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Severe olfactory dysfunction is a prodromal symptom of dementia associated with Parkinson's disease: a 3 year longitudinal study

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Dementia is one of the most debilitating symptoms of Parkinson's disease. A recent longitudinal study suggests that up to 80% of patients with Parkinson's disease will eventually develop dementia. Despite its clinical importance, the development of dementia is still difficult to predict at early stages. We previously identified olfactory dysfunction as one of the most important indicators of cortical hypometabolism in Parkinson's disease. In this study, we investigated the possible associations between olfactory dysfunction and the risk of developing dementia within a 3-year observation period. Forty-four patients with Parkinson's disease without dementia underwent the odour stick identification test for Japanese, memory and visuoperceptual assessments, ^{18}F-fluorodeoxyglucose positron emission tomography scans and magnetic resonance imaging scans at baseline and 3 years later. A subgroup of patients with Parkinson's disease who exhibited severe hyposmia at baseline showed more pronounced cognitive decline at the follow-up survey. By the end of the study, 10 of 44 patients with Parkinson's disease had developed dementia, all of whom had severe hyposmia at baseline. The multivariate logistic analysis identified severe hyposmia and visuoperceptual impairment as independent risk factors for subsequent dementia within 3 years. The patients with severe hyposmia had an 18.7-fold increase in their risk of dementia for each 1 SD (2.8) decrease in the score of odour stick identification test for Japanese. We also found an association between severe hyposmia and a characteristic distribution of cerebral metabolic decline, which was identical to that of dementia associated with Parkinson's disease. Furthermore, volumetric magnetic resonance imaging analyses demonstrated close relationships between olfactory dysfunction and the atrophy of focal brain structures, including the amygdala and other limbic structures. Together, our findings suggest that brain regions related to olfactory function are closely associated with cognitive decline and that severe hyposmia is a prominent clinical feature that predicts the subsequent development of Parkinson's disease dementia.

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Abbreviations: OSIT-J = odour stick identification test for Japanese; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Advances in treating motor symptoms have dramatically improved the clinical course of Parkinson's disease (Curtis *et al*., 1984; Uitti *et al*., 1993). With the increased disease duration, cognitive impairments have become a major issue in the management of Parkinson's disease cases and have attracted increasing attention (Hely *et al*., 2008). Despite its clinical importance, the diagnosis of dementia associated with Parkinson's disease at early stages remains controversial (Docherty and Burn, 2010). Many demographic and clinical features have been assessed as potential risk factors for developing dementia in Parkinson's disease. More severe parkinsonism, advanced age and mild cognitive impairment (Caviness *et al*., 2007) at baseline have been identified as risk factors in some longitudinal studies (Aarsland and Kurz, 2010). However, the predictive value of these features is relatively low and inconsistent. Therefore, a better strategy for detecting Parkinson's disease dementia in the early stages is eagerly awaited.

In our previous study, we identified odour-identification performance as being closely associated with cortical hypometabolism in Parkinson's disease without dementia (Baba *et al*., 2011). This result suggests that severe olfactory dysfunction may be correlated with severe metabolic abnormalities in the brain and may predict future dementia in Parkinson's disease. However, no studies have assessed the predictive importance of olfactory testing for identifying dementia in Parkinson's disease. Thus, we designed the present study to investigate the possible associations between baseline olfactory function and the development of dementia within a 3-year observation period and to elucidate the accompanying cerebral metabolic and structural abnormalities.

Materials and methods

Patients

We analysed the data from a 3-year longitudinal study of patients with Parkinson's disease at Tohoku University. The design of this study has been previously described (Abe *et al*., 2009; Hosokai *et al*., 2009; Nishio *et al*., 2010; Baba *et al*., 2011; Ishioka *et al*., 2011). In brief, 82 consecutive patients with Parkinson's disease without dementia were enrolled and underwent a 3-year follow-up investigation. The survey included olfactory, neurological, neuropsychological and neuroradiological examinations. In principle, only those patients who completed both baseline and follow-up surveys were included in this study, but the patients who lacked follow-up data because of a conversion to severe dementia were conditionally included in the analyses of the clinical data. Furthermore, those who showed significant sinunasal pathological changes in MRI were excluded from the analysis. Of the 82 potentially eligible cases, 38 were excluded from the analysis. The details of the excluded patients were as follows: seven patients went to other hospitals; two patients moved out of the area; two patients were unable to visit the hospital because of acute myocardial infarction or cerebral infarction; seven patients did not return for follow-up visits for unknown reasons; one patient died of pharyngeal cancer; three patients were diagnosed as having a disorder other than Parkinson's disease during the follow-up period; 13 patients were excluded because of incomplete medical records or imaging data; and the imaging data for one patient were lost through computer error.

