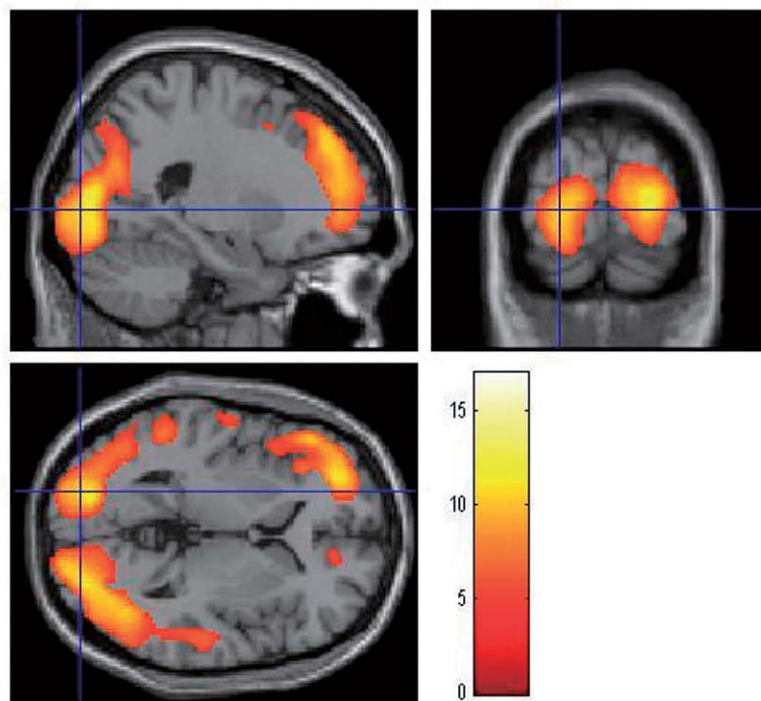
Fig. 1：Brain regions with hypoperfusion in patients with DLB (n＝28) compared with NC (n＝32) using SPM analysis of cerebral perfusion SPECT.
Patients with DLB showed a hypoperfusion in a wide range of cerebral cortex included posterior, frontal and parietal lobe (Voxel level：p＜0.001 uncorrected；cluster level：p＜0.05 FWE corrected). The color bar represents the range of the T value.
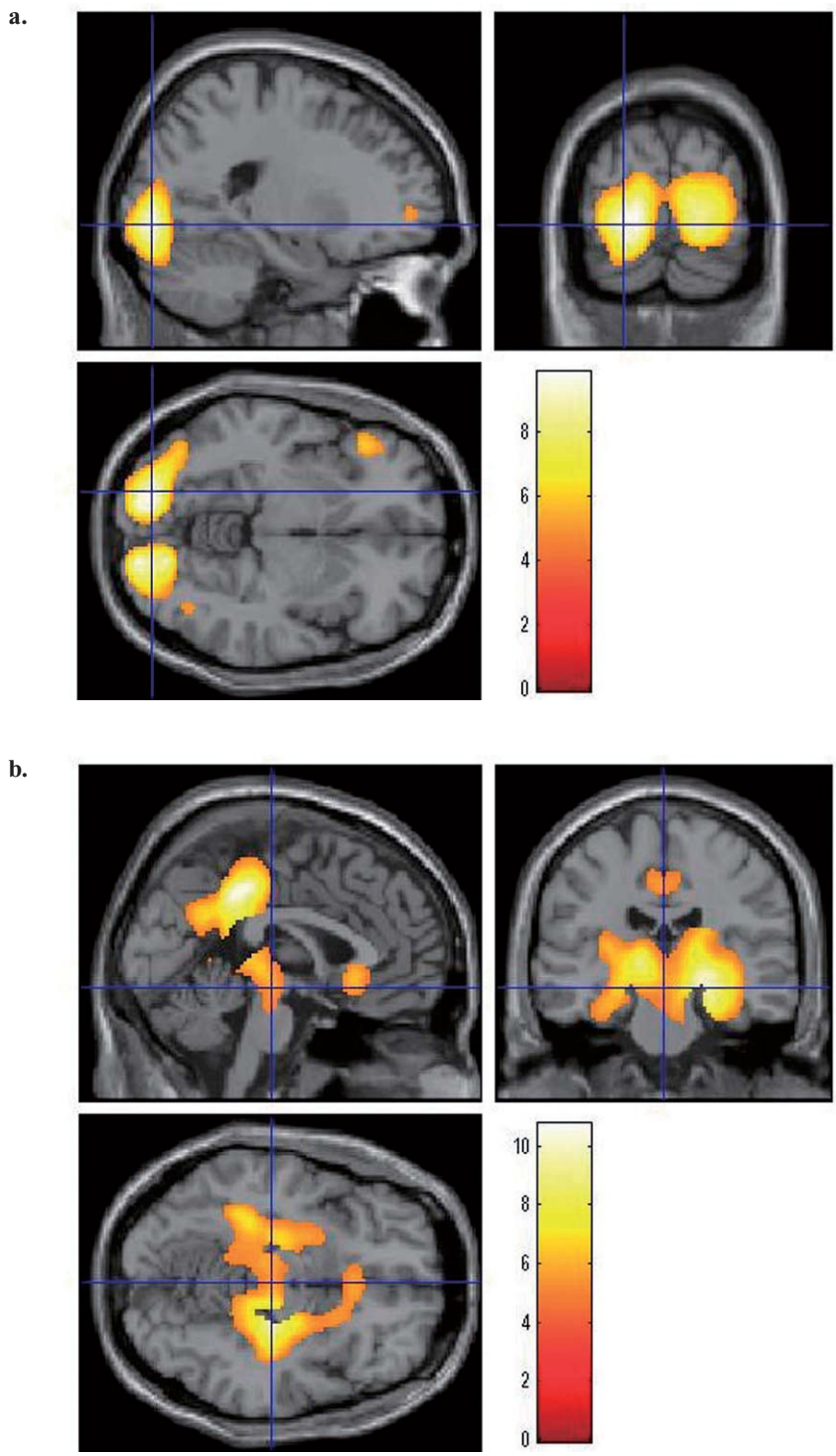
Fig. 2：Brain regions with hypoperfusion in patients with DLB（n＝28）compared with AD（n＝37）using SPM analysis of cerebral perfusion SPECT.
   a. Patients with DLB showed a hypoperfusion in the medial occipital lobe（Voxel level：p＜0.001 uncorrected；cluster level：p＜0.05 FWE corrected）． The color bar represents the range of the T value.
   b. Patients with AD showed a hypoperfusion around the hippocampus and in the posterior cingulate gyrus and precuneus（Voxel level：p＜0.001 uncorrected；cluster level：p＜0.05 FWE corrected）． The color bar represents the range of the T value.
