we hypothesised that an intermediate condition exists between these two conditions: seeing something meaningful in meaningless visual patterns. In the current study, we developed a test that evoked this particular type of misperception, which we termed the noise pareidolia test, and we administered this test to patients with DLB. If patients falsely observe meaningful objects in meaningless visual stimuli, this finding would support the hypothesis that similarities and continuity exist between visual hallucinations and pareidolias along with the existence of an abnormal proactive perceptual process in misperceptions in DLB.

Pareidolias and visual hallucinations are behaviourally similar phenomena, and whether the two conditions share common neural mechanisms remains unknown. One of the well-known mechanisms of visual hallucinations in DLB is cholinergic insufficiency. Previous neuropathological and neuroimaging studies have demonstrated that cholinergic neuronal degeneration is more severe in patients with DLB or Parkinson's disease (PD) who experience visual hallucinations (Ballard et al., 2000; Halliday, 2005; Harding, Broe, & Halliday, 2002; Perry et al., 1990). The effectiveness of cholinesterase inhibitors on visual hallucinations has been established by several intervention studies (McKeith et al., 2000; Mori et al., 2012; Mori, Mori, Iseki, & Kosaka, 2006). In the current study, we performed a longitudinal analysis on pareidolias before and after the treatment with donepezil to investigate whether cholinergic mechanisms are involved in both pareidolias and visual hallucinations.

2. Methods

2.1. Participants

We recruited 34 patients with probable DLB and 34 with probable Alzheimer's disease (AD) from the dementia clinics at the Tohoku University Hospital, the Akita Prefectural Centre of Rehabilitation and Psychiatric Medicine and the Minami Tohoku Hospital. Twenty-eight healthy controls (HC) were recruited from the local community through an advertisement. There was no overlap between the subjects included in the current study and those in our previous study (Uchiyama et al., 2012). The three groups were comparable in age, sex and visual acuity. The severity of cognitive impairment, which was assessed by the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), was matched between the DLB and AD groups (Table 1). All patients underwent an examination by experienced behavioural neurologists, an MRI and routine laboratory investigations. Probable DLB was diagnosed according to the international workshop criteria of DLB (McKeith et al. 2005), and probable AD was diagnosed based on the standard guidelines set by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984). The exclusion criteria were as follows: (i) a history of other neurological or psychiatric diseases or of severe ocular diseases, (ii) a best-corrected acuity of at least 0.4 (LogMAR) and (iii) language deficits hindering task executions. At the time of the examination, nine patients with DLB were treated with donepezil, three were treated with levodopa, two were treated with quetiapine, and one was treated with pramipexole. In the AD group, 24 patients were treated with donepezil, four were treated with trazodone, two were treated with fluvoxamine, and one was treated with risperidone. The demographic and clinical characteristics of the participants are summarised in Table 1.

2.2. Background neuropsychological and behavioural assessments

The Digit Span and Spatial Span subtests from the Japanese version of the Wechsler Memory Scale-Revised test (Sugishita, 2001) were used to assess attention/working memory. Visuoperceptual and visuospatial functions were assessed using the Shape Detection Screening and Position Discrimination subtests of the Visual Object and Space Perception battery (Warrington & James, 1991), the Object Decision subtest (Easy B) of the Birmingham Object Recognition Battery (Riddoch & Humphreys, 1992) and the Face Recognition subtests (face-to-face matching of unknown faces, same/different judgment of unknown faces in different views, gender and age judgments of unknown faces) of the Visual Perception Test for Agnosia (Japan Society for Higher Brain Dysfunction Brain Function Test Commitee, 1997). The Japanese versions of the Frontal Assessment battery (FAB) (Kugo et al., 2007) and the Phonological Verbal Fluency (Fu/A/Ni) test were used to assess executive functions.

The Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) was administered to the caregivers of the patients. The original NPI consists of the following 10 behavioural domains: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity. We made several modifications to the original NPI. First, the 'delusion' domain was separated into two different categories: persecutory delusions and delusional misidentifications. The questions regarding the former included 'believing that others are planning to hurt him/her' and 'believing that others are stealing from him/her', and the questions regarding the latter included 'believing that unwelcome guests are living in the house', 'believing that television or magazine figures are actually present in the home' and 'believing that patient's family is an imposter'. Second, we employed an additional domain for fluctuations in cognition, which included questions such as 'does the patient sometimes show a lack of attention or a slow reaction to others' calls than usual?' and 'does the patient sometimes show a poor understanding of things that he can usually understand?' (Mori et al., 2006). A total of 12 domains of neuropsychiatric symptoms were evaluated based on the clinical status of patients during the past one month. The frequency (range 1–4), severity (1–3) and domain total scores (the product of the frequency score multiplied by the severity score) were recorded for each behaviour.

2.3. The pareidolia tests

2.3.1. The noise pareidolia test

Examples of the stimuli are shown in Fig. 1. Two versions of the noise pareidolia tests were developed: the object version and the face version. The object version was used to investigate the content of pareidolic illusions, and the face version was employed because previous studies demonstrated that human faces are one of the most frequent subjects of pareidolias and visual hallucinations (Ballard et al., 1997; Uchiyama et al., 2012). Both versions consist of 40 black and white images (16×16 cm^2) with a spatial frequency of $1/f^3$ (Fig. 1A). We chose this specific frequency for two reasons: (1) previous studies have demonstrated that the power spectra of natural images conform to $1/f^n$, where f is the spatial frequency and the parameter n varies at approximately 2 (Field, 1987; Ruderman, 1994), and (2) our preliminary experiments showed that an image with a $1/f^3$ frequency best discriminated patients experiencing visual hallucinations from the HC. In the object version, silhouette images of objects (two whole bodies of humans, two animals, two plants and two man-made objects) were embedded in 8 of the 40 stimuli (Fig. 1B). In the face version, black and white images of human faces were embedded in 8 of the 40 stimuli (Fig. 1C).