We assessed olfactory performance using the odour stick identification test for Japanese (OSIT-J, Daiichi Yakuhin Co.) (Saito *et al*., 2006). The procedure for the OSIT-J has been previously described (Baba *et al*., 2011). In the present study, patients with OSIT-J scores $\leqslant 4$ (min = 0) were defined as having Parkinson's disease with severe hyposmia, and the patients with OSIT-J scores $\geqslant 5$ (max = 12) were defined as having Parkinson's disease without severe hyposmia. The validity of this cut-off score was retrospectively confirmed by a receiver-operating characteristic analysis (Supplementary Fig. 1). We evaluated motor impairment using the Hoehn and Yahr stage (Hoehn and Yahr, 1967) and Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987). Then, we classified the enrolled patients into postural instability–gait difficulty, tremor-dominant and indeterminate subtypes according to the method proposed by Jankovic *et al*. (1990). We examined general cognitive dysfunction using the Mini-Mental State Examination (Folstein *et al*., 1975) and the Clinical Dementia Rating scale (Hughes *et al*., 1982). We assessed memory and visuoperceptual abilities at the same time because disabilities in these cognitive domains lead to the diagnosis of dementia associated with Parkinson's disease (Emre, 2003). Short-term memory was assessed using the word recall task of the Alzheimer's Disease Assessment Scale (Mohs *et al*., 1983). We defined the word recall score as the total number of properly recollected answers (max = 30). Visuoperceptual performance was assessed using the overlapping-figure identification test, as described previously (Ishioka *et al*., 2011). We defined the correct response score as the number of objects correctly identified from 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). We used Mini-Mental State Examination and Clinical Dementia Rating as screening tools to detect dementia during the follow-up. Practically, when a patient showed a score <25 on the Mini-Mental State Examination or a score $\geqslant 1$ on the Clinical Dementia Rating scale, expert neuropsychologists evaluated several cognitive functions and diagnosed Parkinson's disease with dementia based on the criteria for probable Parkinson's disease with dementia (Emre *et al*., 2007).

After a full explanation of the entire 3-year longitudinal study, written informed consent was obtained from all of the recruited patients in accordance with the Declaration of Helsinki. The study was approved by the Ethical Committee of the Tohoku University Graduate School of Medicine.

Statistical analysis

For the cross-sectional analyses at baseline and follow-up, the continuous demographic characteristics of the patients with and without severe hyposmia were compared using the two-sample *t*-test. In the longitudinal analyses, the within-group differences of the patients with and without severe hyposmia were assessed using paired *t*-tests. We

also compared the clinical characteristics of Parkinson's disease with dementia converters and non-converters.

We then performed multivariate backward step-wise logistic regression analysis using a standard statistical package (JMP Pro 9.0.0, SAS Institute) to generate odds ratios to estimate the relative risk of developing dementia. The variables included in this analysis were; OSIT-J score, age, UPDRS 3, Mini-Mental State Examination score, Alzheimer's Disease Assessment Scale word recall score and correct response and illusory response scores of the overlapping figure identification test. All of the variables were transformed to *z*-scores, and the relative risks of dementia associated with 1 SD changes in the variables were calculated.

Neuroimaging data acquisition

Each patient underwent MRI and ^{18}F-fluorodeoxyglucose-PET scans at baseline and after 3 years of follow-up. The same scanners and the same acquisition parameters were used for all patients. The MRI data were obtained on a 1.5-T GE Sigma Horizon system (General Electric Medical Systems) using a SPGR (spin gradient recalled) sequence (repetition time = 20 ms; echo time = 2.1 ms; field of view = 250 mm; matrix = 256 × 256) with a slice thickness of 2 mm. The PET data were collected using a Siemens biograph Duo PET/CT scanner (Siemens Medical System Inc.) with a resolution of 3.38 mm full width at half maximum. A 185–218 MBq injection of ^{18}F-fluorodeoxyglucose was administered intravenously under resting conditions (i.e. with eyes closed and wearing an eye mask). We used a 10-min static acquisition protocol beginning 60 min after the injection of the ^{18}F-fluorodeoxyglucose. Image reconstruction was performed using an ordered subset expectation maximization (with 16 subsets) and a six-iteration reconstruction algorithm (with a Gaussian filter and filter full width at half maximum = 2.0 mm). The attenuation correction was performed using the built-in CT scan.

Neuroimaging data processing and analysis

Each scan was preprocessed before statistical analysis using SPM8 software (Wellcome Department of Cognitive Neurology) running under MATLAB R2008a (MathWorks Inc.). The cross-sectional and longitudinal analyses were performed for both the fluorodeoxyglucose-PET and the MRI data.

First, we performed cross-sectional analyses of the fluorodeoxyglucose-PET data at baseline and follow-up. The PET images were normalized to the ^{18}F-fluorodeoxyglucose template (modified from a standard template in SPM2b; http://www.fil.ion.ucl.ac.uk/spm/software/spm2b/) and smoothed with a 10-mm Gaussian kernel. Then, the regional metabolic abnormalities in the patients with Parkinson's disease with and without severe hyposmia at baseline and follow-up were estimated by comparison with the 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. Next, we assessed the longitudinal cerebral glucose metabolism changes in patients with Parkinson's disease with and without severe hyposmia. Within-group differences were analysed using the paired *t*-test option implemented in SPM8. The statistical threshold was $P < 0.05$ (family-wise error corrected), with an extent threshold of 50 voxels.

Second, voxel-based morphometry (Ashburner and Friston, 2005) was applied to detect any grey matter atrophy associated with reduced olfactory performance in the patients with Parkinson's disease. The MRI images were registered and segmented using the DARTEL (diffeomorphic anatomical registration through exponentiated lie algebra) algorithm (Ashburner, 2007), normalized to the Montreal Neurological Institute (MNI) space, and smoothed with an 8-mm full width at half maximum filter. The grey matter atrophy in the patients with Parkinson's disease with and without severe hyposmia was estimated at baseline and follow-up by comparison with the 14 age-matched control subjects (seven females, seven males; mean age 63.1 ± 4.4 years; mean Mini-Mental State Examination score 29.0 ± 1.4). We then analysed the longitudinal cortical atrophy in the patients with Parkinson's disease with and without severe hyposmia using the paired *t*-test option implemented in SPM8. The statistical threshold selected for these analyses was $P < 0.001$ (uncorrected), with an extent threshold of 50 voxels.