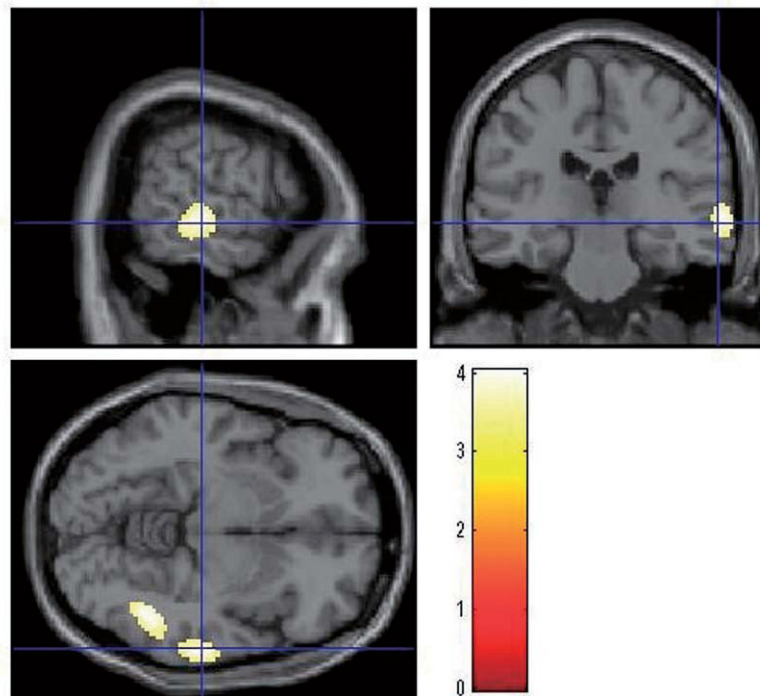
Fig. 3 : Brain regions with hypoperfusion in patients with visual hallucinations (n＝17) compared with patients without visual hallucinations (n＝11) in DLB using SPM analysis of cerebral perfusion SPECT.
Patients with visual hallucinations in DLB showed a hypoperfusion in the right middle temporal gyrus (Voxel level : p＜0.001 uncorrected ; cluster level : p＜0.05 FWE corrected). The color bar represents the range of the T value.
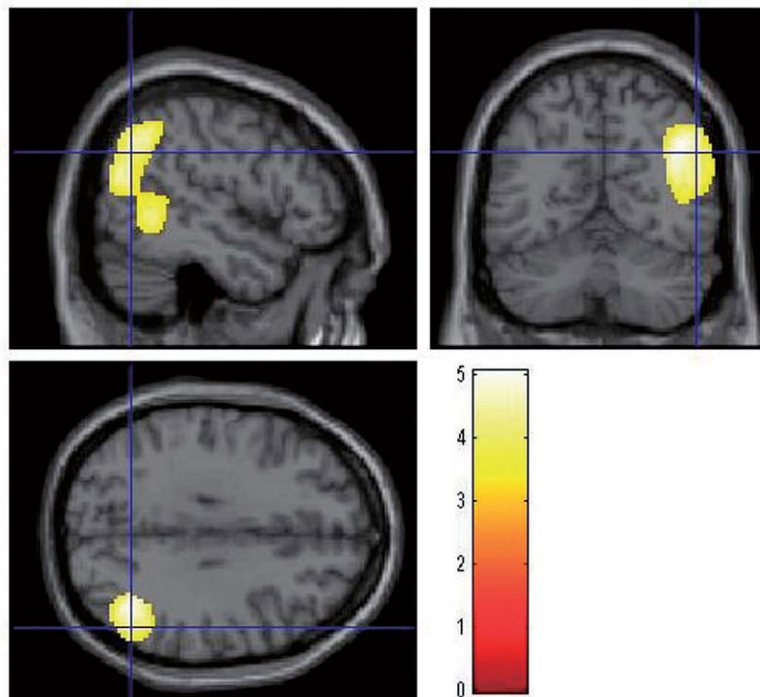
Fig. 4 : Brain regions with hypoperfusion in patients with depressive symptoms (n＝18) compared with patients without depressive symptoms (n＝10) in DLB using SPM analysis of cerebral perfusion SPECT.
Patients with depressive symptoms in DLB showed a hypoperfusion in the right superior temporal gyrus (Voxel level : p＜0.001 uncorrected ; cluster level : p＜0.05 FWE corrected). The color bar represents the range of the T value.

