のグルコース代謝の低下が示されている。認知症を発症するPDがDLB、ADの血流低下パターンをとるのか、またはそれ以外のパターンをとるのか、治療研究中の3例においても検討する。また、抑うつと認知症発症との関連も検討を要する。

E：結論

研究計画に従って3症例の経過を追跡中。

F：健康危険情報

なし

G：研究発表

1：論文発表

なし

2：学会発表

なし

H：知的所有権の取得状況（予定を含む）

1：特許取得

なし

2：実用新案登録

なし

3：その他

Ⅲ. 研究成果の刊行に関する一覧

研究成果の刊行に関する一覧

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Ⅳ. 研究成果に関する刊行物

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Neural Substrates of Cognitive Subtypes in Parkinson's Disease: A 3-Year Longitudinal Study

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Abstract

Background: The neuropsychological features and neuropathological progression patterns associated with rapidly evolving cognitive decline or dementia in Parkinson's disease (PD) remain to be elucidated.

Methods: Fifty-three PD patients without dementia were recruited to participate in a 3-year longitudinal cohort study. The patients were grouped according to the Clinical Dementia Rating (CDR). Group-wise comparisons were made with regard to demographic characteristics, motor symptoms, neuropsychological performances and 18F-fluorodeoxyglucose positron emission tomography.

Results: Patients who had memory-plus cognitive impairment (patients whose CDR was 0 at baseline and 0.5 in memory and other domains at follow-up, and those whose baseline CDR was 0.5 in memory and other domains) exhibited higher age at onset, visuoperceptual impairment, non-tremor-dominant motor disturbance, rapid symptomatic progression and posterior neocortical hypometabolism. In patients who were cognitively unimpaired and those who had memory-dominant cognitive impairment (patients whose CDR was 0 at baseline and 0.5 only in memory domain at follow-up, and those whose baseline CDR was 0.5 only in memory domain), the posterior neocortex was relatively unaffected until a later stage of the disease.

Conclusions: These results suggest that visuoperceptual impairment and the early involvement of the posterior neocortex may be risk factors for rapid symptomatic progression and dementia in PD.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper.

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Introduction

The cognitive features of Parkinson's disease (PD) are heterogeneous and can be categorized into several major subtypes. [1,2] However, the neural substrates underlying the cognitive subtypes remain to be elucidated. Recent studies have demonstrated that there are correlations between cognitive impairment and non-cognitive features in PD: patients who develop dementia have a higher age of onset, rapid symptomatic progression, anosmia and a non-tremor-dominant motor subtype. [3,4,5,6] Consistent with these observations, neuropathological studies have suggested that the anatomical distribution of Lewy-related pathology differs depending on the clinical subtypes. The pathology rapidly evolves from the brainstem into the cerebral cortex in patients with the non-tremor-dominant motor subtype and/or dementia, whereas it is relatively confined to the brainstem for a longer period of time in patients with a tremor-dominant motor subtype and no cognitive impairment. [7] If such provisional clinico-pathological relationships are genuine and if specific subtypes of cognitive impairment are associated with the future development of dementia, these cognitive subtypes may be associated with specific clinico-pathological subtypes.

Previous morphometric MRI and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) studies have demonstrated greater frontal, temporal and occipital gray matter volume reduction and greater frontal and parietal cortical hypometabolism in PD patients with dementia or mild cognitive impairment (MCI) compared with cognitively unimpaired patients. [8,9,10,11,12] In agreement with these neuroimaging findings, several neuropathological studies demonstrated the relationship

between dementia and limbic and/or neocortical neurodgeneration. [13,14,15] However, there is only a little evidence for neuroimaging features predictive of later development of dementia and for distinctive progression patterns of cortical lesions among the PD subtypes. The sole previous longitudinal FDG-PET study of PD demonstrated that patients who developed dementia 1 to 3 years later exhibited occipito-parietal hypometabolism at baseline. [16] To further address this issue, we investigated the relationship among cognitive subtypes, other clinical features and changes in regional brain glucose metabolism (CMRglc) over 3 years in a cohort of PD patients.

