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Longitudinal study of cognitive and cerebral metabolic changes in Parkinson's disease

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Title: Longitudinal study of cognitive and cerebral metabolic changes in Parkinson’s disease

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Abbreviations: Parkinson’s disease (PD); PD with mild cognitive impairment (PD-MCI); PD dementia (PDD); cognitively normal PD (PD-CogNL); Mini-Mental State Examination (MMSE); 18F-fluorodeoxyglucose positron emission tomography (FDG-PET); Alzheimer’s Disease Assessment Scale (ADAS); analyses of variance (ANOVAs); dorsolateral prefrontal cortex (DLPFC).
Abstract

Objective: To investigate the cortical metabolic alterations that precede longitudinal cognitive decline in Parkinson’s disease (PD).

Methods: We analyzed the data of 46 PD patients who did not have dementia at baseline and completed 3-year follow-up. Based on the results of general cognitive, memory and visuospatial tests, patients were classified into cognitively normal PD (PD-CogNL), PD with mild cognitive impairment (PD-MCI), and PD dementia (PDD). The regional cerebral glucose metabolism at rest was measured using 18F-fluorodeoxyglucose positron emission tomography. Voxel-wise effect size analyses were performed to delineate abnormal metabolic patterns associated with changes in cognitive status in PD.

Results: At baseline, 29 patients had PD-CogNL and 17 patients had PD-MCI. At follow-up, 28 patients had PD-CogNL, 12 patients had PD-MCI, and 6 patients developed PDD. Seventeen of 29 PD-CogNL patients remained to be PD-CogNL, and 9 PD-CogNL patients converted to PD-MCI. Eleven PD-MCI patients reverted to normal cognition during follow-up. 3 PD-CogNL and 3 PD-MCI patients developed PDD. Cognitively stable PD-CogNL group had frontal predominant hypometabolism. PDD converters showed parieto-occipital hypometabolism at baseline regardless of whether a patient’s initial cognitive status is PD-CogNL or PD-MCI.

Conclusions: Parieto-occipital hypometabolism is a good predictor of early dementia conversion in PD.

Key words: PD-MCI, longitudinal study, dementia conversion, cognitive reversion, cortical glucose metabolism
1. Introduction

The need to develop strategies for detecting early dementia associated with Parkinson’s disease (PD) is considered urgent [1]. It is well known that dementia is one of the factors that most affect activities of daily living and mortality in patients with PD [2]. A recent longitudinal study found that most PD patients eventually developed dementia over the long course of the disease [3]. Moreover, some PD patients exhibit a rapid cognitive decline that leads to dementia in the early phase of the disease.

Therefore, early diagnosis and treatment of PD dementia (PDD) are of great importance in clinical practice. Thus, the syndrome of mild cognitive impairment in PD (PD-MCI) has drawn considerable attention as a high risk group for developing dementia [4].

Recent imaging studies demonstrated that PD-MCI and PDD patients showed gradually more severe hypometabolism in frontal and parieto-occipital cortices compared to cognitively normal PD (PD-CogNL) patients [5, 6]. However, cortical metabolic changes associated with cognitive decline in PD has been mainly inferred from cross-sectional studies, but there is only limited evidence from longitudinal study [7]. Our objective in this study was to confirm the cortical metabolic changes associated
with longitudinal cognitive decline and progression to dementia in PD.

2. Materials and Methods

2.1. Subjects

We analyzed the data from a 3-year longitudinal study of patients with PD at Tohoku University. The design of this study has been described previously [8]. Inclusion criteria were 55–75 years old at entry into this study, with disease onset after age 40. Exclusion criteria were any history of other neurological or psychiatric diseases, any focal brain lesions diagnosed by MRI, any family history of parkinsonism, and probable dementia as defined by a score <26 on the Mini–Mental State Examination (MMSE). The baseline and 3-year follow-up data for PD patients without dementia at baseline were entered into a database from 2005 to 2012. Only those patients who completed both baseline assessment and follow-up survey at 3-years later with 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans were included in this study. Of 88 consecutive PD patients who visited the movement disorders clinic at Tohoku University Hospital, 46 subjects who completed 3-year
follow-up surveillance with FDG-PET scans were enrolled in the present study; 35 of these subjects were included in our previous study [8]. No PD patients received trihexyphenidyl or deep brain stimulation. In addition, healthy volunteers, comparable to the patients in terms of sex, age, and education, were recruited from the general population to determine normative performance levels on neuropsychological tests (n=37, 23 females, 14 males; age, 72.9±7.1 years; educational level, 11.9±2.8 years) and to obtain normative PET data (n=11, 6 females, 5 males; age, 63.3±4.7 years; mean Mini-Mental State Examination [MMSE] score, 28.8±1.5). Written informed consent was obtained from all recruited participants in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Tohoku University Graduate School of Medicine.