Results

Clinical data

The demographic and clinical characteristics at baseline and follow-up are presented in Table 1. Twenty patients were classified as Parkinson's disease without severe hyposmia, and 24 patients were classified as Parkinson's disease with severe hyposmia. Demographics of motor subtypes in the Parkinson's disease with and without severe hyposmia groups are shown in Tables 1 and 2 and Supplementary Fig. 2. At baseline, there were no significant between-group differences in age at disease onset, duration of illness, Hoehn and Yahr scale, UPDRS 3, proportion of motor subtypes or levodopa equivalent dose. However, the patients with Parkinson's disease with severe hyposmia showed a male predominance and had relatively lower performance on the Mini-Mental State Examination, Alzheimer's Disease Assessment Scale word recall and overlapping figure identification test at baseline. At the 3-year follow-up, the patients with Parkinson's disease with severe hyposmia had significantly greater motor, general cognitive and visuoperceptual impairment than the patients with Parkinson's disease without severe hyposmia (Table 1). Whereas, at follow-up, there were no significant differences in the proportions of motor subtypes between the Parkinson's disease with and without severe hyposmia groups. In the longitudinal analysis, the patients with Parkinson's disease with severe hyposmia had significant deterioration in the Hoehn and Yahr scale, levodopa equivalent dose, Mini-Mental State Examination score and illusory response score, whereas the patients with Parkinson's disease without severe hyposmia had only slightly worse Hoehn and Yahr scale scores and increased levodopa needs. As for olfactory function, serial OSIT-J scores for 15 patients in the Parkinson's disease without severe hyposmia group and seven patients in the Parkinson's disease with severe hyposmia group were available (Supplementary Fig. 3). There was a mild longitudinal worsening in olfactory function in the Parkinson's disease without severe hyposmia group, and 7 of 15 patients had developed severe olfactory deficits during the 3-year study period. Meanwhile, there were no significant longitudinal changes in overall olfactory performance in the Parkinson's disease with severe hyposmia group. Thus, longitudinal changes in the OSIT-J score did not reach statistical significance in the entire cohort, although some cases

Table 1 Demographic and clinical data of patients with Parkinson's disease at baseline (t_0) and at follow-up (t_3)

	Parkinson's disease without severe hyposmia		Parkinson's disease with severe hyposmia		All PD patients	
	t_0	t_3	t_0	t_3[a]	t_0	t_3[a]
Number	20		24		44	
Age at t_0 (years)	65.5 ± 6.1		65.0 ± 6.2		65.3 ± 6.1	
Sex (female/male), *n*	14/6		7/17		21/23	
OSIT-J score (max = 12)	7.1 ± 1.3		2.3 ± 1.4		4.5 ± 2.8	
Duration (years)	5.8 ± 6.0		4.4 ± 3.3		5.0 ± 4.7	
Hoehn and Yahr scale	2.4 ± 0.7	2.7 ± 0.4**	2.5 ± 0.5	3.2 ± 0.7***	2.4 ± 0.6b	2.9 ± 0.6***
UPDRS 3	18.2 ± 7.9	18.9 ± 7.1	18.9 ± 7.4	24.3 ± 11.6	18.6 ± 7.5	21.6 ± 10.0
Levodopa equivalent dose (mg)	360.7 ± 280.7	540.0 ± 282.9***	335.7 ± 248.1	554.9 ± 276.4***	347.1 ± 260.6	547.6 ± 276.2***
Motor subtype (PIGD, TD, ID), *n*	14/4/2	18/1/1	19/4/1	22/0/2	33/8/3	40/1/3
CDR (0/0.5/1/2/3), *n*	18/2/0/0/0	15/5/0/0/0	17/7/0/0/0	9/8/3/1/3	35/9/0/0/0	24/13/3/1/3
MMSE	29.0 ± 1.2	28.3 ± 1.8	27.4 ± 1.9	22.5 ± 9.5*	28.1 ± 1.8[b,c]	25.1 ± 7.6*
Word recall score (max = 30)	20.0 ± 3.3	20.5 ± 4.1	17.0 ± 3.4	15.4 ± 7.3	18.4 ± 3.6[b,c]	17.7 ± 6.5
Overlapping figure identification test						
Correct response score (max = 40)	32.6 ± 3.5	32.8 ± 4.4	29.8 ± 5.2	26.3 ± 7.2*	31.0 ± 4.6[b,c]	29.4 ± 6.8
Illusory response score (max = 40)	2.3 ± 2.0	2.2 ± 1.7	4.0 ± 3.0	3.8 ± 2.8	3.2 ± 2.7[b,c]	3.0 ± 2.4

Data are given as mean ± SD.
a In this group, three patients developed severe dementia before t_3. Therefore, motor and visuoperceptual functions of these patients were not assessed. Mini-Mental State Examination score and word recall score of these patients were counted as zero.
b Significant difference between Parkinson's disease with severe hyposmia and Parkinson's disease without sever hyposmia groups at baseline t_0 $P < 0.05$.
c Significant difference between Parkinson's disease with severe hyposmia and Parkinson's disease without severe hyposmia groups at follow-up t_3 $P < 0.05$.
Significant difference between t_0 and t_3: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
CDR = clinical dementia rating; ID = indeterminate; MMSE = Mini-Mental State Examination; PIGD = postural instability–gait difficulty; TD = tremor-dominant.