Methods

All procedures in this study followed the clinical study guidelines of Tohoku University Hospital and were approved by its ethics committee. The patients gave written informed consent after receiving a detailed explanation of the study. When the patients had a compromised ability to consent, their family members gave consent on behalf of the patients.

Subjects

We analyzed 55 patients with PD without dementia (mean age 65.4±6.5 years; 27 women) who participated in a 3-year longitudinal study at Tohoku University Hospital. Details of the study design have been described elsewhere. [3,9,17] Briefly, outpatients at the movement disorder clinic who met the following criteria were recruited in the study: fulfillment of the diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank; aged 50 years or more; absence of dementia according to the Diagnostic Statistical Manual-IIIR [18] and a Clinical Dementia Rating (CDR) [19] overall score of 0 or 0.5, no evidence of diabetes mellitus; no history of other neurological or psychiatric diseases; and no evidence of infarcts, bleedings, tumors and other focal brain lesions on MRI. Of 88 consecutive patients, 33 patients dropped out for the following reasons: 4 patients died; 4 were institutionalized; 1 developed psychosis; 2 developed myocardial infarction or cerebral infarction; 9 moved to hospitals near their homes; 6 did not return for follow-up visits for unknown reasons; the initial diagnosis of PD was dismissed in 3 patients; and 4 were excluded because of incomplete clinical or imaging data. Fourteen healthy volunteers (mean age 63.1±4.4 years; 6 women) were recruited as controls for neuroimaging. There were no significant differences in age ($t = 1.6$, $p = 0.1$) or sex ($x^2 = 0.2$, $p = 0.7$) between the patient and control groups.

Comparison of patient classification procedures: the neuropsychology-based criteria versus the Clinical Dementia Rating

Measuring cognitive changes is challenging because there is no very reliable change measures. Practice effects associated with the repeated administration have a great impact on neuropsychological test performance, yielding spurious cognitive improvement over time. [20,21,22,23] A recent study demonstrated that previous test exposures lead to bias towards normal cognition in the diagnosis of MCI. [24]In addition, cognitive assessment in PD is complicated by motor symptoms, such as bradykinesia and tremor, and medication-related effects. [2] To take these problems into account, global cognitive measures and/or caregiver interviews have been used in longitudinal intervention trials for cognitive disorders. [25,26,27,28] According to this convention, we have introduced the CDR, a global cognitive measure based on examinations by clinicians and caregiver interview, in our cohort study of PD. [3,9,17] To examine the rationality of the use of the CDR in the classification of cognitive status in PD, we compared the 3-year cognitive changes based on the neuropsychology-based criteria for MCI in PD (PD-MCI) and those based on the CDR in the patients (n = 46) who completed neuropsychological tests for memory, visuoperceptual ability and attention/working memory (see below for the details of the neuropsychological tests). PD-MCI was defined according to the Movement Disorder Society Guideline for PD-MCI Level I (MDS PD-MCI criteria), in which the diagnosis of PD-MCI required impairments of 1 to 2 standard deviations (SDs) below norms on at least 2 neuropsychological tests. [29] In the CDR-based criteria, the patients were classified as CDR 0 (unimpaired cognition) or CDR 0.5 (cognitive impairment which mildly affecting their everyday life).

Patient classification based on the Clinical Dementia Rating

The CDR, which was designed to provide a rating scale for subjects from normal cognition through various stages of dementia, is widely considered to be a reliable scale for staging the severity of cognitive dysfunction. [19] The CDR comprises 6 subdomains, i.e., memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. In matters related to the domains of community affairs, home and hobbies, and personal care, we asked the patients and their caregivers about cognition-related functional decline separately from disability arising from physical impairment in order to eliminate as far as possible the effects of non-cognitive symptoms. [9,17].