2.2. Clinical assessment

We evaluated motor impairment using the Hoehn and Yahr scores [9] and the Unified Parkinson’s Disease Rating Scale (UPDRS) part III [10]. We examined general cognitive function using the MMSE [11]. Only patients without dementia at baseline,
based on a recommended algorithm for the diagnosis of PDD [12, 13], were included in this study; thus, all the participants in the study had MMSE scores of 26 or higher at baseline. In addition, we assessed memory and visuospatial abilities with a battery of neuropsychological tests. Verbal memory function was assessed using the 10-word list recall subtest of the Alzheimer’s Disease Assessment Scale (ADAS) [14]. We defined the word recall score as the total number of properly recalled answers from the three trials (max=30). Visuoperceptual ability was examined using the overlapping-figure identification test [15]; we defined the correct-response score on this test as the number of objects correctly identified from among 10 overlapping figures consisting of four common objects (max=40), and we defined the illusory-response score as the number of erroneously identified objects that were not in the figures (max=40). In this study, patients were diagnosed with PD-MCI when both verbal memory and visuoperceptual ability were impaired (1 SD or more below the mean for controls); which fulfilled the MDS Level 1 criteria for PD-MCI [4]. At follow-up, conversion to PDD was defined using the same algorithm that was used to diagnose PDD in potential subjects at baseline (level 1 criteria) [12, 13]. We then classified patients into the following six
groups based on cognitive status at baseline and follow-up evaluation: the

PD-CogNL-PD-CogNL group (group A); the PD-MCI-PD-CogNL group (group B); the

PD-CogNL-PD-MCI group (group C); the PD-MCI-PD-MCI group (group D); the

PD-CogNL-PDD group (group E); and the PD-MCI-PDD group (group F).

2.3. Statistical analysis

For cross-sectional analysis, the continuous demographic characteristics of
PD-CogNL and PD-MCI patients at baseline were compared using two-sample t-tests,
and the demographic characteristics of the patients with PD-CogNL, PD-MCI and PDD
at follow-up were analyzed by one-way analyses of variance (ANOVAs) with post-hoc
Tukey’s test. The differences in dementia conversion rate from PD-CogNL and PD-MCI
groups to PDD were analyzed using chi-squared tests. These analyses were performed
using a standard statistical software package (JMP Pro 11.0.0, SAS Institute). All results
were expressed as mean±SD.

2.4. Neuroimaging data acquisition, processing and analysis
Each patient underwent 18F-FDG-PET scans at baseline and after 3 years of follow-up, using a protocol described previously [8]. Each scan was preprocessed before statistical analysis using SPM8 software (Wellcome Department of Cognitive Neurology) running under MATLAB R2013b (The MathWorks, Inc.). The PET images were spatially normalized to the 18F-fluorodeoxyglucose template and smoothed with a 10-mm Gaussian kernel.

Cross-sectional and longitudinal analyses were performed using the FDG-PET data. First, we analyzed the regional metabolic abnormalities in PDD converter group and non-converter group both at baseline and at follow-up. The metabolic topography in each group at each time point were estimated by comparing each group’s data with the normative data obtained from 11 age-matched control subjects (six females, five males; mean age 63.3 ± 4.7 years; mean Mini-Mental State Examination score 28.8 ± 1.5) using proportional scaling. The statistical threshold in this analysis was P<0.001 (uncorrected), with an extent threshold of 50 voxels. Second, we performed subanalyses to delineate the pattern of cortical metabolic abnormalities associated with the gradual changes in cognitive status in PD groups (groups A to F).
Because the number of patients in each group varied widely, we computed voxel-wise maps of the effect size to display group differences unbiased by sample size. Cohen's effect size (d) was calculated as the difference in the mean of regional cerebral glucose metabolism between in each PD group and normal control group divided by the pooled SD. The statistical threshold for the effect size analysis was d>0.8, corresponding to a large effect size [16]. Next, we assessed longitudinal changes in cortical metabolism in each group using the paired t-test. The statistical threshold for longitudinal analysis was P<0.05 (family-wise error-corrected), with an extent threshold of 50 voxels.