Table 2 Baseline background characteristics of non-converters and converters to dementia associated with Parkinson's disease

	Non-converters		Converters	
	t_0	t_3	t_0	t_3[a]
Number	34		10	
Age at t_0 (years)	64.7 ± 6.3		67.0 ± 5.1	
Sex (female/male), *n*	20/14		2/8	
OSIT-J score (max = 12)	5.2 ± 2.6		1.9 ± 1.5	
Duration (years)	5.0 ± 5.0		5.1 ± 4.1	
Hoehn and Yahr scale	2.4 ± 0.6	2.8 ± 0.4*	2.7 ± 0.4	3.9 ± 0.7*,b
UPDRS 3	18.5 ± 7.9	18.9 ± 7.0	18.9 ± 6.2	35.0 ± 11.8*,b
Levodopa equivalent dose (mg)	318.1 ± 257.8	549.2 ± 279.4*	445.4 ± 258.3	539.7 ± 281.2
Motor subtype (PIGD, TD, ID), *n*	25/6/3	30/1/3	8/2/0	10/0/0
CDR (0/0.5/1/2/3), *n*	30/4/0/0/0	24/10/0/0/0	5/5/0/0/0	0/3/3/1/3
MMSE	28.4 ± 1.6	28.0 ± 1.7	26.9 ± 2.0	15.3 ± 11.4*,b,c
Word recall score (max = 30)	19.1 ± 3.2	20.1 ± 3.6*	15.9 ± 4.2	9.6 ± 7.7b,c
Overlapping figure identification test				
Correct response score (max = 40)	31.4 ± 4.7	31.2 ± 5.4	30.0 ± 4.6	20.7 ± 6.2*,b
Illusory response score (max = 40)	2.8 ± 2.4	2.7 ± 2.3	4.7 ± 3.4	4.4 ± 2.7

a In this group, three patients developed severe dementia before t_3. Therefore, motor and visuoperceptual functions of these patients were not assessed. Mini-Mental State Examination score and word recall score of these patients were counted as zero.
b Significant difference between Parkinson's disease with severe hyposmia and Parkinson's disease without severe hyposmia groups at follow-up t_3 $P < 0.05$.
c Significant difference between Parkinson's disease with severe hyposmia and Parkinson's disease without sever hyposmia groups at baseline t_0 $P < 0.05$.
Significant difference between t_0 and t_3: *$P < 0.05$.
CDR = Clinical dementia rating; ID = indeterminate; MMSE = Mini-Mental State Examination; PIGD = postural instability–gait difficulty; TD = tremor-dominant.

without initial severe hyposmia developed severe olfactory deficits during the follow-up.

Over the 3-year follow-up period, 10 of the 44 patients with Parkinson's disease (22.7%) converted to Parkinson's disease-associated dementia. All converters showed severe olfactory dysfunction (OSIT-J score $\leqslant 4$) at baseline. The incidence of dementia within 3 years was 0% for the patients with Parkinson's disease without severe hyposmia versus 41.7% for the patients

Table 3 Relative risk of dementia according to the severity of hyposmia and illusory response

Variable	Standardized relative risk (95 % CI[a])	*P*-value[b]
OSIT-J score	18.7 (3.1–425.2)	0.02
Illusory response score	3.7 (1.3–18.0)	0.04

Multiple logistic regression was used to generate odds ratio as an estimate of relative risk. Relative risks have been adjusted for age.
a Standardized relative risk was defined as the relative risk for each worsening of 1 SD in the variable.
b Wald Chi-square test results.

with Parkinson's disease with severe hyposmia. The converters showed significant decreases in the Hoehn and Yahr scale, UPDRS 3, Mini-Mental State Examination and correct response scores over the 3-year interval, whereas the non-converters only showed mild declines in the Hoehn and Yahr scale and word recall scores. Furthermore, the converters showed more severe motor and cognitive impairments than the non-converters in the follow-up evaluation (Table 2). There were no significant differences in the proportions of motor subtypes between the Parkinson's disease with and without severe hyposmia groups both at baseline and at the follow-up period.

The multivariate step-wise logistic regression analysis identified two significant predictive markers for the risk of developing dementia within 3 years: olfactory dysfunction and the illusory response score (Table 3). As shown in Table 3, a 1-SD (2.8) change in the OSIT-J score resulted in an 18.7-fold increase [95% confidence interval (CI) = 3.1–425.2, $P = 0.02$], and a 1-SD (2.7) change in the illusory response score resulted in a 3.7-fold increase (95% CI = 1.3–18.0, $P = 0.04$) in the risk of developing Parkinson's disease with dementia.

Neuroimaging data

The metabolic reduction patterns from baseline to follow-up in the patients with Parkinson's disease with and without severe hyposmia are illustrated in Fig. 1. At baseline, the patients with Parkinson's disease without severe hyposmia showed reduced metabolism in the right dorsolateral prefrontal cortex and medial occipital cortex (Fig. 1A). In addition to these areas, the patients with Parkinson's disease with severe hyposmia showed reduced metabolism in the bilateral medial prefrontal cortex and parieto-occipito-temporal cortex (Fig. 1D). At the 3-year follow-up, both groups of patients with Parkinson's disease showed broader cortical hypometabolism in the bilateral dorsolateral prefrontal cortex, medial prefrontal cortex, cingulate cortex and midbrain (Fig. 1B and E). In addition, the patients with Parkinson's disease with severe hyposmia showed a marked metabolic reduction in the more posterior regions, such as the posterior cingulate, precuneus, medial occipital and parieto-occipito-temporal cortex (Fig. 1E). The longitudinal changes in metabolic reductions between the baseline and follow-up evaluations in the patients with Parkinson's disease with and without severe hyposmia are presented in Fig. 1C and F. In the patients with Parkinson's disease without severe hyposmia, the longitudinal differences were significant in the midbrain, medial prefrontal and cingulated cortex (Fig. 1C). In addition, the patients with Parkinson's disease with severe hyposmia showed significant changes in the right dorsolateral prefrontal cortex, posterior cingulate and precuneus (Fig. 1E).