Immediately before administering the tests, a detailed explanation and three training trials were given to the participants. In the object version, the participants were instructed to state whether an object or nothing was present in each stimulus. When the participants saw an object, they were asked to point at and name the object. In the face version, the participants were instructed to state whether a face was present in each stimulus. When the participants observed a face, they were requested to point at it.

The responses of the participants were classified into three types: (1) illusory responses, in which the subjects falsely found objects or faces at locations where the object or face images did not actually exist, (2) detection misses, in which the subjects did not detect the embedded face or object images, and (3) correct responses, in which the participants correctly responded "nothing exists" to the noise stimuli or correctly detected the embedded images in the stimuli containing the object or face images. We did not use the correct responses for analysis because these selections were nearly equivalent to the total number of stimuli (40) minus the sum of the illusory responses and detection misses. To conduct a phenomenological analysis of pareidolias using the object version, the contents of the illusory responses were classified into five categories: (1) people, (2) animals (e.g., dogs, birds and insects), (3) plants (e.g., vegetables and flowers), (4) man-made objects, and (5) other (e.g., letters and footprints). The order of administration of the two versions was counterbalanced across the participants.

2.3.2. The scenery pareidolia test

To evaluate concurrent validity between the newly developed noise pareidolia test and the one used in our previous study, the pareidolia test with scenery pictures (Uchiyama et al., 2012), was administered to 11 patients with DLB.

2.4. Statistical analysis

A one-way analysis of variance (ANOVA) and a post-hoc Scheffe test were used for the between-group comparisons of the pareidolia test and other neuropsychological tests. The Mann–Whitney U-test was used for the between-group comparisons of the NPI subscores. A receiver operating curve (ROC) analysis was used to evaluate the ability of the tests to differentiate DLB from AD. To investigate the relationships among illusory responses, stimulus detection sensitivity and response bias, the sensitivity (d') and response bias (c) were calculated according to signal detection theory: $d' = Z(\text{hit rate}) - Z(\text{illusory response rate})$; $c = -(Z(\text{hit rate}) + Z(\text{illusory response rate}))$ (Macmillan & Creelman, 1990). The group-wise comparisons were conducted using a one-way ANOVA. The relationship between the performance during the pareidolia tests and other neuropsychological and behavioural variables was assessed using Pearson's correlation coefficient or Spearman's rank correlation coefficient. To evaluate the

Table 1
Demographic and clinical profiles of the participants.

		DLB (n=34)	AD (n=34)	HC (n=28)	p-Values
Age, years		79.4 (0.9)	77.7 (0.8)	78.0 (0.5)	0.280
Sex (female/male) [†]		21/13	25/9	16/12	0.371
Education, years		10.3 (0.4)	10.8 (0.4)	12.2 (0.4)	0.012 [b]
Visual acuity [‡]		0.8 (0.2)	0.8 (0.0)	0.9 (0.0)	0.086
Neuropsychology					
MMSE [30]		20.0 (0.8)	19.4 (0.8)	28.8 (0.2)	< 0.001 [b, c]
Digit span [24]		8.3 (0.5)	9.1 (0.5)	12.0 (0.5)	< 0.001 [b, c]
Spatial span [26]		10.5 (0.6)	11.9 (0.5)	14.7 (0.4)	< 0.001 [b, c]
Shape detection [20]		18.2 (0.4)	18.8 (0.2)	19.5 (0.1)	0.001 [b]
Position discrimination [20]		18.3 (0.4)	19.2 (0.2)	19.6 (0.1)	0.006 [b]
Object decision [32]		24.6 (0.4)	25.3 (0.5)	28.2 (0.4)	< 0.001 [b, c]
Face recognition [30]		25.1 (0.7)	26.6 (0.5)	28.3 (0.4)	0.001 [b]
FAB [18]		10.5 (0.6)	12.3 (0.5)	16.7 (0.2)	< 0.001 [a, b, c]
Verbal fluency (FU/A/Ni)		12.9 (1.4)	17.3 (1.6)	26.6 (1.5)	< 0.001 [b, c]
NPI [§]					
Persecutory delusions		0.0 (1.0)	0.0 (1.0)		0.760
Delusional misidentifications		0.0 (1.0)	0.0 (0.0)		0.025
Hallucinations		1.0 (3.0)	0.0 (0.0)		< 0.001
Agitation/aggression		0.0 (2.5)	0.0 (2.3)		0.263
Dysphoria		0.0 (1.0)	0.0 (0.0)		0.180
Anxiety		0.0 (1.3)	0.0 (0.0)		0.488
Euphoria		0.0 (0.0)	0.0 (0.0)		0.021
Apathy		4.0 (4.0)	0.0 (4.0)		0.011
Disinhibition		0.0 (0.0)	0.0 (0.0)		0.240
Irritability/lability		0.0 (1.3)	0.0 (2.0)		0.887
Aberrant motor behaviour		0.0 (0.8)	0.0 (4.0)		0.034
Fluctuations in cognition		2.0 (3.0)	0.0 (0.0)		< 0.001
Prevalence [/34] [†]	Delusional misidentifications	9	2		0.022
	Visual Hallucinations	21	1		< x0.001
	Fluctuations in cognition	21	5		< 0.001

[†] Chi-squared test.
[‡] Kruskal–Wallis test.
[§] Mann–Whitney U test. The remaining variables were tested using one-way analysis of variance (ANOVA) and post-hoc Scheffé tests.
[a–c] Scheffé test ($p < 0.05$).
[a] DLB < AD.
[b] DLB < HC.
[c] AD < HC.

