to the overlapping figure identification test in PD patients without dementia, in whom impairments of visual processes are not necessarily related to visual recognition specifically but to cognitive slowing.[17] Therefore, there is currently no direct evidence of a disability in visual recognition related to identification of overlapping figures in PD patients without dementia. Also, the brain regions responsible for this deficit in PD remain unclear. In this study, we assessed visual recognition deficits with the Poppelreuter-type overlapping figure identification test in PD patients without dementia and used ^{18}F-fluorodeoxyglucose (FDG) and PET with voxel-by-voxel whole-brain analysis to identify the brain regions responsible for these deficits.

Patients and Methods

Subjects

The participants were 44 idiopathic PD patients and 24 healthy controls recruited from local communities and matched for age, sex, educational level, visual acuity, and Mini–Mental State Examination (MMSE) score[18] whose demographics and clinical characteristics are shown in Table 1. No difference was found between 40 PD patients (excluding 4 patients with missing data) and controls in the Digit-Span and Tapping-Span subtests of the Wechsler-Memory Scale–Revised (t test, $P > .1$). Diagnosis of PD was made by board-certified neurologists according to UK PD Society Brain Bank criteria.[19] Patients' motor symptoms were evaluated using Hoehn and Yahr staging[20] and the Unified Parkinson's Disease Rating Scale (UPDRS) motor part,[21] which recorded "on" medication for patients who were prescribed antiparkinsonian drugs. The inclusion criteria for patients in this study were: (1) study-entry age 55–75 years, (2) disease onset age ≥40 years, (3) Hoehn and Yahr stages 1–3, (4) no ocular disease, and (5) best-corrected visual acuity in either eye better than 20/70. The exclusion criteria were: (1) any complication due to other neurological, psychiatric or ocular diseases (excluding mild cataracts); (2) any magnetic resonance imaging (MRI) evidence of focal brain lesions; and (3) dementia, that is, Clinical Dementia Rating (CDR) ≥1.[22] Ten PD patients had never been prescribed antiparkinsonian drugs; the remaining patients, including 5 who were given trihexyphenidyl hydrochloride, were being treated with antiparkinsonian drugs. None of the patients had visual hallucinations during the month prior to participating in the study, according to the Neuropsychiatric Inventory.[23]

All patients gave written informed consent after they and their relatives were given a detailed description of the study, which was approved by the Ethical Committee of Tohoku University Graduate School of Medicine and conducted in accordance with the Declaration of Helsinki.

TABLE 1. Demographic and clinical characteristics of the PD patients and healthy controls

	PD (n = 44)	Controls (n = 24)	P value[a]
Age, mean (SD), y	66.3 (5.5)	66.1 (5.3)	.89
Education, mean (SD), y	11.8 (2.2)	11.3 (2.0)	.31
Sex (female/male), n	19/25	12/12	.59
Visual acuity, median (range)	1.0 (0.4–1.0)	0.8 (0.4–1.0)	.39
MMSE, mean (SD); max. 30	27.8 (2.0)	28.5 (1.5)	.10
Span task,[a] mean (SD), n			
Digit span (forward)	5.4 (0.9)	5.3 (0.8)	.55
(backward)	4.0 (1.0)	4.0 (0.6)	.91
Tapping span (forward)	5.3 (0.9)	5.5 (0.9)	.57
(backward)	4.8 (0.9)	5.0 (0.8)	.16
CDR (0/0.5), n	31/13	—	—
Disease duration, mean (SD), y	4.9 (4.4)	—	—
Onset age, mean (SD), y	61.4 (6.7)	—	—
Daily levodopa equivalent dosage, mean (SD), mg	649.0 (717.0)	—	—
Hoehn and Yahr, median (range)	2.5 (1.0–3.0)	—	—
UPDRS motor part, mean (SD)	19.7 (7.6)	—	—

CDR, Clinical Dementia Rating; MMSE, Mini–Mental State Examination; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; SD, standard deviation; —, no data.
[a]t Test was used except for sex ratio (chi-square test) and visual acuity (Mann–Whitney test).
[a]Four patients were not assessed (n = 40).

Overlapping Figure Identification Test

We devised an overlapping figure identification test consisting of 10 materials, each composed of 4 overlapping, achromatic line drawings of common objects selected from a standardized picture set,[24] examples of which are shown in Figure 1. Mean size of the materials was 12.3 ± 1.8 cm × 9.5 ± 1.2 cm, with a high contrast of 0.996. The contrast of those stimuli was greater than the contrast of the visual acuity chart (0.896) used in the present study. The overlapping figure identification test was administrated "on" medication for those who were prescribed antiparkinsonian drugs. The materials were presented one by one at the center of a display placed 75 cm from the subject in a standardized, darkened environment. The test started with a trial number presented on the display; then the test material appeared for a maximum of 1 minute. After each test material disappeared, the experimenter pressed a button to bring up the next trial number. At the beginning of the test, subjects were instructed to name the 4 objects in each trial and say, "That is all" if they could not identify any more objects. When a subject said this or could not name any of the 4 objects within 1 minute, the material was deleted

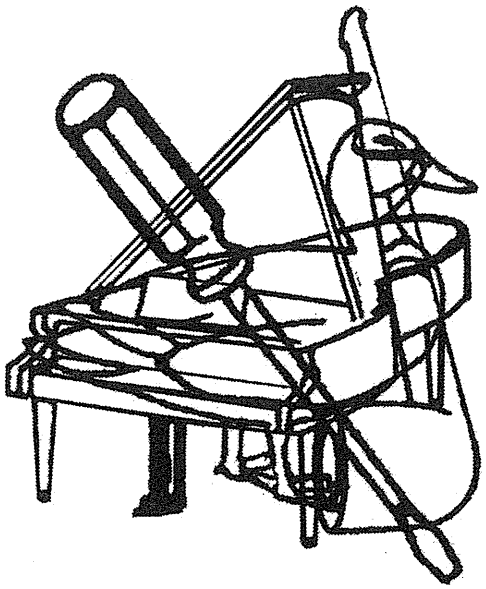

FIG. 1. An example of the material used for the overlapping figure identification test. The materials were composed of 4 overlapping, achromatic line drawings of common objects. Examples: a duck, a grand piano, a pipe, and a flathead screwdriver.

from the display. We considered a response to have been given only when a subject clearly identified an object.

We used 2 indices: (1) a correct response score, that is, the number of objects correctly identified; and (2) an illusory response score, that is, the number of objects identified that did not correspond to any of the 4 drawings used in a trial. Illusory responses were defined as answers that were completely irrelevant to the stimuli either in concept or visual form. Simple comprehensible misnaming (eg, pigeon for duck) or superordinate substitutions (eg, bird for duck) were classified as correct responses. Classification of equivocal responses was determined by 3 raters.

To test the possibility that PD patients' lower performance was a result of executive dysfunctions (cognitive slowing or verbal fluency deficits), we performed an additional analysis on the total number of responses (correct response score plus illusory response score). If executive dysfunctions would affect performance of the test, the patients' total number of responses would be decreased compared with that of the controls.

Positron Emission Tomography Study

Regional cerebral metabolic rate of glucose (rCMRglc) utilization at rest was measured using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). All patients fasted for more than 5 hours before the scan and were injected with 185–218 MBq of FDG intravenously 1 hour prior to scanning. Patients prescribed antiparkinsonian drugs were scanned "off" medication, more than 5 hours after last dosing. To minimize the effects of external stimuli during the 1-hour FDG-uptake period, the subjects stayed in a quiet room and wore eye masks. Scanning took place with subjects under resting conditions, with eyes closed and ears unplugged. PET images were obtained using a Siemens Biograph DUO PET/computed tomography (CT) scanner (Siemens Medical System, Inc., Knoxville, TN) for 10 minutes. In-plane and axial resolutions of the scanner were 3.38 × 3.38 mm full width at half maximum (FWHM), respectively. Image reconstruction was performed using an ordered subset expectation maximization and 16 subsets and a 6-iteration reconstruction algorithm (Gaussian filter; filter FWHM, 2.0 mm) and displayed in a 256 × 256 matrix (pixel size, 1.33 × 1.33 mm, with a slice thickness of 2.0 mm). Attenuation correction was performed with the built-in CT scan. The interval between neuropsychological testing and PET scanning was less than 4 weeks.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS version 16.0) was used for statistical analysis. Analysis of variance (ANOVA) was used to analyze the 3 scores (ie, correct response score, illusory response score, and total number of responses) of the overlapping figure identification test. In addition, analysis of covariance (ANCOVA) was used to analyze performance while controlling for MMSE score to exclude possible effects of the severity of general cognitive impairment. The performance was compared between the 5 patients who received trihexyphenidyl hydrochloride and the remaining 39 patients using the Student t test to clarify the effect of trihexyphenidyl hydrochloride. For the PD group, Pearson's product moment correlation coefficient was calculated to analyze the relationship between test scores and demographic or clinical characteristics, except for visual acuity (Spearman rank-correlation coefficient).