The primary aim of the current study is to discover clinical features and distinctive brain metabolic patterns of patients who have rapid cognitive deterioration. To this end, we first focused on 40 patients who were cognitively unimpaired (CDR 0) at baseline. Among these patients, 26 patients were cognitively unchanged over 3 years (CDR 0 at the third year; non-converters), 7 worsened only in the memory domain (memory-only converters) and 6 worsened in the memory and non-memory domains (memory-plus converters). The remaining patient, who showed deterioration only in a non-memory domain, was excluded from the analyses. Second, we analyzed patients whose overall CDR scores were 0.5 at baseline to investigate longitudinal brain metabolic changes after PD patients developed mild cognitive deficits. Eight patients who scored ≥0.5 only in the memory domain at baseline (baseline memory-only) and 6 patients who scored ≥0.5 in the memory and other domains (baseline memory-plus) were recruited for the study. We speculated that the baseline memory-only and the baseline memory-plus patients may represent the clinico-pathological stages following the memory-only converters and the memory-plus converters, respectively. We conducted group comparisons separately among the groups of baseline CDR 0, specifically non-converter, memory-only converter and memory-plus converter patients, and between the groups of baseline CDR 0.5, specifically baseline memory-only and baseline memory-plus patients, because our interest was in longitudinal changes in clinical symptoms and brain glucose metabolism.

Cognitive and motor assessments

The Mini-Mental State Examination (MMSE) and the Word Recall subtest of the Alzheimer's Disease Assessment Scale (ADAS) were used to assess general cognitive function and episodic memory, respectively. [30,31] Visuoperception was assessed using the correct response score on the overlapping-figure identification test. [32] A subset of patients underwent the backwards digit-span test to assess their working memory (the number of patients is indicated in **Tables 1 and 2**). [29] Further

details have been described elsewhere. [17,32] Motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III. We calculated the rate of progression indices for the clinical measures described above using the following formula: (rate of progression) = [(third year score)-(baseline score)]/(years of interval). [33] The tremor and non-tremor motor scores were calculated based on the UPDRS parts II and III. [5].

Statistical analyses

Group-wise comparisons of demographic data and baseline scores and progression rates of the cognitive and motor measures were analyzed using the statistical methods described in the captions of **Tables 1 and 2**. Two-way repeated-measures analysis of variance (ANOVA) with motor subtypes (the tremor and non-tremor scores of UPDRS) and time (baseline and third year) was performed to characterize the motor features of the groups. To enable comparisons with previous studies in which cognitive subtypes were determined by neuropsychological test scores, we investigated the number of patients whose scores were 1 SD or more below the mean of normative data for the ADAS-word recall, overlapping figure and backwards digit-span tests.

18F-fluorodeoxyglucose positron emission tomography

The mean interval between the clinical assessments and the positron emission tomography (PET) scan was 4.6 days. Each patient had fasted, and dopaminergic medication had been discontinued for at least 5 hours before the scan. Scanning was performed after an injection of 185–218 MBq 18F-fluorodeoxyglucose (FDG). After an FDG-uptake period of 1 hour, a 20-minute scan was acquired while the patient was at rest. Details of the scanning procedures have described elsewhere. [17,32] Image pre-processing and statistical analysis were performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). All images were normalized onto the standard FDG template with nonlinear warping algorithms, reconstructed into 2 mm^3 isotropic voxels and smoothed with 10 mm full width at half-maximum. Global normalisation was performed using proportional scaling, and threshold masking was set at 0.8. Cross-sectional comparisons between the patient groups and the controls were performed using *t*-test. Two-way repeated-measures ANOVA was used for cross-sectional and longitudinal comparisons of the patient groups. Age and sex were included as nuisance variables in all of the comparisons. The UPDRS part III score was included as a nuisance variable in the comparisons among the patient groups. The statistical threshold was set at an uncorrected $p<0.001$ at the voxel level and at 20 voxels at the cluster level.

Results

Comparison between the neuropsychology-based criteria and the Clinical Dementia Rating-based criteria

The results are summarized in **Figure 1.** The neuropsychology-based classification according to the MDS PD-MCI criteria exhibited a spurious improvement over 3 years in 5 of the 12 patients who were classified to PD-MCI at baseline, whereas such an effect was observed only in 1 of the 11 patients who scored 0.5 on the baseline CDR (**Figure 1**). Based on these preliminary findings, we decided to employ the CDR-based cognitive criteria in the current study.

Clinical profiles of the patient groups of baseline Clinical Dementia Rating 0

The results are summarized in **Table 1**. There were no significant differences among the non-converters, memory-only converters and memory-plus converters in sex, education, disease duration, levodopa equivalent dose or test-retest interval. The memory-plus converters had a significantly higher age of onset and a higher age at baseline than did the non-converters.