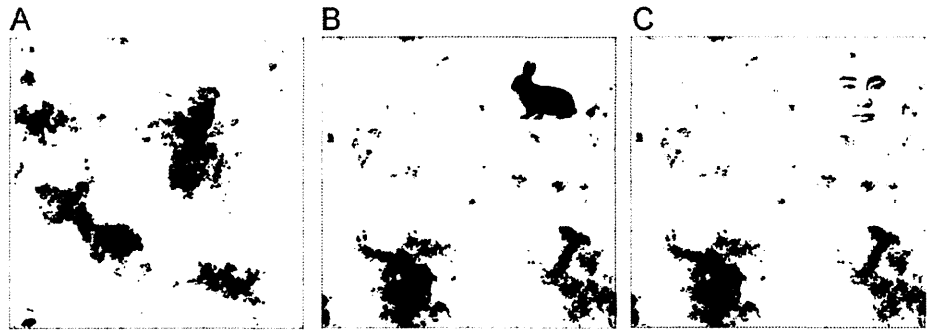

Fig. 1. Examples of the stimuli: (A) noise stimulus without objects or faces; (B) noise stimulus with an embedded object image (the object version); (C) noise stimulus with an embedded face image (the face version).

longitudinal changes before and after administering donepezil, a paired t-test was performed for the pareidolia test and other neuropsychological tests, and a Wilcoxon signed-rank test was utilised for the NPI subscores.

3. Results

3.1. Background neuropsychological and behavioural assessments

The results are summarised in Table 1. The DLB group performed worse than the AD group on the FAB. No significant differences were observed between the DLB and AD groups using the other tests (attention/working memory, visuoperceptual, visuospatial and executive function tests).

The DLB group had significantly higher scores for delusional misidentifications, hallucinations, euphoria, apathy and fluctuations in cognition than the AD group on the NPI assessment. All of the patients with DLB with a positive NPI hallucination score had visual hallucinations, and three of those patients also experienced auditory hallucinations.

3.2. Comparisons between the noise and scenery versions of the pareidolia tests

Significant correlations were observed between the illusory responses obtained using the scenery pareidolia test and the noise pareidolia test (object version, rs=0.74, p=0.009; face version,

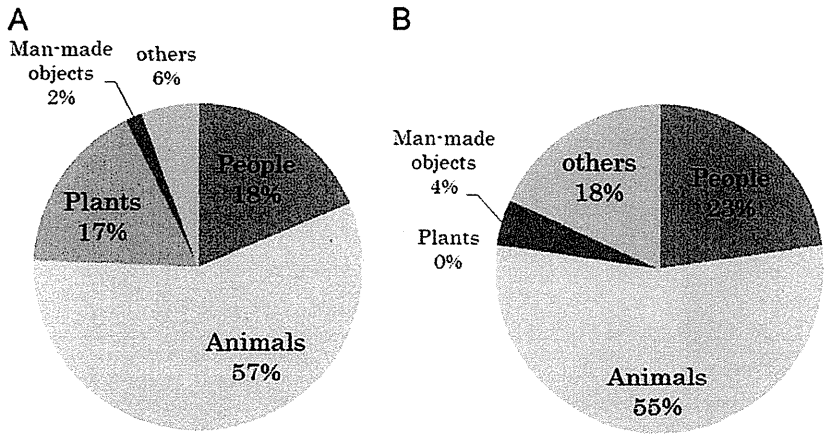

Fig. 2. Contents of the illusory responses in (A) DLB and (B) AD.

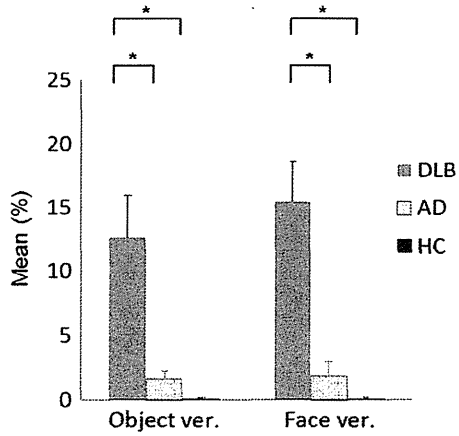

Fig. 3. Percentages of illusory responses in the noise pareidolia tests. Asterisks denote $p < 0.001$.

$rs = 0.87$, $p = 0.001$) and between the illusory responses obtained using the object and face versions ($r = 0.630$, $p < 0.001$).

The content of the illusory responses obtained using the object version is shown in Fig. 2. Illusions of people and animals accounted for > 70% of the pareidolias in both the DLB and AD groups.