Table 1. Demographics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P-value</th>
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<tr>
<td></td>
<td>PD-CogNL</td>
<td>PD-MCI</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>29</td>
<td>17</td>
<td>0.73</td>
</tr>
<tr>
<td>Age</td>
<td>65.6 ± 6.4</td>
<td>64.9 ± 6.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex (female/male), n</td>
<td>16/13</td>
<td>10/7</td>
<td></td>
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<tr>
<td>Education (y.)</td>
<td>11.9 ± 2.3</td>
<td>12.7 ± 2.7</td>
<td>0.75</td>
</tr>
<tr>
<td>Disease duration (y.)</td>
<td>4.9 ± 4.0</td>
<td>4.4 ± 5.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Hoehn and Yahr scale</td>
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<td>2.5 ± 0.5</td>
<td>0.90</td>
</tr>
<tr>
<td>UPDRS3</td>
<td>19.6 ± 8.0</td>
<td>19.9 ± 6.4</td>
<td>0.90</td>
</tr>
<tr>
<td>Levodopa equivalent dose (mg)</td>
<td>386.5 ± 283.4</td>
<td>293.6 ± 254.7</td>
<td>0.27</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.5 ± 1.4</td>
<td>28.5 ± 1.6</td>
<td>0.98</td>
</tr>
<tr>
<td>Word recall score (max = 30)</td>
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<td>18.9 ± 3.8</td>
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<td>Overlapping figure identification test</td>
<td>31.7 ± 4.9</td>
<td>30.2 ± 6.5</td>
<td>0.37</td>
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<tr>
<td>Correct response score (max = 40)</td>
<td>30.6 ± 5.5</td>
<td>32.6 ± 6.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Note: *P<0.05
3. Results

3.1. Clinical data

The demographic and clinical characteristics are presented in Table 1.

At baseline, 29 patients had PD-CogNL, and 17 patients had PD-MCI. The demographic findings were comparable between the groups. At follow-up, 28 patients had PD-CogNL, 12 patients had PD-MCI, and 6 patients developed PDD. One-way ANOVAs and post hoc Tukey’s tests indicated that the MMSE score, word-recall score, and correct-response score for the overlapping-figure identification test differed significantly between the PDD group and the remaining groups.

The changes in and between different cognitive stages in the 3-year study period are presented in Figure 1.
Approximately two-thirds of the patients who were initially classified as having PD-CogNL remained cognitively normal at follow-up (Figure 1, group A); and the remaining one-third of these patients showed cognitive decline and were classified in the PD-MCI group (Figure 1, group C). Three patients who had PD-CogNL at baseline developed PDD within the 3-year study period (Figure 1, group E). Eleven of the 17 patients who had been classified as having PD-MCI at baseline reverted to the PD-CogNL group 3 years later (Figure 1, group B). Only 3 patients who were classified with PD-MCI at baseline maintained that diagnosis at follow-up (Figure 1, group D).
Three of the 17 patients classified as having PD-MCI at baseline developed PDD at follow-up (Figure 1, group F). Dementia progression rates in the PD-CogNL group and the PD-MCI group were 10.3% and 17.6%, respectively. The chi-squared test showed that the differences in the dementia conversion rates between these two groups were not statistically significant (P=0.48).

3.2. Neuroimaging data

The patterns of cortical metabolic abnormalities in the PDD converters and the non-converters are illustrated in Figure 2. Dementia converters showed hypometabolism in the bilateral DLPFC and in the occipital and parietal cortices with predominance in both the medial and lateral parieto-occipital areas both at baseline and at follow-up, unsurprisingly more marked in the latter (Figure 2, A-1 and A-2). On the other hand, non-converters showed frontal predominant metabolic reduction (Figure 2, B-1 and B-2).
The effect-size maps generated using FDG-PET data to compare the PD groups and the control subjects at baseline and at follow-up are shown in Figure 3, columns 1 and 2, respectively. Longitudinal metabolic changes within the PD groups...
are shown in Figure 3, column 3.