The cortical atrophy profiles from baseline to follow-up in the patients with Parkinson's disease with and without severe hyposmia are illustrated in Fig. 2. At baseline, the patients with Parkinson's disease without severe hyposmia showed mild atrophy, mainly in the right lateral prefrontal area (Fig. 2A). In contrast, the patients with Parkinson's disease with severe hyposmia showed marked atrophy in several regions, including the bilateral amygdala and bilateral lateral prefrontal, medial prefrontal, temporal, medial occipital and cingulate cortices (Fig. 2D). At the 3-year follow-up, the atrophy distributions were mildly magnified in the patients with Parkinson's disease without severe hyposmia (Fig. 2B). In the longitudinal analysis, the patients with Parkinson's disease without severe hyposmia had a statistically significant volume reduction in the right amygdala and bilateral temporal cortex (Fig. 2C), whereas the patients with Parkinson's disease with severe hyposmia had only a few longitudinal volume changes (Fig. 2F).

Discussion

In this study, the prevalence of severe hyposmia was ~55% at baseline, which was consistent with a previous report using the same olfactory test (Iijima *et al*., 2008). In contrast to the patients with Parkinson's disease without severe hyposmia, the patients with Parkinson's disease with severe hyposmia exhibited mild impairments in general cognitive, memory and visuoperceptual functioning at baseline (Table 1), as has been previously reported by our group (Baba *et al*., 2011; Ishioka *et al*., 2011) and others (Bohnen *et al*., 2010; Morley *et al*., 2011). After the 3-year follow-up period, the cognitive impairment in the patients with Parkinson's disease with severe hyposmia was more severe. Specifically, their scores on the Mini-Mental State Examination and the overlapping figure identification test became significantly worse (Table 1). Short-term memory, as measured by the Alzheimer's Disease Assessment Scale word recall task, also tended to deteriorate longitudinally, but this change did not reach statistical significance. Consistent with these results, a recent retrospective study has reported an association between baseline olfactory dysfunction and future visual hallucinations and cognitive decline (Stephenson *et al*., 2010). It is therefore plausible that the patients with Parkinson's disease with severe hyposmia shared major clinical features with patients with Parkinson's disease with mild cognitive impairment (Caviness *et al*., 2007) and tended to show a more prominent cognitive decline, leading to Parkinson's disease with dementia.

In this cohort, 10 of the 44 patients converted to Parkinson's disease with dementia during the 3 years of observation (Table 2). It is notable that all 10 Parkinson's disease with dementia converters showed severe hyposmia at baseline. Conversely, none of the patients with Parkinson's disease without severe hyposmia converted to Parkinson's disease with dementia. Another interesting