3.3. Discriminating between DLB and AD using the noise pareidolia test

In the object version, the mean percentages (standard errors, SE) of the illusory responses were 12.6 (3.3) for the DLB group, 1.7 (0.6) for the AD group and 0.1 (0.1) for the HC group (Fig. 3). The one-way ANOVA demonstrated a significant group difference ($F = 11.3$, $p < 0.001$). The percentage of illusory responses in the DLB group was significantly larger than those in the AD ($p < 0.001$) and HC ($p < 0.001$) groups. No significant difference was observed between the AD and HC groups. The mean percentages (SE) of the detection misses were 5.5 (2.3) for the DLB group, 2.9 (1.1) for the AD group and 0.0 (0.0) for the HC group, and no significant differences were observed among the groups (one-way ANOVA test, $F = 3.0$, $p = 0.055$). There was no significant correlation between detection misses and pareidolias in the DLB group.

In the face version, the mean percentages (SE) of illusory responses were 15.4 (3.2) for the DLB group, 1.9 (1.1) for the AD group and 0.1 (0.1) for the HC group (Fig. 3). The one-way ANOVA demonstrated a significant difference among the groups ($F = 16.2$, $p < 0.001$). The percentage of illusory responses in the DLB group was significantly larger than those in the AD ($p < 0.001$) and HC ($p < 0.001$) groups. No significant difference was observed between the AD and HC groups. The mean percentages (SE) of the detection misses were 8.8 (2.1) for the DLB group, 11.8 (2.9) for the AD group and 2.7 (1.2) for the HC group. The AD group had significantly more detection misses than the HC group ($p = 0.024$), but no significant differences were observed between the DLB and AD groups or between the DLB and HC groups (one-way ANOVA, $F = 4.0$, $p = 0.022$). The detection misses correlated with pareidolias in the DLB group ($r = -0.490$, $p = 0.003$).

In the ROC analysis, we used the following variables of interest: the neuropsychological and behavioural tests in which the DLB and AD groups significantly differed, i.e., FAB and the domain total scores of delusional misidentifications, hallucinations, euphoria, aberrant motor behaviour and fluctuations, and the illusory responses in the noise pareidolia tests. The measures in which the areas under the curves (AUC) were 0.7 or more were the NPI hallucination score (AUC, 0.80; 95% confidence interval, 0.69–0.91), the illusory responses in the face version (0.79; 0.67–0.90), the NPI fluctuation score (0.75; 0.63–0.87) and the illusory responses in the object version (0.72; 0.60–0.85). The optimal screening cut-off point for the illusory responses obtained using the face version was ≥ 2.5% (sensitivity = 0.71, specificity = 0.80). With this criterion, 24 patients with DLB were correctly classified as DLB, and 7 patients with AD were incorrectly classified as DLB. The optimal screening cut-off point for the illusory responses in the object version was ≥ 2.5% (sensitivity = 0.65, specificity = 0.71). With this criterion, 22 patients with DLB were correctly classified as DLB, and 10 patients with AD were incorrectly classified as DLB.

3.4. Signal detection analysis

We adjusted the data because the correct responses (hit rates) were at ceiling levels. We used the following formula: rates of 0 and 1 were replaced with $0.5/n$ and $(n-0.5)/n$, respectively, where n is the number of trials for noise plus face stimuli or noise only stimuli (Stanislaw & Todorov, 1999). Although seven patients with DLB produced illusory responses on the noise plus face trials in which they failed to detect faces, those responses were classified as 'misses' in the signal detection analysis.

A one-way ANOVA with a post-hoc Scheffé test revealed that the signal detection sensitivity was significantly lower in the DLB group ($d' = 3.1$ (0.3)) than in the AD (4.0 (0.2)) and HC (4.8 (0.1)) groups and lower in the AD group than in the HC group ($F = 16.9$,

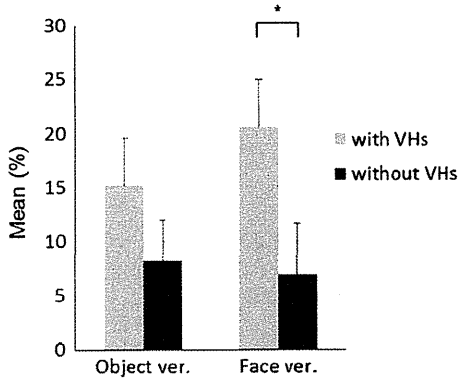

Fig. 4. Illusory responses in DLB patients with and without hallucinations. An asterisk indicates $p < 0.05$. VHs: visual hallucinations.

$p < 0.001$). The DLB group showed a response bias toward the existence of a face ($c = -0.2$ (0.1)), whereas the AD (0.3(0.1)) and HC (0.1 (0.1)) groups showed a conservative bias ($F = 10.3$, $p < 0.001$; DLB < AD; DLB < HC).

3.5. Illusory responses in DLB with and without visual hallucinations

We examined the impact of the presence or absence of visual hallucinations on the pareidolias (Fig. 4). In the object version, the mean percentages (SE) of illusory responses in the DLB patients with ($n = 21$) and without ($n = 13$) hallucinations were 15.2 (4.4) and 8.3 (4.7), respectively. No significant difference between these two groups was observed ($t = -1.04$, $df = 32$, $p = 0.306$). In the face version, the mean percentages (SE) of illusory responses in the DLB patients with and without hallucinations were 20.6 (4.4) and 6.9 (3.7), respectively. A significant difference between these two groups was observed ($t = -2.38$, $df = 31.8$, $p = 0.023$).