Fig. 3

In group A (PD-CogNL both at baseline and at follow-up), glucose metabolism was markedly reduced in the dorsolateral prefrontal cortex (DLPFC) at baseline (Figure 3, A-1). Glucose metabolism in the caudate, thalamus, parietal and occipital cortices was
also reduced in group A at follow-up (Figure 3, A-2), and the longitudinal metabolic reduction was significant in the thalamus and medial occipital cortex (Figure 3, A-3). In group B (PD-MCI at baseline and PD-CogNL at follow-up), glucose metabolism in the DLPFC, thalamus, parietal and medial occipital cortex was reduced at both baseline (Figure 3, B-1) and follow-up (Figure 3, B-2), but no longitudinal change was statistically significant (Figure 3, B-3). In group C (PD-CogNL at baseline and PD-MCI at follow-up), the pattern of metabolic changes was essentially similar to that observed in group B both at baseline and follow-up (Figure 3, C-1 and C-2), and no significant longitudinal change in cortical metabolism was observed in this group, as well (Figure 3, C-3). In group D (PD-MCI both at baseline and at follow-up), cortical metabolism in the frontal lobe and brainstem was reduced, and significant longitudinal changes were observed in these areas (Figure 3, D-1 to 3). In group E (PD-CogNL at baseline and PDD at follow-up), reduced cortical metabolism was observed in the DLPFC and in the occipital and parietal cortices at baseline; the greatest reductions were observed in the posterior area (Figure 3, E-1). At follow-up, the metabolic abnormalities involved cortical midline structures, including the medial prefrontal and posterior cingulate
cortices (Figure 3, E-2 and 3). In group F (PD-MCI at baseline and PDD at follow-up),
the patterns of and longitudinal changes in cortical metabolism were similar to, but
slightly more severe than, those observed in group E (Figure 3, F-1 to 3).

4. Discussion

In this study, we analyzed longitudinal changes in cognitive status and cortical
metabolism in non-demented PD patients over 3 years. After a 3 year observation period,
3 of 29 PD-CogNL patients (10.3%) and 3 of 17 PD-MCI patients (17.6%) developed
dementia (Figure 1). The conversion rate to dementia in PD-MCI group in this study
was nearly identical to the rates reported in other recent longitudinal studies; in these
studies, the rates of conversion to dementia in PD-MCI group ranged from 11 to 27%
within a few years [17-20]. Results of our study seemed to support the view that
patients with PD-MCI have a higher risk of developing dementia, however the
difference in the dementia conversion rates between the PD-CogNL and PD-MCI
groups was not statistically significant in this study.

We used cutoff values of 1 SD below the mean scores for the normal controls
on the memory and visuospatial tests to diagnose PD-MCI in this study. When intermediate cutoff values of 1.5 SD below the means were applied, 5 patients were classified as having PD-MCI at baseline, and only one patient in this group developed dementia. In addition, with the more stringent cutoff values of 2 SD below the means, only 3 of 46 patients were initially classified as having PD-MCI, and none of these PD-MCI patients developed PDD (data not shown). These results suggest that adjusting cutoff values may not significantly improve predictive ability of the PD-MCI criteria for the development of dementia. Furthermore, cognitive performances in the PD-CogNL and PD-MCI groups were nearly identical in this study. There are several possible reasons for this apparently inconsistent finding. First, most of participants in our study were postural instability gait difficulty type, and thus even in the PD-CogNL group had certain level of cognitive dysfunction compared to the healthy controls and the difference in cognitive performance between in the PD-CogNL and PD-MCI groups was small. Second, PD patients with with single domain MCI were erroneously classified into the PD-CogNL group based on the level 1 PD-MCI criteria. Taken together, predicting dementia conversion only using verbal memory and visuospatial
testings is expected to be difficult in PD.

On the other hand, our FDG-PET results highlight the utility of neuroimaging in the prediction of dementia in PD. Regardless of whether a patient’s initial cognitive status was PD-CogNL or PD-MCI, individuals who converted to PDD showed reduced metabolism at baseline in the bilateral DLPFC and in the occipital and parietal cortices, with a predominance in both the medial and lateral parieto-occipital areas (Figure 2; Figure 3, E-1 and F-1). A recent longitudinal study reported that hypometabolism in the visual association cortex and the posterior cingulate cortex heralded the development of dementia in PD [7]. Our results are consistent with the results of that study and also provide a detailed temporal profile of changes in cognitive status and cortical metabolism that occur in PD. It has recently been reported that PD-MCI patients exhibit hypometabolism especially in the parieto-occipital and frontal cortices [21]. Moreover, another recent study demonstrated a close correlation between the severity of this pattern of metabolic change and the degree of cognitive impairment in PD [22]. Thus, parieto-occipital hypometabolism has been associated with PD-MCI. However, in this study, a similar distribution of hypometabolism was also observed in PD-CogNL.
patients who rapidly developed dementia (Figure 3, E-1). Therefore, it is likely that parieto-occipital-predominant hypometabolism may be present not only in PD-MCI patients but also in PD-CogNL patients at high risk for developing dementia.