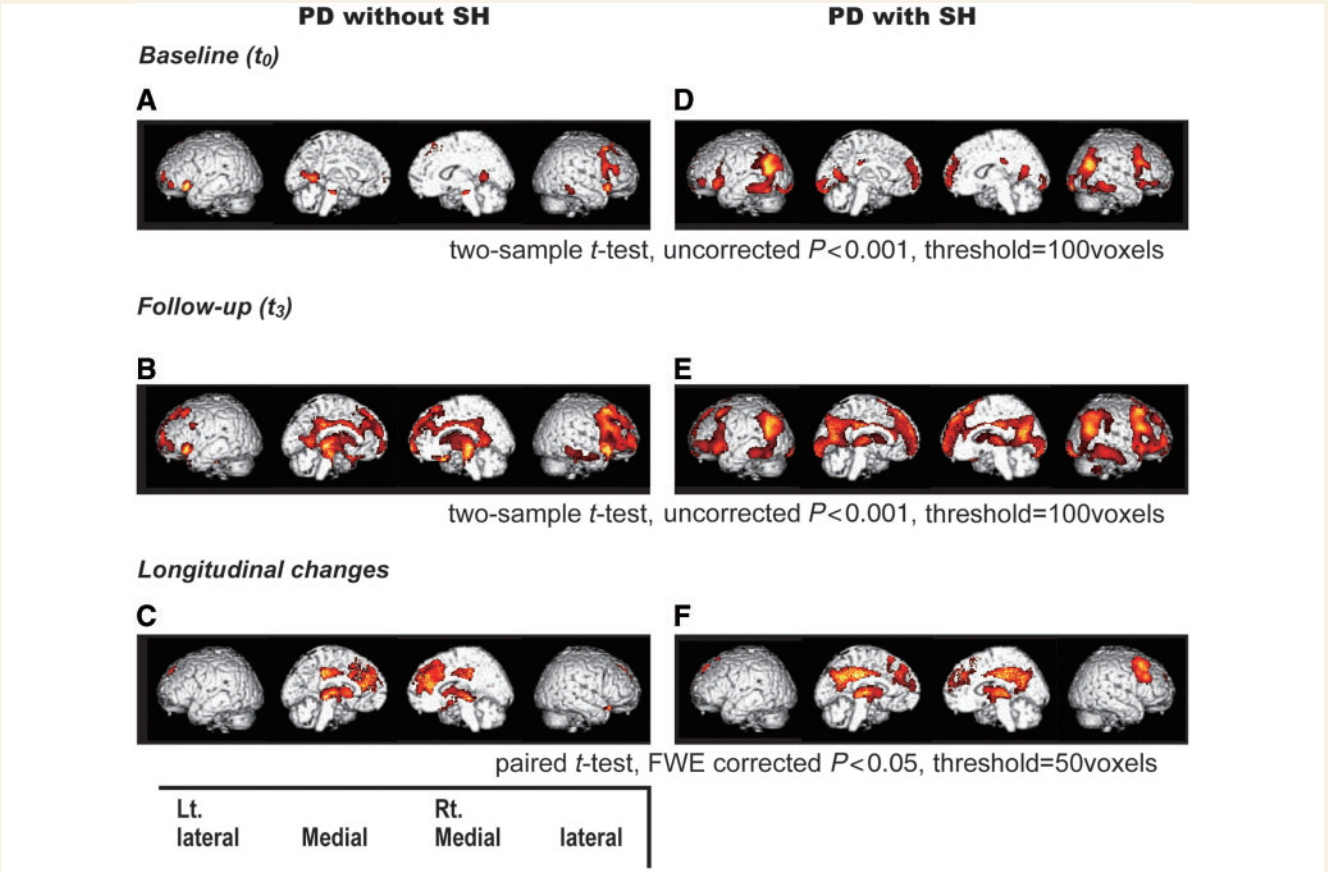

Figure 1 The distributions of cortical hypometabolism in the Parkinson's disease subgroups compared with the normal controls. (**A**) At baseline (t_0), the patients with Parkinson's disease without severe hyposmia showed a mild metabolic reduction in the frontal regions and medial occipital cortex. (**B**) At follow-up (t_3), the patients with Parkinson's disease without severe hyposmia showed a metabolic reduction in the midbrain and broader frontal regions as well as the medial prefrontal, cingulate and medial occipital cortices. (**C**) In the patients with Parkinson's disease without severe hyposmia, longitudinal metabolic changes (t_0–t_3) were identified in the medial prefrontal and anterior cingulate cortices. (**D**) At t_0, the patients with Parkinson's disease with severe hyposmia showed a metabolic reduction in the bilateral dorsolateral prefrontal, medial prefrontal and medial occipital cortices as well as the bilateral parieto-occipito-temporal area. (**E**) At t_3, the metabolic reduction became more prominent, and an additional metabolic reduction appeared in the posterior cingulate and precuneus. (**F**) In the patients with Parkinson's disease with severe hyposmia, the longitudinal metabolic changes (t_0–t_3) were distributed in the right frontal, medial prefrontal, anterior cingulate and posterior cingulate cortices as well as the precuneus. PD = Parkinson's disease; SH = severe hyposmia.

point was that non-converters did not progress markedly on the UPDRS motor score, while converters showed a prominent motor progression. This type of slow progression was often observed in tremor-dominant patients. However, the proportions of the tremor-dominant subtype were comparable between the converter and the non-converter groups. Furthermore, the levodopa equivalent dose in the non-converter group was increased significantly at the follow-up point compared to the baseline (Table 2). These results suggested that the apparent slow progression on UPDRS 3 in the non-converter group was not associated with a specific motor subtype and that motor symptoms in the non-converter group worsened longitudinally but were relatively mild and controllable by medication. Taken together, it was plausible that the patients with Parkinson's disease without severe hyposmia showed a relatively benign clinical course regardless of their motor subtypes.

In the multivariate analysis (Table 3), low OSIT-J scores were strongly associated with the risk of subsequent dementia. Indeed, the risk of developing dementia significantly increased (odds ratio = 18.7) for every 1 SD (2.8) change in the OSIT-J score. The illusory response score was also identified as an independent predictor of Parkinson's disease with dementia, but the magnitude of the effect size was less prominent (odds ratio = 3.7). We also calculated the odds ratios for developing dementia for other clinical features, including age, UPDRS 3 score, motor subtype, Mini-Mental State Examination score, Alzheimer's Disease Assessment Scale-word recall task score and correct response score in the overlapping figure identification test. As a result, the Mini-Mental State Examination and Alzheimer's Disease Assessment Scale-word recall task scores showed modest but significant effects, but age, UPDRS 3 score, motor subtype and correct response score had no significant effects (data not shown). In