Discussion

This study revealed differences between DLB and NC or AD groups in SPECT imaging and demonstrated changes in CBF with different neuropsychiatric symptoms of DLB.

In patients who met the clinical criteria for DLB, statistical analysis of SPECT images revealed hypoperfusion in the occipital lobes of DLB compared with AD, while AD had hypoperfusion in the posterior cingulate gyrus and precuneus compared with DLB；this pattern of decreased CBF has been shown in previous studies[13]–[17].

With visual hallucinations, there was a significant decrease in CBF in the right middle temporal gyrus. The medial temporal gyrus is involved in different processes such as distance recognition, face recognition, and word recognition during reading tasks[18]. The lower two–thirds of the temporal gyrus（middle and inferior temporal gyrus）are involved in morphological vision and perception. Disruption of this area may result in color blindness, image agnosia, and prosopagnosia. Lanctot et al. showed that CBF in the right middle temporal gyrus was relatively low in AD in association with aggression[19]. Although visual hallucinations are known to be associated with reduced occipital lobe blood flow in DLB[11], the results of our study with and without visual hallucinations of DLB patients suggest that another mechanism may be involved in visual hallucinations. Hypoperfusion in the medial temporal gyrus may cause visual illusions and misidentification, which may manifest as visual hallucinations. In addition, when visual hallucinations occur, patients are often clinically aggressive, which suggests that the appearance of aggression may promote visual hallucinations.

With depressive symptoms, there was a significant decrease in CBF in the right superior temporal gyrus in our result. The right superior temporal gyrus consists of the primary auditory cortex and auditory areas[20] and is involved in emotional processing and social cognition[21].

A meta–analysis of fMRI studies of depression noted that the right superior temporal gyrus is one of the most consistently identified areas involved in its pathophysiology[22]. It is also reported that smaller volumes of the left hippocampus and right superior temporal gyrus on MRI in patients with depression are related to longer durations of depressive symptoms[23], suggesting a close relationship between the right superior temporal gyrus and depressive symptoms. In addition, fMRI studies have shown that depressed patients with AD have reduced functional connectivity between the hypothalamus and the superior temporal gyrus[24]. In PD patients with depressive symptoms, decreased CBF is also observed in the right superior temporal gyrus and right medial orbitofrontal cortex[25], supporting the results of this study. Abnormal superior temporal gyrus activity was observed in the background of patients with depressive symptoms, suggesting that depressive symptoms in DLB also show similar changes.

The present study has several limitations. First, the sample size was small, and the statistical power was therefore low. Future studies will need to use larger sample sizes to increase statistical power. Second, neuropsychiatric symptoms were assessed only for their presence and absence, and symptom degree was not assessed using a rating scale. In addition, although symptoms were evaluated by a trained psychiatrist, they may have been underestimated or overestimated. Thus, we will consider using an evaluation scale in the future. Third, a group of patients with major depressive disorder （MDD）should be included in future studies. A comparison of patients with MDD and DLB will provide more detailed information about the pathophysiology of depression in DLB patients.

Conclusions

In patients with DLB, SPECT imaging and statistical analysis revealed areas of CBF that differed in the presence or absence of neuropsychiatric symptoms. It was suggested that neuropsychiatric symptoms of DLB may be associated with specific areas of brain dysfunction.

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