The data for the group of patients whose cognitive status maintained PD-CogNL throughout the observation period may further support the importance of parieto-occipital hypometabolism in estimating the prognoses of patients with PD. In this study, approximately two-thirds of PD-CogNL patients remained cognitively normal at follow-up, as well (Figure 1), and these patients appeared to have the most benign subtype of PD. Investigations of glucose metabolism showed that this benign group exhibited frontal-predominant hypometabolism both at baseline and at follow-up, but glucose metabolism in the parieto-occipital area was largely preserved in this group (Figure 3, A-1 and A-2). These results can be interpreted as suggesting that a lack of parieto-occipital hypometabolism may be associated with a benign clinical course in terms of cognition. Thus, parieto-occipital hypometabolism appears to be a more reliable marker of cognitive decline in PD, and testing for parieto-occipital hypometabolism may be complementary to cognitive testing.
Abnormal metabolism in the parieto-occipital cortex may reflect dysfunction in non-dopaminergic systems in PD. It is widely accepted that dopamine deficiency causes frontal executive dysfunction in PD [23]. This type of cognitive impairment is very common and is not directly associated with early conversion to dementia in PD [24]. By contrast, accumulating evidence indicates that some PD patients have dysfunction in multiple neurotransmitter systems early in the course of the disease [25]. Among the different neurotransmitter systems that can be affected, cholinergic dysfunction is assumed to be of particular importance with respect to cognitive impairment in PD. Cholinergic neurons in the basal forebrain project widely to the neocortex. Considerable neuron loss in this area is observed in demented PD patients [26]. A recent study demonstrated that cholinergic deafferentation began in posterior cortical regions, even in PD without dementia [27]. In addition, the severity of cognitive impairment and the degree of cholinergic dysfunction in PD are closely correlated [27, 28]. Recent studies have also demonstrated that anosmia [8] and rapid eye movement behavior disorder [19], common non-motor features of PD, are both closely associated with cholinergic dysfunction and with higher risks for developing dementia. Moreover,
visual hallucinations, a common symptom of PDD, are known to be associated with cholinergic dysfunction [29] and parieto-occipital hypometabolism [30]. Overall, it is plausible that parieto-occipital hypometabolism in PD is closely associated with cholinergic denervation and thus heralds early conversion to dementia. Incorporating clinical and imaging biomarkers that reflect cholinergic dysfunction into the PD-MCI criteria may improve its predictive accuracy for early conversion to PDD.

Our results may offer new insight into the neurobiological basis of cognitive reversion phenomenon in PD-MCI. In spite of their higher overall rate of conversion to dementia, many of the patients classified as having PD-MCI reverted to normal cognition in the follow-up evaluation (Figure 1). This phenomenon has already been noted in recent longitudinal studies of PD [17, 18, 20], and it seems likely that cognitive reversion may be a common problem in the PD-MCI criteria. The cognitive reversion phenomenon is partially attributable to the cognitive fluctuations commonly observed in PD, as well as to intrinsic test-retest variability and to practice effects. In the FDG-PET analysis in our study, the cognitive reversion group exhibited medial occipital and prefrontal hypometabolism both at baseline and at follow-up, without significant
longitudinal changes, whereas the reduction in parieto-occipital metabolism in this group was less remarkable (Figure 3, B-1 to 3). It is worth noting that the distribution of hypometabolism in the PD-CogNL-PD-MCI group was similar to that observed in the cognitive-reversion group (Figure 3, C-1 to 3). Such patterns of metabolic changes are known to be common in PD; they probably primarily reflect dopaminergic deficiency and usually occur independent of the development of cognitive impairment. These findings indicate that many of the PD-MCI patients without a malignant metabolic pattern have a relatively stable disease course and that the boundary between normal cognition and MCI can be ambiguous in such cases. Therefore, it can be assumed that there are at least two types of PD-MCI; one is the more common type that exhibits a relatively stable course with regard to cognition, and another type that results in rapid cognitive decline to dementia.