Baseline performance of the overlapping figure test was lower in the memory-plus converters than in the non-converters ($F = 10.1$, $p<0.001$). The baseline performance of the backwards digit-span was worse in the memory-only converters than it was in the non-converters ($F = 7.1$, $p<0.01$). No group differences were observed in baseline MMSE or baseline ADAS word recall. There were no significant differences in the progression rate on any of the cognitive tests.

No significant difference was observed in the baseline UPDRS part III among the three groups. The progression rate of the UPDRS part III was greater in the memory-plus converters than it was in the non-converters and the memory-only converters ($F = 6.8$, $p<0.01$). The UPDRS non-tremor score was higher in the memory-plus converters than it was in the other groups ($F = 18.8$, $p<0.001$), and no significant main effect of time or interaction between motor subtypes and times was observed.

Clinical profiles of the patient groups of baseline Clinical Dementia Rating 0.5

The results are summarized in **Table 2**. There were no significant differences between the baseline memory-only and the baseline memory-plus patients in age at baseline, sex, education, age of onset, disease duration, levodopa equivalent dose or test-retest interval. No significant group differences were observed in the baseline scores or progression rates on any of the cognitive tests. No significant difference was observed in the baseline UPDRS part III score. The UPDRS part III progression rate was greater in the baseline memory-plus patients than it was in the baseline memory-only patients ($t = -2.4$, $p<0.05$). The UPDRS non-tremor score was higher in the baseline memory-plus patients than it was in the baseline memory-only patients ($F = 8.0$, $p< 0.001$).

Positron emission tomography: comparisons between patient groups and controls

Compared with the controls, the non-converters and memory-only converters exhibited patchy, discrete areas of hypometabolism in the frontal, temporal and occipital cortices at baseline (**Figures 2A and 2B**). The memory-plus converters showed extensive hypometabolic areas in the temporo-parietal and occipital cortices compared with the controls (**Figure 2C**).

The regional pattern of metabolic reduction relative to the controls was similar among the baseline memory-only patients, the non-converters and the memory-only converters (**Figure 2D**). The baseline memory-plus patients showed a similar but more extensive hypometabolism compared with the memory-plus converters, in whom the metabolic reduction relative to controls was greatest in the temporo-parietal and medial parietal cortices (**Figure 2E**).

Positron emission tomography: comparisons among the patient groups of baseline Clinical Dementia Rating 0

At baseline, there was no significant difference in regional glucose metabolism between the non-converters and memory-only converters (**Figure 3A**). The memory-plus converters showed a

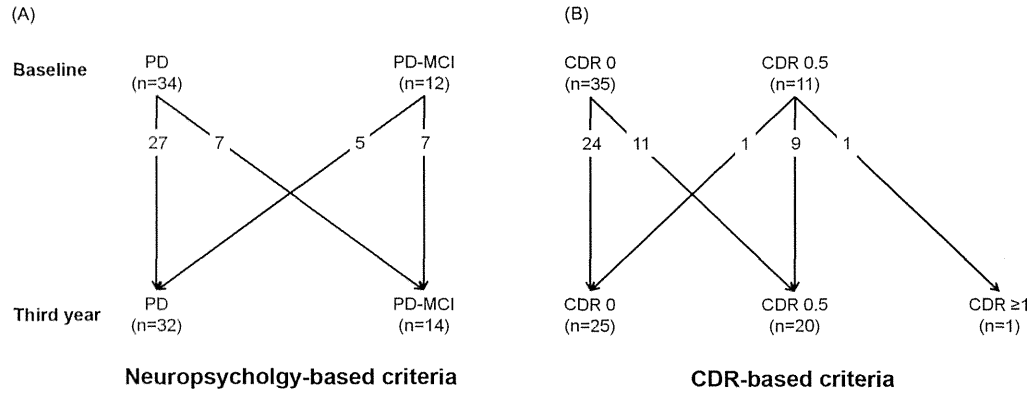

Figure 1. Diagrams of the 3-year cognitive changes observed in patients. In (A), the patients were classified as having Parkinson's disease without cognitive impairment (PD) or PD with mild cognitive impairment (PD-MCI) based on neuropsychological tests. (B) shows the results based on the Clinical Dementia Rating (CDR)-based patient classification.
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stronger metabolic reduction in the parietal and occipital cortices compared with the non-converters and amnesic converters at baseline (**Figures 3B and 3C**).