3.6. The correlation between performances during the noise pareidolia tests and other clinical variables in patients with DLB

The results are shown in Table 2. There were no significant correlations between pareidolias and age, education or visual acuity. In the object version, the percentage of illusory responses was significantly correlated with the performances on the spatial span ($r = -0.410$, $p = 0.016$) and shape detection ($r = -0.484$, $p = 0.004$) subtests and with the domain total, severity and frequency scores of the NPI delusional misidentifications ($rs = 0.394$, $p = 0.021$) and fluctuations ($rs = 0.402$, $p = 0.049$). In the face version, significant correlations were observed between the percentage of illusory responses and the performances on the spatial span ($r = -0.549$, $p = 0.001$), shape detection ($r = -0.509$, $p = 0.002$) and face recognition ($r = -0.560$, $p = 0.001$) tests and with the domain total, severity and frequency scores of the NPI hallucinations ($rs = 0.483$, $p = 0.004$) and fluctuations ($rs = 0.365$, $p = 0.034$).

Because the illusory responses during the face version test showed a better correlation with the hallucinations and discriminatory ability between the DLB and AD groups than the object version, we only used the face version in the following analyses.

3.7. Longitudinal changes in the illusory responses of patients with DLB before and after donepezil treatment

To investigate the impact of cholinergic enhancement on pareidolias, the noise pareidolia test and other neuropsychological and behavioural assessments were given to 15 DLB patients without medication at baseline and again after administering donepezil. The follow-up sessions occurred 1 month later after the dosage of donepezil was increased to 5 mg/day in all patients. The mean interval (SD) between the first and second sessions was 141 ± 61.7 days. The demographic and clinical profiles of the patients are shown in Table 3. Significant improvements were observed in the FAB ($p = 0.007$), verbal fluency ($p = 0.018$), NPI hallucination ($p = 0.028$), apathy ($p = 0.015$) and illusory responses during the noise pareidolia test ($p = 0.033$).

Table 2
Correlation between illusory responses on the noise pareidolia tests and neuropsychological and behavioural variables in patients with DLB.

	Objects version ($n = 34$)		Face version ($n = 34$)	
	r, *rs*	*p*-Values	*r*, *rs*	*p*-Values
Age †	−0.059	0.739	0.057	0.748
Education †	0.330	0.061	0.074	0.681
Visual acuity ‡	−0.141	0.425	−0.321	0.064
Neuropsychology‡				
MMSE	−0.108	0.543	−0.191	0.280
Digit span	−0.192	0.276	−0.315	0.070
Spatial span	−0.410	0.016*	−0.549	0.001**
Shape detection	−0.484	0.004**	−0.509	0.002**
Position discrimination	−0.218	0.217	−0.264	0.132
Object decision	0.203	0.249	0.052	0.771
Face recognition	−0.211	0.231	−0.560	0.001**
FAB	−0.118	0.506	−0.331	0.056
Fu/A/Ni	−0.101	−0.569	−0.129	0.467
NPI ‡				
Delusional misidentification				
Domain total	0.394	0.021*	0.175	0.323
Frequency	0.423	0.013*	0.193	0.273
Severity	0.376	0.029*	0.168	0.344
Hallucinations				
Domain total	0.291	0.095	0.483	0.004**
Frequency	0.289	0.097	0.508	0.002**
Severity	0.318	0.067	0.415	0.015*
Fluctuations in cognition				
Domain total	0.402	0.049*	0.365	0.034*
Frequency	0.397	0.020*	0.404	0.018*
Severity	0.371	0.031*	0.322	0.063*

† Pearson's correlation coefficient.
‡ Spearman's rank correlation coefficient.
* $p < 0.05$.
** $p < 0.01$.

The results of the correlations between the illusory responses and the neuropsychological/behavioural variables at the baseline and follow-up are shown in Table 4. At baseline, there were significant correlations between the illusory responses and the performance on the span tasks and all visuoperceptual/visuospatial tests. The percentage of illusory responses was also significantly correlated with the NPI hallucination and fluctuation scores. At follow-up, significant correlations were observed between the illusory responses and the performances on the spatial span subtest, shape detection and FAB. The percentages of illusory responses also significantly correlated with the NPI hallucination score. To further explore the impact of the cholinergic status on the relationships between the illusory responses and neuropsychological/behavioural variables, we conducted a supplementary correlation analysis on cross-sectional data, which included 25 DLB patients without donepezil (all at baseline) and 24 patients with donepezil (9 at baseline and 15 at follow-up). The results of the correlations between the illusory responses and neuropsychological/behavioural variables in the DLB patients with and without donepezil are shown in Supplementary table. In the patients without donepezil, significant correlations were observed between the illusory responses and performances on the digit span subtest ($r = 0.545$, $p = 0.005$), shape detection ($r = -0.678$,

Table 3
Demographic and clinical profiles at baseline and follow-up in patients with DLB ($n=15$).