This study had several limitations. First, the sample size was relatively small, and only 6 patients eventually developed PDD. Therefore, the findings in the imaging analysis remain inconclusive. Second, repeated testing may have caused a practice effect that obscured longitudinal cognitive decline, although these procedures were
approved in the PD-MCI criteria. Furthermore, we assessed general cognition using the MMSE instead of using the MoCA, because the Japanese version of MoCA was not validated at the beginning of this study. Relatively higher rate of cognitive reversion in this study may in part be due to the choice of cognitive test in this study.

5. Conclusion

We investigated the temporal profiles of cognitive decline and longitudinal metabolic changes in PD. Our results suggest that parieto-occipital hypometabolism is predictive of early conversion to dementia in PD, regardless of whether a patient’s initial cognitive status is normal or MCI. Furthermore, our study showed that there are benign and malignant types of PD-MCI. The use of imaging biomarkers may improve the predictive accuracy of cognitive decline in PD and may increase the clinical value of the diagnosis of PD-MCI.

6. Acknowledgement: This work was supported by a Grants-in-Aid for Scientific Research from the Japan Foundation for Neuroscience and Mental Health.
References


Figure Captions

Figure 1. Occurrence of and changes in and between different cognitive stages in the 3-year study period.

Three of 29 PD-CogNL patients and 3 of 11 PD-MCI patients developed dementia within 3 years. One-thirds of PD-CogNL patients converted to PD-MCI, whereas two-thirds of PD-MCI patients reverted to normal cognition after 3 years.

Figure 2. The distributions of cortical hypometabolism in the Parkinson’s disease subgroups compared with the normal controls.

The PDD converter group showed parieto-occipital predominant cortical hypometabolism at baseline (A-1), and the finding become pronounced over time (A-2). The non-converter group showed frontal predominant cortical hypometabolism at baseline (B-1). At follow-up, the non-converter group showed more widespread hypometabolism involving the frontal and occipital cortices and brainstem, whereas the parietal cortex was relatively spared (B-2).

Figure 3. The distributions of and longitudinal changes in cortical hypometabolism in the Parkinson’s disease subgroups.

Column 1, Effect size maps of cortical hypometabolism at baseline in the PD subgroups compared with normal controls. Column 2, Effect size maps of cortical hypometabolism at follow-up in the PD subgroups compared with normal controls. Column 3, Longitudinal changes in cortical metabolism in each PD subgroup during 3-years. The group A (normal cognition both at baseline and follow-up) showed frontal predominant cortical hypometabolism both at baseline (A-1) and follow-up (A-2) with longitudinal metabolic reduction in thalamus and medial occipital cortex (A-3). The groups B (PD-MCI at baseline and reverted to normal cognition at follow-up) and C (normal cognition at baseline and progressed to PD-MCI at follow-up) showed medial occipital
predominant hypometabolism both at baseline (B-1 and C-1) and follow-up (B-2 and C-2) without significant longitudinal change in cortical metabolism (B-3 and C-3). The group D (PD-MCI both at baseline and follow-up) showed frontal and brainstem hypometabolism both at baseline and follow-up (D-1 and D-2) with longitudinal metabolic reduction in these areas (D-3). The groups E (normal cognition at baseline and progressed to PDD at follow-up) and F (PD-MCI at baseline and progressed to PDD at follow-up) showed parieto-occipital predominant hypometabolism both at baseline (E-1 and F-1) and follow-up (E-2 and F-2) with significant metabolic reduction in the medial prefrontal and posterior cingulate cortices (E-3 and F-3).
Author roles: Atsushi Takeda and Etsuro Mori conceptualized and organized the study. Toru Baba, Yoshiyuki Hosokai, Yoshiyuki Nishio and Akio Kikuchi executed the study and analyzed the data. Atsushi Takeda and Etsuro Mori reviewed the statistical analyses of the study. Toru Baba made a draft of the article. Kazumi Hirayama, Kyoko Suzuki, Takafumi Hasegawa, Masashi Aoki, Atsushi Takeda and Etsuro Mori revised the article.

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Research Highlights

- Longitudinal changes in cerebral glucose metabolism in 46 patients with Parkinson’s disease (PD) were retrospectively analyzed.
- $^{18}$F-fluorodeoxyglucose positron emission tomography was undertaken both at baseline and after 3 years of follow-up.
- Three of 29 cognitively normal PD patients and 3 of 17 PD patients with mild cognitive impairment (PD-MCI) developed dementia during follow-up.
- Dementia converters showed parieto-occipital hypometabolism at baseline regardless of their initial cognitive status.
- A finding of parieto-occipital hypometabolism is useful in predicting dementia in PD.