PET images were analyzed with statistical parametric mapping software version 5 (SPM5; Wellcome Department of Imaging Neuroscience, London, UK), implemented on MATLAB 7.0.4 (The Math Works Inc., Natick, MA). PET images were normalized to the FDG template based on the Montreal Neurological Institute reference brain (the resampled voxel size was $2 \times 2 \times 2$ mm^3) and smoothed using an isotropic 10-mm FWHM Gaussian kernel to increase the signal-to-noise ratio and compensate for differences in gyral anatomy between individuals. To reduce between-subject variation in global metabolic rates, the count of each voxel was normalized to the total count of the brain using proportional scaling. Poor performances on the overlapping figure identification test were entered as covariates of interest in the correlation analyses for the PD patients, with the aim of

identifying regions showing decreased metabolism associated with defective visual recognition detected by the overlapping figure identification test. As correlation analysis was confined to regions showing hypometabolism in the PD patients relative to healthy participants, the PET data obtained from the PD patients were contrasted with those obtained from 14 age-, sex-, and education-comparable healthy elderly subjects without poor vision or cognitive impairment (7 women, 7 men; mean age, 64.0 ± 4.2 years; mean educational attainment, 12.3 ± 2.5 years; mean MMSE score, 29.1 ± 1.3). A resulting map with a liberal statistical threshold ($P < .05$, uncorrected) was used for the mask image in the correlation analysis.

All PET images were obtained with the same machine and conditions. The statistical threshold chosen for correlation analysis was $P < .001$ (uncorrected for multiple comparisons), with an extension threshold of 20 voxels (greater than 2 times the FWHM).[25] In addition, the effects of 2 biological factors (age and sex) and 3 clinical factors (daily levodopa equivalent dose, according to the following conversion formula: regular levodopa dose 1 + slow-release levodopa × 0.75 + bromocriptine × 10 + apomorphine × 10 + ropinirole × 20 + pergolide × 100 + pramipexole × 100 + [regular levodopa dose + (slow-release levodopa × 0.75)] × 0.2 if taking entacapone,[26,27] UPDRS motor part, and MMSE score), all of which are possible confounding factors for rCMRglc, were controlled for by entering these variables into the model. To confirm the results of the regression analysis, and avoid potential problems caused by multiple regressors, that is, multicollinearity among confounding variables and losing statistical power, the 3 clinical factors and 2 biological factors were controlled for by entering each variable into the model with separate models.

Results

Overlapping Figure Identification Test

Results of the performances in the overlapping figure identification test in PD patients and healthy controls are illustrated in Figure 2. The difference in the correct responses between the PD patients (30.7 ± 5.4) and the controls (32.9 ± 4.4) was not significant (ANOVA: $F_{1,66} = 2.95$, $P = .091$; ANCOVA: $F_{1,65} = 1.67$, $P = .201$). However, there was a significant increase in illusory response score in the PD patients (3.0 ± 3.2) relative to the controls (1.0 ± 1.1); ANOVA: $F_{1,66} = 9.11$, $P = .004$; ANCOVA: $F_{1,65} = 6.51$, $P = .013$. Total numbers of responses were comparable between the PD patients (33.7 ± 3.6) and the controls (33.9 ± 4.0); ANOVA: $F_{1,66} = 0.18$, $P = .86$.

Neither the correct response score nor the illusory response score was significantly correlated with any of the demographic/clinical data except for the MMSE score (correct response score, $P = .050$; illusory response score, $P = .001$) and the forward tapping span (correct response score, $P = .013$; illusory response score, $P = .002$) in the PD patients. Scores were similar in subjects taking and not taking trihexyphenidyl hydrochloride ($P > .1$).

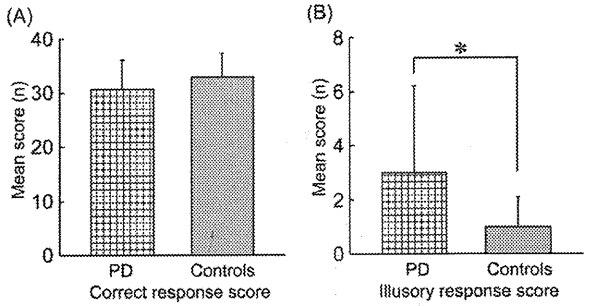

FIG. 2. Mean scores on the overlapping figure identification test for Parkinson's disease (PD) patients and controls. All results represent means ± SD. Significance is denoted by an asterisk ($P < .05$). **A:** Correct response score. **B:** Illusory response score.

Voxel-Based Cognitive-Metabolic Correlation Analyses

The illusory response score was negatively correlated with glucose metabolism in the bilateral inferior temporal gyrus, bilateral TPO junction, bilateral inferior parietal lobule, right middle frontal gyrus, and left superior temporal pole (Table 2, Fig. 3A). After the effects of 2 biological factors (ie, age and sex) and 3 clinical factors (ie, daily equivalent levodopa dosage, UPDRS motor score, and MMSE score) were covariated out, the regions with significant negative correlations between the illusory response score and rCMRglc were in the right inferior temporal gyrus, right inferior parietal lobule, and bilateral TPO junction (Table 2, Fig. 3B).

The models, in which either daily equivalent levodopa dosage or MMSE score was entered, demonstrated that the illusory response score was negatively correlated with glucose metabolism in the right inferior temporal gyrus, right inferior parietal lobule, and bilateral TPO junction (Table 2). The results were essentially similar to those obtained in the model that simultaneously controlled for effects of the 5 factors. In the model in which the UPDRS motor score was entered, the left inferior parietal lobule was negatively correlated with the illusory response score in addition to the above-mentioned regions (Table 2).

Discussion

In the present study, we found that the Poppelreuter-type overlapping figure identification test detected a specific visual recognition deficit in PD patients. Furthermore, the FDG-PET study revealed that illusory misidentifications in the PD patients were

TABLE 2. Regions showing significant correlations between the illusory response score and regional cerebral glucose metabolism in the PD patients

Regions	BA	Coordinates (mm)			*Z* score	Cluster size
		x	y	z		
Noncontrolling for any confounding effects (Fig. 2A)						
Right middle frontal gyrus	9	48	16	48	3.44	58
Right inferior parietal lobule	40	56	−40	48	3.46	191
Right inferior temporal gyrus	37/20	60	−50	−20	3.86	161
Right middle temporal gyrus	39	52	−70	20	3.63	187
Left superior temporal pole	38	−52	10	−6	3.52	58
Left inferior parietal lobule	48	−56	−44	34	3.79	44
Left middle/inferior temporal gyrus	39/37/20	−56	−64	16	4.07	445
Controlling for confounding effects of age, sex, UPDRS motor score, daily levodopa equivalent dosage, and MMSE score (Fig 2B)						
Right inferior parietal lobule	40	54	−42	48	3.48	86
Right middle temporal gyrus	37	54	−70	0	3.81	256
Right inferior temporal gyrus	37	60	−54	−10	3.41	42
Left middle temporal gyrus	37	−56	−64	14	3.86	235
Controlling for confounding effects of age, sex, and UPDRS motor score						
Right middle temporal gyrus	39	52	−70	18	3.77	241
Right inferior parietal lobule	40	56	−40	48	3.93	281
Right inferior temporal gyrus	20	60	−48	−20	3.64	76
Left inferior parietal lobule	48	−56	−44	34	3.68	37
Left middle temporal gyrus	37	−56	−64	14	4.16	468
Controlling for confounding effects of age, sex, and daily levodopa equivalent dosage						
Right inferior parietal lobule	40	56	−40	48	3.90	591
Right inferior temporal gyrus	20	60	−48	−20	3.64	67
Left middle temporal gyrus	37	−56	−64	16	4.20	577
Controlling for confounding effects of age, sex, and MMSE score						
Right inferior parietal lobule	40	52	−42	48	3.57	90
Right middle temporal gyrus	37	52	−72	14	3.84	263
Right inferior temporal gyrus	37	60	−54	−10	3.37	39
Left middle temporal gyrus	37	−56	−64	16	3.70	174

BA, Brodmann area; MMSE, Mini–Mental State Examination; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

associated with hypofunction in the visual cortical regions including the bilateral inferior temporal gyrus, TPO junction, and inferior parietal lobule in addition to the right middle frontal gyrus and left superior temporal pole. After the confounding 5 factors were covariated out, the regions that negatively correlated with illusory misidentifications were the right inferior temporal gyrus, bilateral TPO junction, and right inferior parietal lobule.