		Baseline	Follow-up	p-Values
Age, years		79.6 (1.7)		
Sex (female/male)		8/7		
Education, years		10.1 (0.7)		
Visual acuity		0.9 (0.1)	0.9 (0.1)	
Neuropsychology†				
MMSE [30]		19.5 (1.1)	20.6 (1.2)	0.365
Digit span [24]		8.0 (0.6)	8.7 (0.6)	0.334
Spatial span [26]		9.7 (0.9)	9.6 (0.7)	0.846
Shape detection [20]		17.7 (0.7)	18.3 (0.5)	0.328
Position discrimination [20]		18.6 (0.5)	18.7 (0.4)	0.908
Face recognition [30]		24.0 (1.3)	24.5 (0.6)	0.700
FAB [18]		10.3 (0.7)	12.7 (0.9)	0.007**
Verbal fluency (FU/A/Ni)		12.3 (2.2)	15.4 (2.5)	0.018*
NPI ‡				
Persecutory delusions		0.0 (2.0)	0.0 (1.0)	0.461
Delusional misidentification		0.0 (0.0)	0.0 (0.0)	1.000
Hallucinations		1.0 (3.0)	0.0 (1.0)	0.028*
Agitation/aggression		1.0 (2.0)	0.0 (0.0)	0.143
Dysphoria		0.0 (1.0)	0.0 (1.0)	1.000
Anxiety		0.0 (0.0)	0.0 (2.0)	0.892
Euphoria		0.0 (0.0)	0.0 (0.0)	0.102
Apathy		4.0 (4.0)	0.0 (4.0)	0.015*
Disinhibition		0.0 (1.0)	0.0 (1.0)	0.892
Irritability/lability		0.0 (2.0)	0.0 (1.0)	0.752
Aberrant motor behaviour		0.0 (4.0)	0.0 (1.0)	0.670
Fluctuations in cognition		3.0 (4.0)	3.0 (2.0)	0.339
Prevalence §	Delusional misidentifications	3	3	1.000
	Visual Hallucinations	10	5	0.019*
	Fluctuations in cognition	11	12	0.582
Face pareidolia test†				
Pareidolias		14.0 (5.6)	4.7 (2.1)	0.033*
Detection misses		9.1 (3.6)	10.7 (3.4)	0.670

† Paired sample t-test.
‡ Wilcoxon signed-rank test.
§ Chi-squared test.
* $p<0.05$.
** $p<0.01$.

$p<0.001$), position discrimination (-0.402, $p=0.047$), face recognition ($r=-0.600$, $p=0.002$) and FAB ($r=-0.437$, $p=0.029$). The illusory responses also correlated with the NPI hallucination and fluctuation scores. In the patients with donepezil, significant correlations were observed between the illusory responses and the performance on the FAB ($r=-0.449$, $p=0.028$) and with the NPI hallucination score. In summary, the illusory responses during the noise pareidolia test were correlated with the visuoperceptual and other cognitive performances and with the severity of the hallucinations regardless of the cholinergic medication status.

Finally, we performed a correlation analysis of the longitudinal changes (differences between the baseline and follow-up session scores) in the noise pareidolia test, neuropsychological tests and NPI to explore the clinical utility of the noise pareidolia test as a marker of the therapeutic response. The change in the illusory responses was correlated with the change in the NPI fluctuation score ($r=0.563$, $p=0.029$) but not with the change in the hallucination score or the neuropsychological performance.

4. Discussion

We investigated abnormal illusory perceptions in patients with DLB by using a newly developed pareidolia test. Our study has three major findings: (1) DLB patients see illusory images (pareidolias) in meaningful scenery pictures and also in meaningless visual patterns; (2) the severity of pareidolias is significantly correlated with that of visual hallucinations; and (3) cholinergic stimulation reduces both the number of pareidolias and the severity of visual hallucinations in patients with DLB.

4.1. Visual hallucinations and pareidolias as active perceptions

Visual hallucinations and illusions are different by definition. The former is defined as seeing something where nothing actually exists, and the latter is the misperception or misinterpretation of real visual stimuli. The critical difference between the two conditions is whether the objects exist (Ey, 1973). However, this classic dichotomy was challenged by a recent study in which visual hallucinations and pareidolias, a specific type of visual illusion, were found to be similar and closely related in patients with DLB (Uchiyama et al., 2012). Pareidolias are misperceptions involving ambiguous forms that are perceived as meaningful visual objects. In the aforementioned study, Uchiyama et al. successfully evoked pareidolias in patients with DLB using picture stimuli containing natural visual scenes. Striking phenomenological similarities were present between the visual hallucinations and pareidolias in DLB in which the vast majority of their content were animals and humans (Ballard et al., 1997). In the current study, we extended the findings of the previous study (Uchiyama et al., 2012) by using visual stimuli composed of meaningless stimuli and demonstrated that DLB patients observed meaningful objects in the meaningless stimuli. These results indicate that pareidolias in DLB do not only result from a failure of object recognition but also represent hallucination-like illusions associated with an active perceptual process that creates meaning from meaningless visual information.

Table 4
Correlation between the illusory responses in the face version of the noise pareidolia test and neuropsychological and behavioural variables in pastients with DLB at baseline and follow-up.