The non-converters showed a significant metabolic decline over 3 years in the frontal, temporal, medial parietal and occipital cortices and the thalamus (**Figure 4A**). In the memory-only converters, regional glucose metabolism was decreased in the anterior cingulate cortex, medial temporal lobe, caudate nucleus and midbrain over 3 years (**Figure 4B**). No significant longitudinal metabolic change was observed in the memory-plus converters (**Figure 4C**). An ANOVA interaction demonstrated that metabolic decline over 3 years in the medial temporal lobe was greater in the memory-only converters than it was in the non-converters (**Figure 4F**).

Positron emission tomography: comparisons between the patient groups of baseline Clinical Dementia Rating 0.5

The baseline memory-only patients had lower baseline regional glucose metabolism in the medial temporal lobe, cingulate cortex and dorsal brainstem regions than did the baseline memory-plus patients, whereas the regional glucose metabolism in the temporo-parietal and medial parietal cortices was lower in the baseline memory-plus patients than it was in the baseline memory-only patients (**Figures 3D and 3E**).

Regional glucose metabolism was decreased over 3 years in the parietal cortex in the baseline memory-only patients, whereas a longitudinal metabolic decline was observed in discrete regions of the basal forebrain and the brainstem in the baseline memory-plus patients (**Figures 4D and 4E**). An ANOVA interaction revealed circumscribed ventral frontal and basal forebrain regions that showed a greater 3-year metabolic decline in the baseline memory-plus patients than in the baseline memory-only patients (**Figure 4G**).

Discussion

Early visuoperceptual impairment and posterior cortical hypometabolism may represent the clinical subtypes of rapidly progressive motor symptoms and severe cognitive impairment

The clinical entity of PD encompasses a wide variety of symptoms, including motor, sensory, cognitive and autonomic disturbances. Recent cluster-analysis studies have suggested that two major clinical subtypes can be extracted from the clinical diversity: one subtype is characterized by a young age of onset, slow disease progression, tremor-dominant motor features and preserved cognition, and the other is associated with an older age of onset, rapid disease progression, non-tremor-dominant motor features and cognitive impairment. [5,6,34] In parallel with these discoveries, there has been growing evidence of the neuropathological diversities underlying these clinical subtypes. Patients with a young age of onset, slow progression and tremor-dominant motor features are reported to have neuropathological features that conform to Braak's pathological staging scheme, in which Lewy-related pathology begins in the lower brainstem (stages 1–2); ascends to the midbrain (stage 3), thalamus and limbic structures (stages 4); and finally reaches the neocortex (stages 5–6). [35] By contrast, patients with an older age of onset, non-tremor-dominant motor features and/or dementia are associated with disproportionately severe neocortical Lewy-related pathology and concomitant Alzheimer's disease-related pathology. [14,15].

In the current study, the memory-only converters showed a metabolic decline over 3 years in the anterior cingulate and medial temporal cortices (**Figure 4B**). The baseline memory-only patients, whose baseline cognitive status was similar to that of the memory-only converters at the third year, showed a metabolic decline in the parietal cortex (**Figure 4D**). Assuming that these patient groups represent a single cognitive subtype at different time points, these results suggest that neurodegeneration first affects the limbic structures and next encroaches on the posterior neocortex. This pattern of brain metabolic changes is largely consistent with Braak's scheme. [7] A longitudinal PET analysis of the non-converters demonstrated 3-year metabolic decline in the thalamus and occipital cortex (**Figure 4A**). A direct comparison between the non-converters and the memory-only converters revealed no significant group difference at baseline but greater metabolic decline over time in the memory-plus converters than in the non-converters (**Figures 3A and 4F**). These two groups of patients may represent slightly different subpopulations of a clinico-pathological subtype that conforms to Braak's scheme.