The present study provides direct evidence that PD patients without dementia have impaired visual recognition characterized by illusory misidentifications in the Poppelreuter-type overlapping figure identification test. The impairments are not likely to be caused by elementary visuoperceptual deficits in PD,[28,29] because the achromatic line drawings used in our study were drawn with adequate luminance contrast to the white background. However, another line of evidence from a previous study has suggested that decreased contrast sensitivities contributed to impairment of visual attention and spatial as well as motion perception in PD patients.[30] Therefore, the results of the present study cannot entirely rule out an effect of defective contrast sensitivity because we did not measure contrast sensitivity in each patient.

Correct identification of overlapping figures was comparable between the PD patients and controls. When the disease progresses or cortical involvement is prominent, as in Lewy-body disease with dementia, correct identifications in the Poppelreuter-type overlapping figure identification test are affected.[14–16] Therefore, an increase in illusory misidentifications might be an initial sign of visual recognition deficits in Lewy-body diseases.

The present study demonstrated that illusory misidentifications were associated with hypofunction in visual cortical regions including the right inferior temporal gyrus, bilateral TPO junction, and right inferior parietal lobule after the 5 confounding factors were covariated out. This finding is consistent with our a priori hypothesis that the ventral stream is responsible for illusory misidentifications in the overlapping figure identification test. The inferior temporal gyrus, including the ventral visual stream, was activated by the visual process of matching visual forms to memory.[31] Damage to the inferior temporal gyrus reportedly

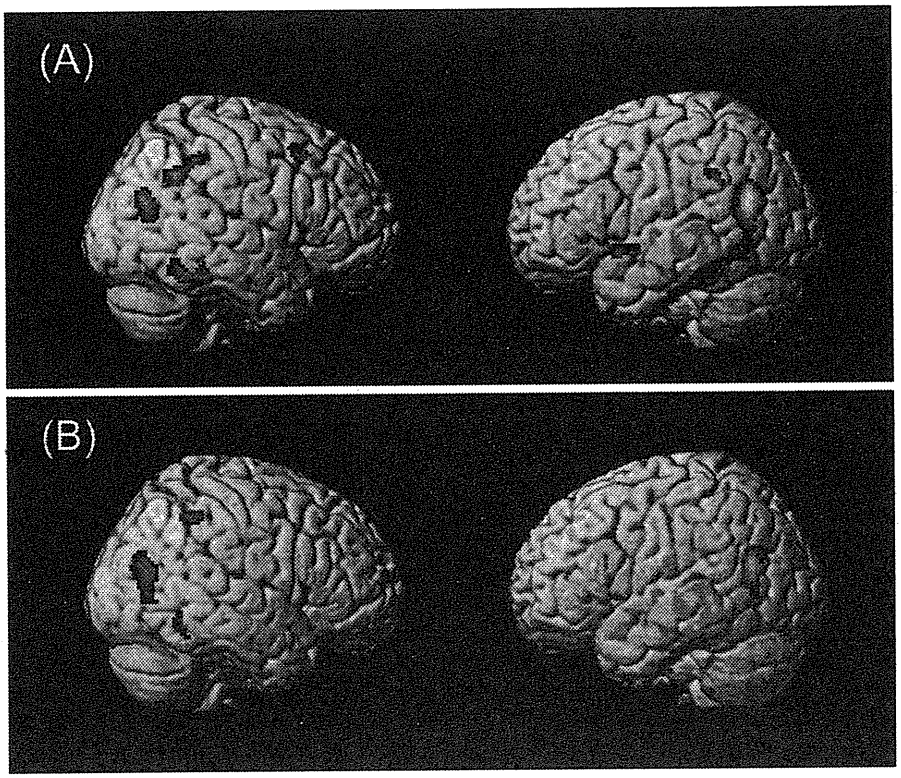

FIG. 3. *Brain.* regions showing significant correlations between illusory response score and regional cerebral glucose metabolism in PD patients. The regions are displayed on a surface-rendered standard brain (uncorrected $P < .001$). Not controlling for confounding effects (**A**) and controlling for confounding effects (**B**) of age, sex, daily equivalent levodopa dosage, UPDRS motor score, and MMSE score.

causes metamorphopsia of objects in the contralateral visual field.[32] Although there is no obvious explanation for the predominance of right-sided hypometabolism, the right hemisphere's superiority in detailed visual processing[33] and anomaly detection[34] may underlie the function involved in checking and rejecting illusory misidentifications.

The TPO junction and inferior parietal lobule are involved in the dorsal visual stream in humans. In addition, dysfunction of the dorsal visual process in PD is consistent with the findings of 2 previous reports.[3,6] The TPO junction was activated once visual attention shifted after being directed toward a wrong location by an invalid cue in Posner's spatial cuing paradigm.[35] Bilateral destruction of the TPO junction causes simultanagnosia.[36–38] In PD, the cortical lesions were not destructive but caused partial dysfunction, which was not enough to cause simultanagnosia but did result in partial inability to shift visual attention from the wrong segmentation to the correct one. The inferior parietal lobule plays a role in visual attention.[39] The illusory response score was significantly correlated with performance on the forward tapping-span tasks, which was comparable to the controls' average performance. The results support the hypothesis that hypofunction of the dorsal visual stream is involved to some extent in illusory misidentifications as well as hypofunction of the ventral visual stream.

The brain regions examined in the present study show results consistent with those of neuroimaging[40–42] and pathological studies[43] of visual hallucinations in PD or dementia with Lewy bodies. Thus, it is plausible that defective visual processing involving identification of overlapping figures underlies visual hallucinations, which are now regarded as a fundamental feature of PD,[44] even though the present study did not reveal a relationship between illusory misidentification and visual hallucinations.

In PD without dementia, executive dysfunction is reportedly the main neuropsychological feature,[45] resting-state glucose hypometabolism is present in cortical regions including the frontal lobe,[5,46] and some behavioral and cognitive deficits are reportedly correlated with prefrontal hypometabolism.[6,47] Thus, it may be supposed that executive dysfunction also contributes to illusory misidentifications. In this study, we did not specifically examine the involvement of executive functions. Defective verbal fluency or cognitive slowing is also unlikely to contribute to illusory responses, as the patients' total number of responses, that is, correct responses plus illusory responses, was not reduced. Other aspects of executive dysfunctions, for example, in error correction, response inhibition, and attentional biasing, might be involved. However, in the present PET study, involvement of the frontal lobe in illusory misidentifications was not demonstrated

except for association of the right middle frontal gyrus in the crude analysis, which was no longer significant when confounding factors were covariated out. These findings suggest that executive dysfunction contributes nonspecifically to the development of illusory responses as a background deficit of illusory misidentifications in PD patients. ■

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Decreased Ventilatory Response to Hypercapnia in Dementia with Lewy Bodies

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A systematic autonomic dysfunction observed among patients with dementia with Lewy bodies (DLB) has recently attracted close attention. Here, we compare cardiovascular and pulmonary autonomic functions among patients with DLB, patients with Alzheimer's disease, and healthy control subjects. All 15 DLB patients demonstrated severely low ventilatory response to hypercapnia, whereas none of the other subjects demonstrated abnormal results. The majority of the DLB patients showed impaired heart rate variability, low uptake on ^{123}I-metaiodobenzylguanidine myocardial scintigraphy, and orthostatic hypotension. Ventilatory response to hypercapnia as a marker of respiratory autonomic function is a promising diagnostic tool for DLB.

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Dementia with Lewy bodies (DLB) is regarded as the second-most common degenerative dementia after Alzheimer's disease (AD).[1] The clinical criteria for DLB alone can separate many patients with DLB from other related disorders including AD. However, despite high diagnostic specificity, such criteria have lower sensitivity, and improved methods of case detection are required.[2] Several articles have emphasized that patients with DLB have autonomic physical symptoms, such as syncope, orthostatic hypotension, urinary incontinence, and constipation.[3–5] These autonomic symptoms, as well as a low uptake on ^{123}I-metaiodobenzylguanidine myocardial scintigraphy,[6,7] are included as a supportive feature of the criteria of the Consortium on DLB.[8] Accordingly, autonomic assessment may prove useful to

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distinguish DLB from other dementing diseases including AD. However, to date, there is only our prior report, in a pilot study examining the diagnostic utility of impairment in ventilatory response to hypercapnia (VRH) in patients with DLB.[9] In this study, we evaluated additional neurologically impaired and healthy control subjects to examine the utility of the decreased VRH for the diagnosis of DLB.