	Baseline ($n=15$)		Follow-up ($n=15$)	
	r, rs	*p*-Values	*r, rs*	*p-Values*
Age †	−0.203	0.469	−0.139	0.621
Education †	0.210	0.470	0.273	0.344
Visual acuity‡	−0.356	0.192	−0.088	0.775
Neuropsychology †				
MMSE	−0.275	0.321	−0.511	0.052
Digit span	−0.678	0.005**	−0.379	0.163
Spatial span	−0.767	0.001**	−0.573	0.026*
Shape detection	−0.755	0.001**	−0.688	0.005**
Position discrimination	−0.765	0.001**	−0.357	0.191
Face recognition	−0.612	0.015*	−0.348	0.204
FAB	−0.503	0.056	−0.799	< 0.001**
Fu/A/Ni	−0.165	0.556	−0.397	0.143
NPI ‡				
Hallucinations				
Domain total	0.573	0.026*	0.683	0.005**
Frequency	0.545	0.035*	0.683	0.005**
Severity	0.624	0.013*	0.624	0.013*
Fluctuations in cognition				
Domain total	0.510	0.052	−0.017	0.952
Frequency	0.561	0.030*	0.055	0.846
Severity	0.311	0.259	−0.066	0.814

† Pearson's correlation coefficient.
‡ Spearman's rank correlation coefficient.
* $p < 0.05$.
** $p < 0.01$.

In psychology, the idea has been proposed that context often biases our perceptions. Bugelski and Alampay (1961) used an ambiguous line drawing that can be perceived as both a man and a rat and found that the perception of the figure was biased by the prior presentation of either human or animal sketches. More recently, visual psychophysical experiments demonstrated that the context of a background scene facilitates or sometimes misleads visual object recognition (Bar, 2004; Biederman, Mezzanotte, & Rabinowitz, 1982). These types of 'predictive' or 'proactive' perception views may be helpful in explaining the nature of the misperceptions of DLB patients. They see visual hallucinations in the visual scenes of their daily lives. Therefore, their experiences and the context of their personal daily living play an important role in their visual hallucinations. Similarly, in the previous study (Uchiyama et al., 2012), patients with DLB described illusory visual experiences that were evoked by the context of the natural scene images. For example, DLB patients often perceived non-existent people in the shade of trees in a park and non-existent young jaguars under the feet of an adult jaguar. The most striking difference between our current study and these previous studies is the meaningfulness of the visual stimuli. In the current study, no clear context was provided by the meaningless visual noise. The participants 'read out' the context of the test from the instructions and their history of previous perceptual experiences (perceptual hysteresis). The Rorschach test (Rorschach, 1942), which has been broadly used in the fields of psychology and psychiatry, is another test consisting of meaningless visual stimuli. In this test, the participants are required to describe what they see in the meaningless pattern of an inkblot. This test is known to reflect suggestibility, and the results can be biased by the instructions (Gibby, 1952; Sarbin, 1939; Yanovski & Fogel, 1978). In a similar manner, our results may be partially ascribed to abnormally heightened suggestibility in patients with DLB. This view is supported by the result of signal detection analysis in the current study, in which patients with DLB showed a strong response bias toward detecting something in meaningless visual noises. Again, we suggest that non-perceptual mechanisms, such as context and suggestibility, make a critical contribution to the development of visual hallucinations and illusions in DLB.

4.2. Relative contributions of perceptual and non-perceptual mechanisms in visual hallucinations and pareidolias

Both perceptual (visual) and non-perceptual mechanisms may be involved in visual hallucinations. Because most people who have visual impairments do not experience visual hallucinations, non-perceptual mechanisms are likely critical. As described above, our study suggests that non-perceptual mechanisms also play a pivotal role in the pareidolias observed in patients with DLB. However, little is known about what 'non-perceptual' mechanisms are specifically involved in these types of misperceptions. In contrast, there is a wealth of neuropsychological evidence for the involvement of visuoperceptual/visuospatial deficits (Mori et al., 2000; Mosimann et al., 2004). Therefore, it may be profitable to consider the non-perceptual mechanisms of visual hallucinations and pareidolias with respect to perceptual mechanisms.

In the current study, the performance on the face recognition test was significantly correlated with the number of illusory reponses in the face-noise pareidolia test but not with the object-noise pareidolia test (Table 2). In addition, there was a stronger correlation between the NPI hallucination scores and the number of illusory responses in the face pareidolia test than those in the object pareidolia test. These findings suggest that the category of faces plays a special role in the visual hallucinations and pareidolias observed in patients with DLB. Two factors, one of which is specific to our tests and another that applies to visual hallucinations and pareidolias in general, may be associated with this face preference. The first factor is the physical similarity between the noise images and the embedded face images. $1/f^3$ noise images, which we used in the noise pareidolia tests, have many different sizes of blobs. Those blobs often create specific patterns of spatial arrangements or contrast polarity that are preferentially recognised as faces by observers (Fig. 1) (Johnson, 2005; Ohayon, Freiwald, & Tsao, 2012). This bias may lead to similarities between the face images and the noises. However, there is no such similarity between the non-face objects and the noise images because the non-face objects are variable in form and do not have stereotypic, schematic patterns. The difficulty in discriminating between faces and the noises may place a higher demand on face recognition and other visuoperceptual/visuospatial abilities in the face-noise pareidolia test than in the object-noise pareidolia test. The other factor relates the ecological value of people and other animals. Previous studies have demonstrated that people account for more than 80% of all the content of visual hallucinations in patients with DLB (Ballard et al., 1997; Nagahama et al., 2007). Similarly, people and other animals account for 70 to 80% of all the content of pareidolias (Fig. 2 in this study; Uchiyama et al., 2012). Nagahama et al. conducted an exploratory factor analysis for psychotic symptoms observed in 100 DLB patients and discovered that the feeling of presence, which is a vivid sensation that somebody is present nearby, is tightly linked to hallucinations of people but not objects (Fenelon, Soulas, Cleret de Langavant, Trinkler, & Bachoud-Levi, 2011; Nagahama et al., 2007). These findings suggest that the specific sensation of the presence of others who can act on a perceiver may be fundamental for hallucinations of people or for hallucinations in general. We argue that faces are special to the perceivers or hallucinators because they represent people and animals, who are potential predators or potentially dangerous to the perceivers/hallucinators (Cheyne, 2001).