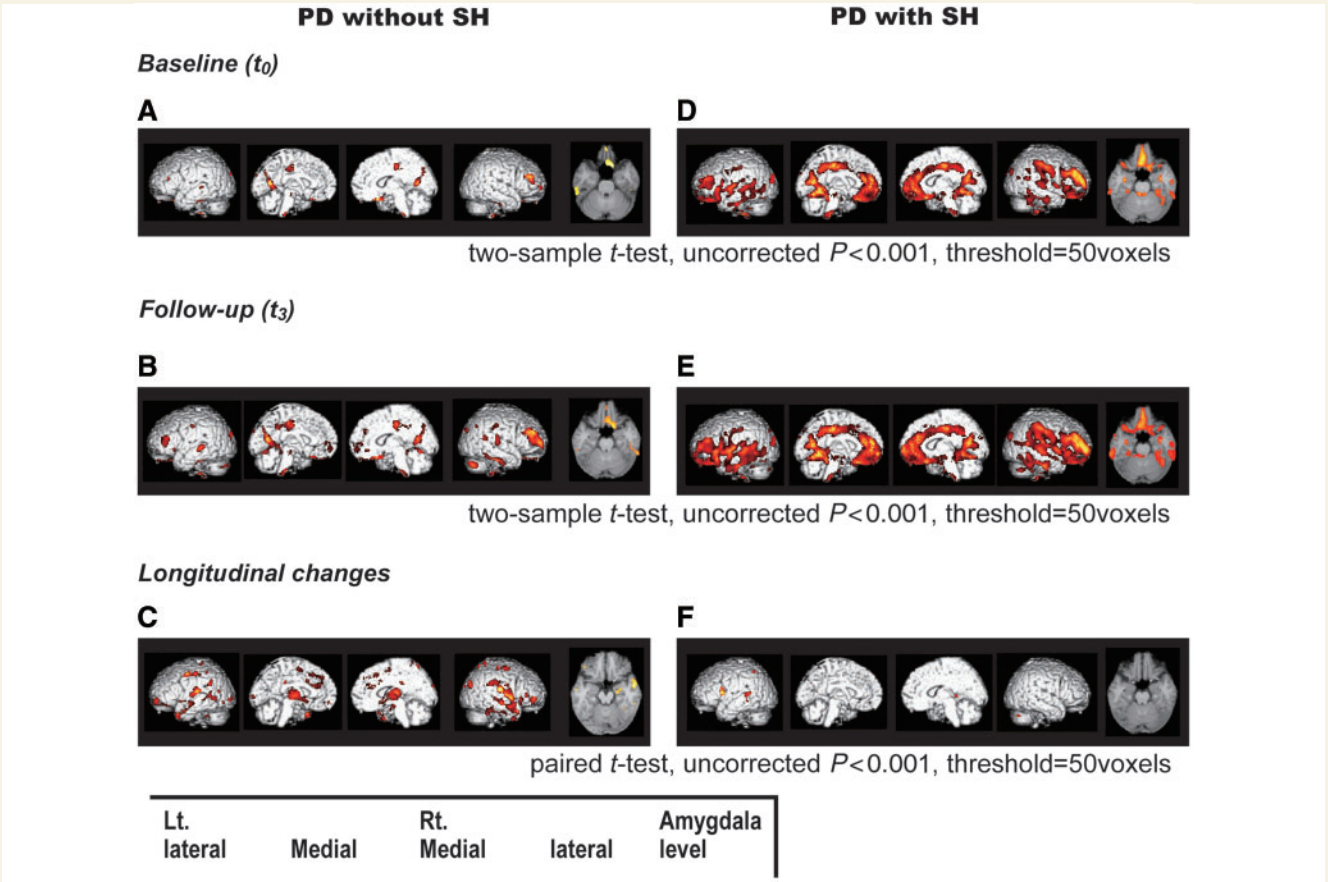

Figure 2 The distributions of cortical atrophy in the Parkinson's disease subgroups compared with the normal control group. (**A**) At baseline (t_0), the patients with Parkinson's disease without severe hyposmia showed no apparent cortical atrophy. (**B**) At follow-up (t_3), the patients with Parkinson's disease without severe hyposmia showed cortical atrophy in the bilateral prefrontal cortex. (**C**) In the patients with Parkinson's disease without severe hyposmia, the longitudinal cortical atrophy (t_0–t_3) was observed mainly in the right medial temporal cortex, including the right amygdala. (**D**) At t_0, the patients with Parkinson's disease with severe hyposmia showed cortical atrophy in the bilateral prefrontal, medial prefrontal, medial temporal, cingulate and medial occipital cortices and precuneus. In the axial section, atrophy in the bilateral amygdala was identified. (**E**) At t_3, the distribution of cortical atrophy was mildly increased in the patients with Parkinson's disease with severe hyposmia. (**F**) However, no significant longitudinal changes were observed during 3-year follow-up in the patients with Parkinson's disease with severe hyposmia. PD = Parkinson's disease; SH = severe hyposmia.

contrast to the present results, several previous reports identified advanced age, severe extrapyramidal involvement and postural instability–gait difficulty motor subtype as consistent risk factors for developing Parkinson's disease dementia (Burn *et al*., 2006; Aarsland and Kurz, 2010). The reason for this discrepancy may be the smaller sample size in the present study. Considering these possibilities, we still suggest that severe hyposmia is one of the more sensitive predictors of future Parkinson's disease with dementia among the other previously reported risk factors.

The PET data also support the hypothesis that severe hyposmia is a prodromal Parkinson's disease with dementia symptom. The cross-sectional analyses of the fluorodeoxyglucose-PET data demonstrated marked differences in cortical metabolism between the patients with Parkinson's disease with and without severe hyposmia. At baseline, the patients with Parkinson's disease with severe hyposmia had lower metabolism than the normal controls in the bilateral dorsolateral prefrontal cortex, medial occipital cortex and parieto-occipito-temporal area. In contrast, the glucose metabolism in the parieto-occipito-temporal area was spared in the patients with Parkinson's disease without severe hyposmia, as has been previously described (Baba *et al*., 2011). Over a 3-year observation period, additional differences in brain metabolism between the two groups became evident. At follow-up, the patients with Parkinson's disease with severe hyposmia exhibited a significant metabolic decrement, mainly in the posterior regions (specifically, the posterior cingulate, precuneus, medial occipital and parieto-occipito-temporal areas; Fig. 1E). This finding is in contrast to that in patients with Parkinson's disease without severe hyposmia, who showed metabolic decrements mainly in the frontal areas (Fig. 1B). Furthermore, the distribution of metabolic reduction in the patients with Parkinson's disease with severe hyposmia (Fig. 1E) appeared to be almost identical to that reported for patients with Parkinson's disease with dementia (Vander Borght *et al*., 1997; Firbank *et al*., 2003;