Subjects and Methods

From a consecutive series of hospitalized dementia cases in our university hospital for their clinical evaluation between January 2006 and December 2007, we recruited 15 patients with probable DLB (6 male and 9 female patients; mean age, 68.8 years [standard deviation (SD), 7.3]), and 7 patients with AD (2 male and 5 female patients; mean age, 76.1 years [SD, 8.6]). We also recruited 12 community-dwelling healthy volunteers as control subjects (6 male and 6 female subjects; mean age, 69.3 years [SD, 4.7]). A diagnosis of probable DLB was made according to the latest clinical criteria.[8] In addition, 12 of 15 patients with DLB (80.0%) showed a reduction in cerebral blood flow in the occipital lobe on single-photon emission computerized tomography, and 11 of 15 patients (73.3%) showed low uptake on ^{123}I-metaiodobenzylguanidine myocardial scintigraphy. Both types of imaging have been reported to be useful in making a diagnosis of DLB.[8] The mean scores of the Mini-Mental State Examination of the DLB, AD, and control subjects were 18.9 (SD, 5.8), 20.6 (SD, 5.1), and 29.3 (SD, 1.0), respectively. The mean duration of the illness of DLB and AD patients was 3.6 (SD, 2.0) and 3.7 (SD, 2.2) years, respectively. None of the DLB or AD patients and only 1 of the 12 control subjects smoked. Some participants had hypertension and received antihypertensives. Otherwise, none of the subjects took medicine affecting autonomic function during the evaluations.

We evaluated respiratory autonomic functions by means of VRH, as well as arterial blood gas, percentage vital capacity, and forced expiratory volume in 1 second. To evaluate cardiovascular autonomic function, we tested for orthostatic hypotension and heart rate variability. This study protocol was approved by the Internal Ethical Review Board of the University of Tsukuba. Patients and their caregivers provided written, informed consent for study participation.

Evaluations

VENTILATORY RESPONSE TO HYPERCAPNIA. VRH was assessed using the dual control system for oxygen and carbon dioxide (Duograph KAY-100; CHEST, Tokyo, Japan). End-tidal oxygen partial pressure ($PETO_2$) was kept constant at 180 Torr during the procedure. VRH was expressed as the slope of the regression line relating ventilation (L/min) to changes in end-tidal carbon dioxide partial pressure ($PETCO_2$), corrected by body surface area (m^2) ($\Delta VE/PETCO_2/BSA$) ($L/min/Torr/m^2$).[9]

HEART RATE VARIABILITY. Twenty-four-hour Holter monitoring was performed with a three-channel recorder (8000T; Marquette Electronics, Milwaukee, WI) to evaluate heart rate variability. Frequency domain indices, that is, low frequency (LF; range, 0.04– 0.15Hz) and high frequency (HF; range, 0.15–0.40Hz), were analyzed using a commercially available software algorithm (MARS; Marquette Electronics). HF is considered to be a marker of parasympathetic activity, whereas LF is considered to be a marker of sympathetic activity.[10,11]

ORTHOSTATIC HYPOTENSION. Orthostatic hypotension, evaluated using a head-up tilt table, is defined as a reduction in systolic blood pressure of at least 20mm Hg or diastolic blood pressure of at least 10mm Hg within 3 minutes of standing.[12] Autonomic testing was performed blind to clinical diagnosis.

Fisher's exact test was used to determine the effect of antihypertensives on the results of orthostatic hypotension, and also was used to determine the significance of the difference between the number of the patients showing decreased parameters among DLB, AD, and control groups. Analysis of variance was used to compare autonomic responses among the three groups, and pairwise comparison was performed by using the Tukey–Kramer test for adjusting for multiple comparisons. Pearson's correlation coefficient was used to examine correlations between age and VRH, HF, or LF from each group, and also to examine a correlation between VRH and clinical data, such as the scores of Mini-Mental State Examination, Barthel index, duration of the disease, and Hoehn and Yahr stage in the DLB patients. In addition, Student's t test was used to examine the differences between VRH, HF, or LF for male and female subjects, and between patients with and without treatment with antihypertensives. Statistical analysis was performed with the use of R as statistical software.[13] p values < 0.05 were considered statistically significant.

Results

The use of antihypertensives was not significantly different among the three groups, and their use showed no significant effect on any results of autonomic assessments. All patients among the three groups showed normal arterial blood gas analysis, percentage vital capacity, and forced expiratory volume in 1 second. However, the indices of VRH of the DLB patients, AD patients, and control subjects were 0.156 (SD, 0.10), 0.431 (0.04), and 0.466 (0.09), respectively. VRH in DLB patients was significantly lower than that of AD ($p < 0.001$) patients and the control subjects ($p < 0.001$), whereas there was no statistical difference between AD patients and the control subjects (Table and Fig 1). All DLB patients demonstrated abnormally low VRH (reference range: male patients, 0.34–1.20; female patients, 0.39–0.95), whereas all of the AD or control subjects had normal VRH. In DLB patients, there was no correlation between VRH and the scores of Mini-Mental State Examination, Barthel index, disease duration, or Hoehn and Yahr stage.

The number of subjects who showed a decrease from

Table. **Comparisons of Respiratory and Cardiovascular Functions**

Items	DLB	AD	Control	
Ventilatory response to hypercapnia	0.156 ± 0.097 (mean ± SD)	0.431 ± 0.040	0.466 ± 0.094	DLB vs control ($p < 0.001$), DLB vs AD ($p < 0.001$), AD vs Control (NS)[a]
n/total (%)[b]	15/15 (100%)	0/7 (0%)	0/12 (0%)	$p < 0.001$[c]
Heart rate variability				
High Frequency (mean ± SD)	36.8 ± 32.2	115.4 ± 54.1	121.7 ± 102.7	DLB vs Control ($p = 0.016$), DLB vs AD (NS), AD vs Control (NS)[a]
n/total (%)[b]	9/13 (69.2%)	1/6 (16.7%)	4/12 (33.3%)	NS[c]
Low Frequency (mean ± SD)	132.6 ± 149.2	208.4 ± 141.9	279.2 ± 173.5	DLB vs control (NS), DLB vs AD (NS), AD vs control (NS)[a]
n/total (%)[b]	9/13 (69.2%)	3/6 (50.0%)	4/12 (33.3%)	NS[c]
Orthostatic hypotension	10/15 (66.7%)	2/7 (28.6%)	2/12 (16.7%)	$p < 0.05$[c]

[a]Results by Tukey–Kramer test.
[b]n = number of the patients showing decreased parameter; total = total patients in group.
[c]Results by Fisher's exact test.
DLB = demential with Lewy bodies; AD = Alzheimer's disease; SD = standard deviation.

the 95% confidence limits of HF (56.5–186.9) and LF (168.9–389.4) were 9 of 13 and 9 of 13 in DLB patients, 1 of 6 and 3 of 6 in AD patients, and 4 of 12 and 4 of 12 in control subjects, respectively (see the Table). Notably, several DLB patients showed extremely low HF and LF values (Fig 2). The average values of HF in DLB patients, AD patients, and control subjects were 36.8 (32.2) msec^2, 115.4 (54.1) msec^2, and 121.7 (102.7) msec^2, respectively. The average value of HF in the DLB group was significantly lower than that in the control group ($p = 0.016$) (see the Table and Fig 2). Likewise, the average values of LF in DLB patients, AD patients, and control subjects

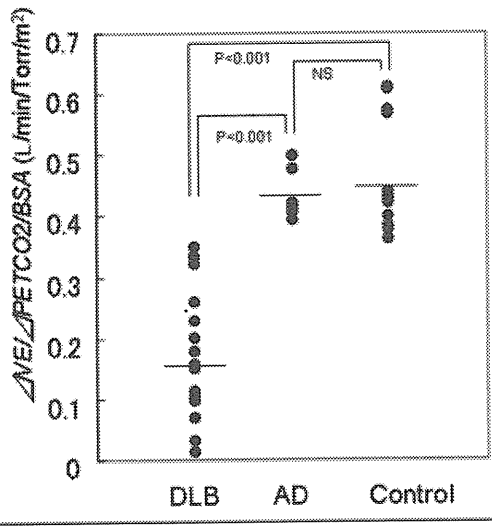

Fig 1. Ventilatory response to hypercapnia for patients with dementia with Lewy bodies (DLB), patients with Alzheimer's disease (AD), and control subjects. ΔVE/PETCO$_2$/BSA = slope of the regression line relating ventilation to changes in end-tidal carbon dioxide partial pressure, corrected by body surface area; NS = not significant.