The memory-plus converters exhibited extensive posterior cortical hypometabolism at baseline compared with the controls and the non-converters (**Figures 2C, 3B and 3C**). Likewise, more extensive posterior cortical hypometabolism was observed in the baseline memory-plus patients compared with the baseline

Table 1. Demographic and clinical profiles of patients with a Clinical Dementia Rating of 0 at baseline.

		Non-converter (N = 26)	Memory-only converter (N = 7)	Memory-plus converter (N = 6)	Differences among groups
Age at baseline (years)		62.2±5.9	67.7±5.5	71.8±2.6	Memory-plus>Non-converters[b]
Gender (male/female)		12/14	2/5	1/5	
Education (years)		11.8±2.5	11.1±2.5	12.0±2.8	
Test-retest interval (days)		1140.2±110.7	1107.7±43.5	1109.7±59.7	
Disease duration at baseline (years)		4.3±3.7	5.0±6.9	5.0±3.2	
Age at onset (years)		58.0±7.3	63.6±6.0	67.2±5.4	Memory-plus>Non-converters[b]
Levodopa equivalent dose at baseline (mg/day)		303.5±233.1	378.9±320.4	533.6±340.2	
UPDRS part III	Baseline	18.0±7.3	18.9±8.0	16.5±6.2	
	Progression rate (/years)	−0.02±2.0	−0.8±0.8	4.0±5.2	Memory-plus>Non-converters[b]; Memory-plus> Memory-only[b]
UPDRS tremor score¶	Baseline	0.5±0.4	0.4±0.6	0.3±0.4	
	Third year	0.3±0.3	0.2±0.2	0.3±0.3	Main effect of non-tremor score: Memory-plus> Non-converters[b]; Memory-plus>Memory-only[b]
UPDRS non-tremor score ¶	Baseline	0.7±0.3	0.7±0.4	0.7±0.2	
	Third year	0.8±0.3	0.7±0.4	1.6±0.2	
CDR sum of boxes	Baseline	0	0	0	NE
	Third year	0	0.5	1.8±0.8	NE
MMSE	Baseline (/30)	28.2±1.8	27.3±2.6	27.5±1.9	
	Progression rate (/years)	0.1±0.6	−0.1±0.9	−0.6±0.7	
ADAS word recall†	Baseline (/30)	19.3±3.4	17.3±4.5	17.8±4.4	
	Progression rate (/years)	0.6±0.9	1.2±1.1	−0.03±1.2	
Overlapping figure‡	Baseline (/40)	33.4±4.0	29.6±2.4	25.3±6.3	Non-converters>Memory-plus[b]
	Progression rate (/years)	−0.2±1.0	0.7±0.9	−0.9±2.0	
Backward digit-span§	Baseline	4.4±0.8	3.0±0.9	4.0±0.7	Non-converters>Memory-only[a]
	Progression rate (/years)	−0.1±0.3	0.1±0.4	−0.2±0.2	
# of patients below −1 SD at baseline and at third year	ADAS word recall †	9/26 3/26	3/7 1/7	3/6 3/6	NE
	Overlapping figure‡	4/26 3/26	2/7 0/7	5/6 5/6	NE
	Backward digit-span§	1/25 5/25	4/6 4/6	1/5 3/5	NE

Analysis of variance with post-hoc Tukey's test was used for group-wise comparisons of baseline scores and progression rates except for the UPDRS tremor/non-tremor scores. Two-way analysis of variance with post-hoc Tukey's test was used for the UPDRS tremor/non-tremor scores. Data are given as the mean±SD except for the fields with asterisks. a and b indicate $p<0.05$ and $p<0.01$, respectively.

*Data are given as (the number of patients below −1 SD)/(the number of patients who underwent the test).

¶The scores were calculated according to Lewis and colleagues. [5] Data were obtained from 21 non-converters, 6 memory-only converters and 5 memory-plus converters.

†The mean score for controls (n = 20, 65.5±4.8 years) is 21.3±3.5. [49].

‡The mean score for controls (n = 24, 66.1±5.3 years) is 32.9±4.4. [32].

§The mean score for controls (n = 20, 65.5±4.8 years) is 4.8±1.0. [49].

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; ADAS, Alzheimer's Disease Assessment Scale; NE, not examined.

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