Yong *et al*., 2007). In the longitudinal analysis with a stringent statistical threshold (family-wise error corrected, $P < 0.05$), the patients with Parkinson's disease with severe hyposmia showed significant metabolic deterioration in the medial frontal (medial prefrontal cortex and anterior cingulate cortex) and postero-medial regions (posterior cingulate cortex and precuneus) (Fig. 1F). In contrast, the patients with Parkinson's disease without severe hyposmia showed longitudinal metabolic decrements only in the medial frontal areas (Fig. 1C). Of course, there was a possibility that we underestimated occipital hypometabolism in both groups, because we assessed cortical metabolism at rest in an eyes closed condition. However, it still appeared that metabolic decline was more prominent in the patients with Parkinson's disease with severe hyposmia than in those without severe hyposmia.

A comparison of the topographical distribution of the PET and MRI findings provided further complementary information. At baseline, the patients with Parkinson's disease without severe hyposmia did not show remarkable MRI findings (Fig. 2A), which was consistent with the PET results (Fig. 1A). In contrast, the patients with Parkinson's disease with severe hyposmia showed broader cortical atrophy in the frontotemporal and posteromedial regions (Fig. 2B). The distribution of PET and MRI findings overlapped in some areas, but abnormalities in the medial temporal area, especially the bilateral amygdala, were only observed in the voxel-based morphometry analysis (Fig. 2D). The amygdala has been shown to be an important structure in higher order olfactory perception (Savic *et al*., 2000) and to be a common site of Lewy pathology (Braak *et al*., 1994; Harding *et al*., 2002; Hubbard *et al*., 2007; Silveira-Moriyama *et al*., 2009). A recent volumetric analysis demonstrated an association between amygdala atrophy and olfactory impairment in Parkinson's disease (Wattendorf *et al*., 2009). Therefore, it has been suggested that severe olfactory dysfunction in Parkinson's disease develops as a consequence of amygdala pathology and that MRI is suitable for detecting this damage.

It is noteworthy that there were some differences between the cortical metabolic and volume changes at the 3-year follow-up. Patients with Parkinson's disease, both with and without severe hyposmia, showed metabolic changes (Fig. 1B, C, E and F) that were broader than the structural changes (Fig. 2B, C, E and F). These findings can be explained by the hypothesis that metabolic changes usually precede structural changes (Blass *et al*., 2000). It was intriguing that the patients with Parkinson's disease with severe hyposmia showed only a few longitudinal changes (Fig. 2F). In the patients with Parkinson's disease with severe hyposmia, marked cortical atrophy was already observed at baseline (Fig. 2D) and was also seen at follow-up (Fig. 2E). These data suggest that the medial temporal atrophy may almost be complete when patients with Parkinson's disease show severe hyposmia, even though the motor symptoms are still modest. Taken together, these findings suggest that severe hyposmia is associated with early structural brain changes that are responsible for the subsequent development of Parkinson's disease with dementia.

A recent longitudinal study demonstrated that up to 80% of patients with Parkinson's disease will develop dementia over a 20-year period (Hely *et al*., 2008). This finding implies that most patients with Parkinson's disease will eventually develop dementia. However, the earliest pathological changes leading to the development of dementia in Parkinson's disease are still elusive. Halliday *et al*. (2008) demonstrated that Parkinson's disease with dementia is associated with early limbic and neocortical pathology, whereas Parkinson's disease without dementia does not have limbic involvement until later in the disease course. Furthermore, the association between limbic and neocortical Lewy pathology and dementia in Parkinson's disease has been reported in several studies (Kovari *et al*., 2003; Kalaitzakis *et al*., 2009; Molano *et al*., 2010). According to these pathological investigations, the early changes in the limbic and neocortical areas seem to be associated with the subsequent development of dementia in Parkinson's disease. In our study, the patients with Parkinson's disease without severe hyposmia showed longitudinal atrophy in the right amygdala (Fig. 2C). Thus, it is plausible that some of the patients with Parkinson's disease without severe hyposmia may have experienced *de novo* limbic involvement during the 3-year follow-up period. Indeed, we observed that about a half of the patients with Parkinson's disease without initial severe hyposmia had developed severe hyposmia during the follow-up period (Supplementary Fig. 3). A previous study demonstrated that the severity of olfactory deficits in Parkinson's disease was not generally associated with the disease duration (Doty *et al*., 1988). This meant that the olfactory dysfunction in Parkinson's disease was rather stable once this occurred. However, our results raised the possibility that olfactory function deteriorated longitudinally in some patients with Parkinson's disease, probably due to *de novo* limbic involvement. Such cases may develop severe hyposmia and eventually convert to Parkinson's disease with dementia. However, further study is needed to confirm this hypothesis.

In summary, we found that severe olfactory dysfunction is associated with cognitive decline, broad metabolic abnormalities and limbic and neocortical atrophy in Parkinson's disease. Furthermore, severe hyposmia was identified as the most important indicator among the cardinal motor and non-motor symptoms for the risk of developing dementia in Parkinson's disease within 3 years. Our results provide a convenient tool for detecting high-risk patients with Parkinson's disease with dementia in the early stages to allow an early therapeutic intervention.

Supplementary material

Supplementary material is available at *Brain* online.

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