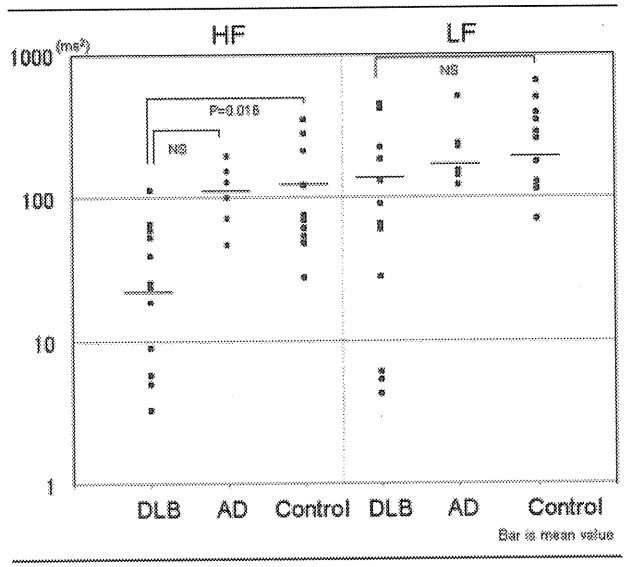

Fig 2. High frequency (HF) and low frequency (LF) of heart rate variability for patients with dementia with Lewy bodies (DLB), patients with Alzheimer's disease (AD), and control subjects. NS = not significant.

were 132.6 (149.2) msec^2, 208.3 (141.9) msec^2, and 279.2 (173.5) msec^2, respectively, and LF in DLB was lower than those in the AD group and control group, although the difference did not reach significance (see the Table and Fig 2).

There were no significant correlations between age and VRH, HF, or LF in any group. In addition, there were no differences in VRH, HF, or LF between the male and female subjects of each group. In 10 of 15 patients with DLB, orthostatic hypotension was observed, whereas only 2 of 7 AD patients and 2 of 12 control subjects showed orthostatic hypotension.

Discussion

In this study, the majority of DLB patients demonstrated abnormal findings in all the examinations of cardiovascular autonomic functions, and the results of the respiratory autonomic function assessments were significantly worse for DLB patients than for AD patients and control subjects. The greater rate of low heart-to-mediastinum (H/M) ratios of ^{123}I-metaiodobenzylguanidine myocardial scintigraphy and orthostatic hypotension in patients with DLB examined in our study is consistent with the results of previous studies.[5–7,14] In addition, our DLB group showed lower values of HF and LF than those in the AD and control groups. To date, only one study has reported HF and LF findings in patients with DLB.[14] Allan and colleagues[14] demonstrated that HF and LF were lower in their patients with DLB than in those with AD and control subjects. All of the earlier mentioned results appear to support the findings of this study.

In addition, all our 15 DLB patients showed abnormally low VRH. Although it is possible that smoking and chronic obstructive pulmonary disease[15] can affect VRH, this has not yet been reported in any study to our knowledge. Only one control subject in our study was a smoker, and no subject in this study suffered from respiratory disease including chronic obstructive pulmonary disease, making these unlikely to have influenced our results.

It remains open whether a low VRH will be proved to be a unique finding in DLB among various neurodegenerative diseases. Two prior studies have reported that patients with neurodegenerative disease involving the autonomic nervous system, such as multiple system atrophy and Parkinson's disease, showed reduced ventilatory response to hypoxia but normal sensitivity to hypercapnia.[16,17] Thus, VRH appears to be a promising diagnostic method for differentiating DLB from AD and possibly other neurological diseases. Finally, decreased VRH may have clinical significance in that patients with DLB may be more susceptible to respiratory compromise.

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ORIGINAL ARTICLE

Depression associated with dementia with Lewy bodies (DLB) and the effect of somatotherapy

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Abstract

Background: Dementia with Lewy bodies (DLB) is a common type of dementia. It is difficult to make an initial diagnosis of DLB because of a variety of early symptoms, including psychosis-like and depressive states. In this study, we examined the characteristic depressive symptoms of the prestage of DLB and the efficacy and safety of somatotherapy for depression accompanying DLB.

Methods: Subjects in the study were 167 consecutive clinical cases aged 50 years or more, hospitalized at Tsukuba University Hospital from December 2002 to September 2007. At the time of admission, patients were diagnosed with certain types of mood disorders according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision. For each subject, a series of neuropsychological tests, along with a standard psychiatric and neurological assessment and biological examinations, were conducted. Using the data from these exams, we diagnosed probable and possible DLB according to the criteria for dementia with Lewy bodies established by McKeith *et al.*

1 We compared patients' depressive symptoms according to the Hamilton Depression Scale, and distinguished between patients with depression associated with DLB and those with other mood disorders.
2 We also examined the efficacy and safety of somatotherapy (electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS)) for patients with drug therapy–resistant depression associated with DLB.

Results:

1 The characteristic symptoms of patients with DLB were classified into two groups: psychotic and non-psychotic. The former consisted of patients with states such as delusion and agitation, and the latter included patients exhibiting psychomotor retardation, loss of insight and hypochondriasis.
2 Eight DLB patients with therapy-resistant depression underwent ECT. After ECT, significant improvement was observed, with no remarkable safety hazards. Six patients with drug therapy–resistant DLB underwent TMS. TMS appears to be an effective, safe remedy for this kind of patient.

Conclusions:

- A total of 13.8% of patients came to be re-diagnosed as having DLB as a consequence of a thorough examination after admission.
- Patients with depression associated with DLB were classified into psychotic and non-psychotic clusters.
- ECT and TMS are effective and safe therapeutic tools for drug therapy–resistant depression observed in DLB patients.

Key words: *agitation, apathy, dementia with Lewy bodies, electroconvulsive therapy, therapy refractory depression, transcranial magnetic stimulation.*

INTRODUCTION

We sometimes encounter presenile or elderly patients with a mood disorder who subsequently develop dementia. They are often referred to us under the diagnosis of refractory depression also showing a variety of adverse effects related to psychotropics.

Dementia with Lewy bodies (DLB) has been established as one of the three major types of dementia, along with Alzheimer's disease (AD) and vascular dementia. According to the diagnostic criteria for DLB, in principle, the typical clinical symptoms include progressive, reduced cognitive function, variable, visual hallucinations and Parkinsonism.[1] It has been said that more than half of DLB patients are diagnosed with depression during their clinical course. Previous researchers have reported that the association between depression and DLB is stronger than that of other dementia causing illnesses. For example, McKeith *et al.* found that the prevalence of depressive symptoms was higher in patients with DLB than in patients with AD.[2]

Some patients develop depression as a prodromal, early symptom and subsequently start to show the symptoms that fulfill the DLB criteria. As early as the 1980s, Reding *et al.* reported that patients with depression who also showed some of the following characteristic symptoms were likely to develop dementia in the future: the manifestation of a confused state after the administration of low-dose tricyclic antidepressants and the presence of extrapyramidal signs. This report seems to indicate the relationship between DLB and depression. In addition, a study examining patients with so-called pseudo-dementia reported that five of 16 patients with dementia secondary to depression were subsequently diagnosed with Parkinson's disease plus dementia.[3] Therefore, accurate early diagnosis may improve the prognosis for such a patient, as well as their quality of life.

It is well known that DLB patients often show hypersensitivity to psychotropics, including antipsychotics. DLB patients also occasionally develop autonomic nervous system (such as respiratory/circulatory system) dysfunction. Taken together, electroconvulsive therapy (mECT, ECT) and repetitive transcranial magnetic stimulation (rTMS) appear to be preferable to pharmacotherapy for patients with DLB. Thus, in this study we also evaluated the efficacy and safety of these treatments.

METHODS

Characteristic depressive symptoms observed in DLB patients

Subjects in the study included 167 consecutive clinical cases aged 50 years or more who were hospitalized in the psychiatric ward of Tsukuba University Hospital between December 2002 and September 2007. They were diagnosed as having mood disorders according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR) at the time of admission, specifically, either major depressive disorder or bipolar I disorder. Our study was confined to a group of patients who completed a series of examinations, as described below. The 'revised criteria for the clinical diagnosis of dementia with Lewy bodies'[1] was used to make a diagnosis of probable and possible DLB. We also used the results of the examinations, which included laboratory testing (hematological, serum chemistry), neuroimaging (magnetic resonance imaging and single-photon emission computed tomography (SPECT)), neuropsychological testing and an examination of autonomic function including hypercapnic ventilation response (HVR).[4–6]

There were a number of patients among the target population who met the following conditions: a score of 24 or more on the mini-mental state examination (MMSE) scale, not meeting the criteria of dementia specified in DSM-IV-TR, and satisfying some of the criteria for DLB but falling short the diagnosis of DLB. We defined such patients as suspected DLB with supportive features (hereinafter referred to as 'suspected DLB'). We then classified patients into three types: probable DLB, possible DLB and suspected DLB. We estimated the prevalence of these three types among the 167 patients. We compared depressive symptoms using the Hamilton Depression Scale (HAM-D) between the pooled subjects of the three DLB groups and patients with other types of depression. For the comparison, we made matches regarding the HAM-D score, along with age and gender between the two groups. The Mann–Whitney *U*-test was used for statistical analyses.

Somatotherapy for depression in DLB patients

Eight patients (one male, seven females, with a mean age (± SD) of 71.6 (± 7.3) years) with a diagnosis of DLB and drug therapy–resistant depression under-

went ECT. Conventionally, therapy-resistant depression has been defined as a pathological condition in which the patient does not respond to more than two antidepressants with different mechanisms of action.[3] We also adopted this definition for our study. Three patients were diagnosed with possible DLB and five with probable DLB.

Six patients (three males, three females, with a mean age (± SD) of 61.9 (± 9.2) years) with DLB underwent TMS. (Five were diagnosed as suspected DLB and one as probable DLB.)

After obtaining informed consent from each patient, ECTs were conducted through electrodes positioned at the standard bifrontotemporal location. For pulse wave stimuli, a Thymatron System IV ECT apparatus (Somatics, Lake Bluff, IL, USA) containing an inbuilt electroencephalography system (Fp1-A 1, Fp2- A2, international 10–20 system) was used. Stimulation dose was calculated using the 'half age' method. A LOW 0.5 preset program using 0.5 ms pulse width was selected, adjusting frequency to maximize duration. The criterion for an adequate seizure was an electroencephalographic seizure lasting 20 s. If no electroencephalographic seizure had occurred after 20 s, re-stimulation at a higher stimulus intensity was immediately performed by increasing voltage by 5~10% for pulse wave stimuli, to a maximum of two stimulations/session.[7] Motor seizures were further monitored in a cuffed arm. Intravenous injection of thiamylal sodium and succinylcholine was performed for patients given pulse wave stimuli. Antidepressants remained unchanged at a minimal dose throughout the course of ECT. Lithium carbonate and sodium valproate were withdrawn before first ECT. A treatment course consisted of six energizations.

We used the Magstim Rapid System (MRS 1000/50) (Magistim Company, Carmarthenshire, UK) as the stimulator for rTMS and selected a 70-mm figure-of-eight coil.[8] We stimulated the dorsolateral prefrontal cortex area, approximately 5 cm ahead of the site where the maximum exercise-induced reaction could be obtained, on the right and left side. The stimulus intensity was adjusted to 110% motor threshold on the right side and 100% motor threshold on the left side. A course consisted of the following treatments. A train of stimuli (1 Hz × 140 s (140 pulses)) was administered on the right side at intervals of 30 s three times a day (420 pulses/day). A train of stimuli (10 Hz × 5 s (50 pulses)) was administered on the left side at intervals of 25 s 15 times a day (750 pulses/day).[8,9] These treatments were repeated for 10 days.

We evaluated the patients' depressive symptoms before and after the ECT and TMS treatment sessions using the HAM-D, and compared the results.

RESULTS

Dementia with Lewy bodies (DLB) and depression

Length of hospitalization, age and gender difference of subjects

The 167 patients were hospitalized for 71 ± 48 days. Their mean age was 63 ± 9 years, ranging from 50 to 83 years. According to the above-described diagnostic procedure, 23 patients were classified into the three DLB groups (13.8%), while the remaining 144 patients were classified into the non-DLB group (86.2%). The male-to-female ratio was 26% vs 74% for the DLB group and 36% vs 64% for the non-DLB group. The ratio was higher for females in the two groups. The mean age was 63.5 ± 9.2 years in the DLB group and 63.2 ± 9.0 years in the non-DLB group.

In our ward, a tentative psychiatric diagnosis for each patient is made on the consensus of two psychiatrists using the DSM-IV-TR at the time of admission. Applying this procedure to our study, of the 23 DLB patients, 22 were diagnosed with major depressive disorder (95.7%) and one with bipolar I disorder at the time of admission (Table 1).

The results of a series of examinations are shown in Table 2. As shown, 50% of the patients with suspected DLB were positive in 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy. Higher positive findings were also obtained in a reduction in

Table 1 Diagnosis of depressive disorders for each type of DLB

	Suspected	Possible	Probable
n	9	10	4
Major depressive disorder	9 100%	10 100%	3 75%
Bipolar disorder	0	0	1 (Bipolar I disorder) 25%
Dysthymic disorder	0	0	0
Mood disorder resulting from general medical condition	0	0	0

DLB, dementia with Lewy bodies.

Table 2. Evaluation in the group of dementia with Lewy bodies (DLB) with the initial episode of mood disorder

	Number of patients who tested positive/number of patients who underwent examination (%)		
	Suspected DLB	Possible	Probable
MIBG	2/4	5/6	0/2
	50%	83.3%	0%
SPECT	8/9	6/8	3/3
(Reduced r-CBF in occipital lobe)	88.9%	75%	100%
Ventilation response	5/6	5/6	0/0
	83.3%	83.3%	–%

DLB, dementia with Lewy bodies; MIBG, 123I-metaiodobenzylguanidine myocardial scintigraphy; r-CBF, regional cerebral blood flow; SPECT, single-photon emission computed tomography.

regional cerebral blood flow revealed by brain perfusion SPECT (88.9%), which is a characteristic finding of neuroimaging for DLB,[10] along with a poor hypercapnic ventilation response (83.3%) (Table 2).

Age, gender and MMSE scores of the patients with the three types of DLB

The group diagnosed as suspected DLB with supportive features consisted of nine patients (one male, eight female) with a mean age of 59.3 ± 10.4 years. The group diagnosed as possible DLB consisted of 10 patients (three male, seven female) with a mean age of 70.1 ± 6.5 years. The group diagnosed as probable DLB included four patients (two male, two female) with a mean age of 69.0 ± 11.3 years. The mean MMSE score was 19.7 ± 3.0 for the possible DLB group, 21.7 ± 1.2 for the probable DLB group and 27.8 ± 1.9 for the suspected DLB group, respectively. The mean score was significantly higher for the suspected DLB group (Table 3).

Characteristic symptoms of depression shown in DLB patients

Our analysis revealed that the scores for several symptoms were higher for the DLB group. They are divided into two clusters: psychotic (agitation, paranoia, depersonalization and derealization) and non-psychotic (psychomotor retardation, loss of insight, hypochondriasis). In general, each patient had either psychotic or non-psychotic symptoms, and the two clusters seldom coexisted in a study subject (Table 4).

Table 3. Three types of DLB with an initial episode of mood disorder

	Suspected	Possible	Probable
n (23/167)	9	10	4
Male/Female	1/8	3/7	2/2
(%)	(11%/89%)	(30%/70%)	(50%/50%)
Mean age (± SD)	59.3 ± 10.4	70.1 ± 6.5*	69.0 ± 11.3*
MMSE	27.8 ± 1.9	19.7 ± 3.0	21.7 ± 1.2

*The patients in the suspected dementia with Lewy bodies (DLB) subgroup were significantly younger than those in the remaining two subgroups ($P < 0.005$). MMSE, mini-mental state examination.

Table 4. Clinical signs of patients with depression accompanying DLB (ratings of depression using the 24-item HAM-D)

Symptoms observed with significant frequency in the three DLB groups were divided into the following two categories:	
(1) Psychotic symptoms	
Agitation	($P = 0.002$)
Paranoid symptoms	($P = 0.001$)
Depersonalization and derealization	($P = 0.023$)
(2) Non-psychotic symptoms	
Psychomotor retardation	($P = 0.022$)
Hypochondriasis	($P = 0.045$)
Lack of insight	($P = 0.007$)

Mann–Whitney *U*-test. DLB, dementia with Lewy bodies; HAM-D, Hamilton Depression Scale.

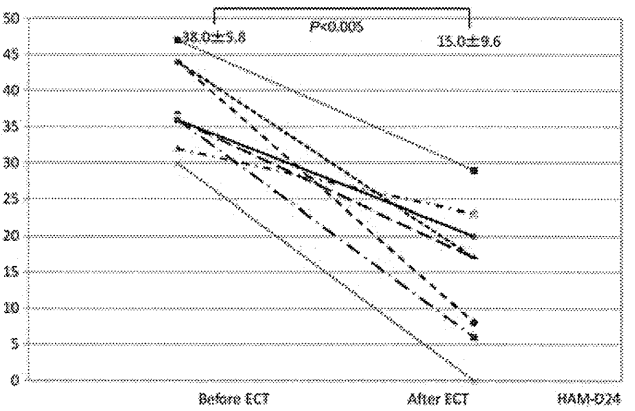

Figure 1 Changes in Hamilton Depression Scale (HAM-D) scores (electroconvulsive therapy (ECT)).

Somatotherapy

Electroconvulsive therapy (ECT)

As shown in Figure 1, the HAM-D score decreased from 38.0 ± 5.8 before ECT to 15.0 ± 9.6 after ECT, a difference that indicates significant improvement ($P < 0.005$).

Transcranial magnetic stimulation (TMS)

Figure 2 shows that the HAM-D score decreased from 24.0 ± 8.0 before TMS to 11.0 ± 5.9 after TMS, a difference that also indicates significant improvement ($P < 0.005$).

Both ECT and TMS posed no safety hazard to the patients.

DISCUSSION

Dementia with Lewy bodies (DLB) and depression

As shown in the results section, approximately 14% of the presenile and senile patients who had been diagnosed as having depression or related disorders before or at the time of admission to our ward came to be re-diagnosed as having DLB at the time of their discharge. For the 10 possible and four probable DLB patients, each diagnosis was made according to the revised diagnosis criteria of DLB including a principal condition of presence of dementia. However, the diagnosis of suspected DLB, which is newly defined by us, is principally based on some clinical features listed on the criteria exclusive of the presence of dementia. With the aid of SPECT, HVR and MIBG myocardial scintigraphy data, we were able to make this diagnosis.

Needless to say, we do not mean to imply that patients with suspected DLB must progress to possible or probable DLB in the future. However, we reported elsewhere[5,6] that no positive findings were observed in SPECT, HVR and scintigraphy data among the healthy elderly. In addition, it has been reported that the mean value for the sensitivity of the former 'criteria for the clinical diagnosis of DLB'[11] was 49%.[12] This value is not so good, but this criteria alone can make a diagnosis of DLB to a certain degree. Because we used the revised version of the criteria,[1] sensitivity is expected to be higher than that for the former. Taken together, we can assume a certain portion of the patients with suspected DLB might convert to possible or probable DLB in the future. In conclusion, on the examination of presenile and senile patients with refractory depression, we must keep in mind the diagnosis of DLB.

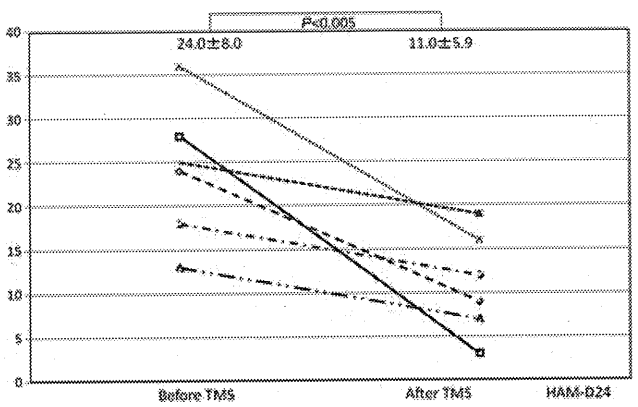

Figure 2 Changes in Hamilton Depression Scale (HAM-D) scores (transcranial magnetic stimulation (TMS)).

Characteristics of depressive symptoms

It is well known that patients with DLB develop psychosis. Kosaka described as follows, 'DLB often starts with psychosis. Before DLB came to be acknowledged as a common pathological condition, not a few patients with DLB had been misdiagnosed as having schizophrenia and received inappropriate treatment, and finally diagnosed as having DLB after autopsy.'[13] In fact, we found a group of patients with a psychosis-like state who had been occasionally diagnosed as having Cotard syndrome.

Regarding this issue, Aarsland *et al.* examined the psychiatric symptoms associated with Parkinson's disease with dementia (PDD) among 537 patients with PDD using the neuropsychiatric inventory. They classified the symptoms into five clusters: few and mild symptoms (52%), mood (11%), apathy (24%), agitation (5%) and psychosis (8%).

As shown above, we analyzed HAM-D subscale scores and found that the DLB group consisted of the following two subgroups: non-psychotic and psychotic. The former is characterized by apathy and paucity of sadness, the latter by prominent psychosis. According to traditional depression diagnoses, patients of this group can be diagnosed as having Cotard syndrome or agitated depression. Although DLB and PDD are distinguishable clinical entities, the two clusters proposed by Aarsland *et al.* (agitation (high score on agitation and high total neuropsychiatric inventory score); psychosis cluster (high scores on delusions and hallucinations)) might correspond to our psychotic group.[14] Our non-psychotic group might correspond to their mood or apathy clusters. Therefore, we should recall DLB when presenile or senile patients with a depressive state show marked apathy or psychotic features.

Somatotherapy for DLB

Electroconvulsive (ECT) and TMS therapy

We made a comparison between the ECT group and the TMS group with respect to clinical variables. According to the results, it appears that ECT was selected as a last resort for patients with DLB who showed the following characteristics: severe depression, poor response to various treatments, and the requirement of urgent psychiatric and physical intervention. On the contrary, TMS seems to have been employed for the patients with a milder form of depression. Regarding the efficacy, both ECT and TMS appear to be useful therapeutic options for drug therapy-resistant DLB.

Adverse reactions and safety of ECT and TMS

Electroconvulsive (ECT) entails the risks of critical circulatory and respiratory accidents, as well as headache and defect of memory.[15] As for TMS, it has been said that 10–20% of patients develop headache as an adverse reaction of rTMS.[16] Compared with ECT, rTMS has been reported to entail fewer risks of critical accidents.

Although both ECT and TMS posed no safety hazards in this study, many of the DLB patients had dysfunction of the autonomic nervous system, including the circulatory and respiratory systems. A thorough pretreatment examination is indispensable before the implementation of ECT for DLB patients.

CONCLUSION

- Of the presenile and senile patients who were hospitalized with a diagnosis of mood disorder, 13.8% came to be re-diagnosed as having DLB as a consequence of a thorough examination after admission.
- The patients with depression associated with DLB were classified into the following two clusters: a psychotic cluster characterized by delusion and agitation and a non-psychotic cluster characterized by psychomotor retardation, loss of insight and hypochondriasis.
- ECT and TMS are effective and safe therapeutic tools for drug therapy–resistant depression observed in DLB patients.

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○抑肝散
○抑肝散加陳皮半夏
○腹症

認知症周辺症状（BPSD）―抑肝散（よくかんさん）

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Headline

1. 認知症の多くの患者に周辺症状（BPSD）がみられる．
2. BPSDに対してはまず非薬物的対応が行われるが，それでは改善しないBPSDに対して薬物療法が行われる．
3. BPSDの薬物療法では安全性が最も大切であり，その点で漢方治療は重要である．
4. 抑肝散（よくかんさん）は認知症全般の興奮や易刺激性に対する第一選択薬である．さらにLewy小体型認知症（DLB）の幻視やレム睡眠行動障害（RBD）に対しても有効である．

はじめに

認知症の症状には認知機能障害の他に，周辺症状あるいはbehavioral and psychological symptoms of demenia（BPSD）とよばれる症状がみられる．BPSDは幻覚，妄想，うつ，不安，興奮，睡眠障害などの精神症状や，攻撃的言動，徘徊，不潔行為，食行動異常をはじめとする行動からなる（表1）．BPSDはおよそ8割の患者に現れ，患者と介護者の心理的・身体的負担を増し，日常生活に多大な支障をきたしてしばしば在宅生活を困難にさせる．BPSDに対してはまず非薬物療法が行われる（図1）[1]．しかしながら，十分な非薬物療法を行っても改善が得られないBPSDも少なくない．そのような場合，薬物療法が併用される（図2）．これまで薬物療法においては，本来統合失調症の治療薬である抗精神病薬がしばしば用いられてきた．しかし，運動機能，認知機能，生活機能への影響が問題であった．さらに，新しく開発され副作用が軽減された非定型抗精神病薬であっても服用中の患者の死亡率が高いことが報告され，安易な抗精神病薬の使用に警鐘が鳴らされた．

BPSDに対する薬物療法で最も大切なことは安全性である．この点で漢方薬が注目されるようになった．特に本稿のテーマである抑肝散（よくかんさん）はBPSDに対する治療薬としてエビデンスが蓄積されつつある．

BPSDの病態と診断

BPSDは患者の元来の性格傾向や，患者と家族との人間関係をはじめとする環境要因から発展してくることが多い．たとえば，もともと一人で何でもこなしてきて自己に自信があるAlzheimer病（AD）の患者は，「しまったはずの場所に財布がない」と動揺し，「（普段から関係がぎくしゃくしている）嫁が盗んだに違いない」と考えるに至るようになり妄想に発展する．このため，BPSDの誘因となった心理・環境的な問題を検討し，それらに対応する非薬物的対応がBPSDの対応の基本である．しかしながら，ADをはじめとする認知症疾患では脳内の様々な神経回路や神経伝達系の障害をきたしており，この生物学的な変化もBPSDの一因と考えられている．たとえば，セロトニン伝達系は攻撃性，不安，抑うつなどと，ドパミン伝達系は幻覚，妄想，

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表1　おもなBPSD（周辺症状）

心理症状
- 幻覚（幻視，幻聴，体感幻覚，幻嗅）
- 妄想（もの盗られ妄想，被害妄想，嫉妬妄想，誤認妄想）
- 睡眠覚醒障害（不眠，レム睡眠行動異常），
- 感情面の障害（抑うつ，不安，興奮，感情失禁）
- 人格面の障害（多幸，脱抑制，易怒性，アパシー，依存）

行動症状
- 攻撃的言動（暴行，暴言），焦燥，叫声，拒絶，火の不始末，不潔行為，脱抑制行為，徘徊，繰り返し質問，つきまとい，独語，食行動の異常（異食，過食，拒食，盗食）

アパシーと，アセチルコリン伝達系はLewy小体型認知症（dementia with Lewy bodies; DLB）でみられる幻視との関連が推察されている．

BPSDに対しては，本人の診察はもとより家族からの病歴聴取が不可欠である．通常，診察場面と実際の生活場面では状態が大きく異なり，診察場面ではBPSDが目立たないことが多い．したがって，生活場面における障害について詳細に情報を収集することが必要である．病歴聴取の際に，時に家族の陰性感情が反映されることがあるため，できる限り客観的な情報収集を心がける．Neuropsychiatry Inventry（NPI）やBEHAVE-ADなどのBPSDに対する評価尺度を用いると収集もれが少なくなる．また，治療効果を判定するにも有用である．

抑肝散の適応とエビデンス

1．抑肝散の研究報告から

抑肝散は「保嬰撮要」に記載された方剤で，釣藤鉤，甘草，川芎，柴胡，当帰，蒼朮，茯苓の七つの生薬からなる．肝気が昂ぶり神経過敏で，もともとは小児の夜泣き，小児疳症に対して用いられた方剤である．しかし，1984年に原が認知症を含む高齢者の情緒障害に対する抑肝散の効果を報告した[2]．この報告では48例の高齢者に対して抑肝散および抑肝散の加味方を投薬し，著効32例（67%），有効11例（23%），やや有効3例，無効2例と，極めて高率の改善率を示した．特に不眠，易怒性，興奮，せん妄に有効だったという．この研究では随証治療が行われており，腹直筋の緊張のある例では抑肝散が投薬され，腹直筋にはりがなく腹部大動脈が触れる例（臍傍悸）に対しては抑肝散加陳皮半夏が投薬されている．現在の臨床研究では証が考慮されることはないが，この研究から腹症によって使い分けることの有用さが示唆される．

この報告以来，認知症のBPSDに対する抑肝散の効果が報告されるようになった．現在ではADをはじめDLB，血管性認知症（vascular dementia; VD），前頭側頭型認知症（frontotemporal dementia; FTD）など各認知症疾患のBPSDに対する効果が報告されている．

2005年Iwasakiら[3]は52例の認知症患者（AD 30例，混合型3例，VD 9例，DLB 10例）を抑肝散投与群27例，非投与群25例に無為作為に分け，4週間の治療効果を観察者ブラインドの単盲験試験で検討した．その結果，抑肝散7.5 g投与群はBPSDが改善した．特に幻覚，興奮，易刺激性，異常行動などに著明な改善効果が認められた．同時に抑肝散服用群は日常生活動作（ADL）も有意に改善した．

筆者らは，関東地区20施設が共同で抑肝散のBPSDに対する効果をクロスオーバーオープン試験で検討した（図3）[4]．この検討には106名のAD，混合型，DLBの患者がエントリーし，前半の4週間抑肝散7.5 gを服用するA群と，後半4週間抑肝散を服用するB群に無作為に分けて検討した．その結果，A群，B群ともに興奮と易刺激性に対する効果を認めた．この他，A群あるいはB群のどちらかで改善した症状は，幻覚，妄想，不安，

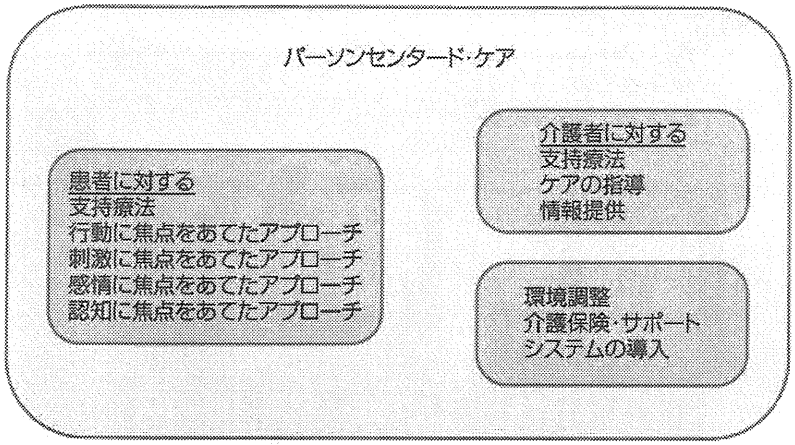

図1　認知症の非薬物療法（文献1）より改変引用）

認知症（AD，DLB，VD，FTD，その他）

症状	評価	→	治療
認知機能障害	本人および家族の問診 神経心理検査		非薬物療法　（図1参照） 薬物療法 AD，DLB：塩酸ドネペジル
BPSD	本人および家族の問診 評価尺度 ・NPI ・BEHAVE-AD		非薬物療法　（図1参照） 薬物療法 抑肝散，他（表2参照）

図2　認知症診療の流れ

うつ，異常行動であった．筆者らの検討で興味深いのは，4週間抑肝散を服用後中止したA群ではその後4週間BPSDの悪化がみられなかった点である．すなわち，本研究から抑肝散は中止しても一定期間効果が持続することが示唆された．なお，ADLや認知機能に対する効果はみられなかった．

2．他の薬剤と併用した場合の抑肝散の効果

この後，ADを対象に抑肝散と抗精神病薬あるいは認知機能障害の治療薬であるドネペジルを併用した検討が行われた．Monjiら[5]は，15例のBPSDを呈したADに対して，スルピリド単独治療群と，スルピリドと抑肝散の併用治療群とに分けて12週間比較検討した．その結果，スルピリドと抑肝散併用群ではNPIが有意に改善し，また抑肝散を併用することによってスルピリドの使用量を減量できた．またOkaharaら[6]は，ドネペジルと抑肝散の併用群29例とドネペジル単独群32例を4週間検討し，ドネペジルと抑肝散併用群のほうが有意に興奮や易刺激性が改善したことを報告した．

臨床場面ではドネペジルを投薬中の患者に抑肝散を追加したり，抑肝散と抗精神病薬を併用することがある．これらの研究はそのような臨床場面の実態に即した用い方でも抑肝散の効果が得られることを示唆している．

AD以外の認知症疾患に対する効果

1．DLBに対する効果

DLBはBPSDが最も現れやすい認知症疾患であり，また抗精神病薬に対する過敏性のため少量の抗精神病薬でも重篤な副作用が現れやすい．したがって，DLBの易刺激性や興奮に対しては抗精神病薬の使用は原則控える