The current and previous studies demonstrated that the patterns of correlations between pareidolias and visuoperceptual/visuospatial measures differed in the scenery, object-noise and face-noise versions of the pareidolia test. In the previous study (Uchiyama et al., 2012), a significant correlation was observed between the scenery pareidolia test and the performance on the face recognition test in DLB patients who received donepezil treatment, whereas no significant correlations were observed between the scenery pareidolia test and any of the visuoperceptual/visuospatial tests in those who did not take donepezil. In contrast, the current study demonstrated more convincing correlations between the noise pareidolia tests and the visuoperceptual/visuospatial tests. The face version was correlated with the shape dection and face recognition tests, wheareas the object version was correlated with the shape detection test but not with the face recognition test (Table 2 and Supplementary table). These differences in the correlation patterns may reflect differences in the relative contributions of the perceptual and non-perceptual mechanims in the three versions of the paredolia test. The stronger and more convincing correlations between the noise pareidolia tests and the visuoperceptual/visuospatial tests suggest that the contribution of perceptual mechanisms may be larger in the noise versions than in the scenery version of the pareidolia test. In contrast, non-perceptual mechanisms may be larger in the scenery version than in the noise versions. In addition, the scenery pareidolia test was better correlated with NPI misidentification scores than the noise versions, suggesting the importance of abnormal beliefs or delusional mechanisms, which are surely non-perceptual, in the scenery pareidolia test (delusional mechanisms in visual hallucinations and pareidolias are discussed more in depth in the next section) (Uchiyama et al., 2012).

4.3. Non-perceptual mechanisms of visual hallucinations and pareidolias

Attention deficits have been proposed to be the major non-perceptual mechanism for visual hallucinations. Specifically, the perception and attention deficit (PAD) model offers an integrative theory regarding the visual and attentional mechanisms of visual hallucinations (Collerton, Perry, & McKeith, 2005). The central idea of this model is that the impairment of top-down attention results in defective gate control to internally generate false images. Under normal conditions, many 'proto-objects' are evoked from memory storage by bottom-up sensory information, but only one object is permitted to pass through the gate control to consciousness. In patients with DLB, who have deficits in both bottom-up visual perception and executive/attention functions, proto-objects that normally remain at the subconscious level are aberrantly excited by bottom-up perceptual dysfunction and reach consciousness due to the disrupted top-down gate control. Empirical support exists for this hypothesis in which both executive/attention and visuoperceptual deficits are associated with visual hallucinations (Cagnin et al., 2013; Collerton, Burn, McKeith, & O'Brien, 2003; Mori et al., 2000; Mosimann et al., 2004). Despite these findings, questions remain that are not answered by this model: (1) Why do other neurological conditions associated with both attention/executive and visuoperceptual deficits (AD, multi-infarct dementia and traumatic brain injury) not develop visual hallucinations as frequently as DLB patients? And (2) Does this particular combination of cognitive deficits provide a plausible explanation for the mechanisms of other psychotic symptoms that are frequently observed in Lewy body diseases, such as the variety of delusions and hallucinations in other sensory modalities (Hirono & Cummings, 1999; McKeith et al., 2005)?

Most DLB patients show a lack of or impaired insight into their visual hallucinations (Ballard et al., 1997), which may result in secondary delusions associated with the content of their visual hallucinations (McKeith et al., 2005). Other evidence regarding the relationship between abnormal insights or delusional beliefs and visual hallucinations have been provided by peduncular hallucinosis (Feinberg & Rapcsak, 1989; Kolmel, 1991; Benke, 2006; Nishio, Ishii, Kazui, Hosokai, & Mori, 2007) (for a counter view, see Manford & Andermann (1998)). Similarly, in the previous study (Uchiyama et al., 2012), most DLB patients believed the reality of their non-existent, pareidolic visual images, and there was a significant correlation between pareidolias and NPI delusional misidentification scores. Attention deficits, which were assessed by the digit span test, were not correlated with the illusory responses on the scenery pareidolia test, suggesting that abnormal insights or beliefs may play a larger role than attention deficits in this type of pareidolia. Although the contributions of attention and visuoperceptual/visuospatial deficits may be larger in noise pareidolias than in scenery pareidolias (Tables 2 and 4 and Supplementary table), the current study indicates that the suggestibility to non-visual contexts may play a role in noise pareidolias. Overall, we argue that impaired reality monitoring, abnormal reasoning and suggestibility, which have been implicated in the mechanisms of delusion formation in psychosis, play a role in the development of visual hallucinations and pareidolias. Visual hallucinations and pareidolias may share underlying mechanisms with several types of delusional symptoms.

4.4. Roles for cholinergic insufficiency in visual hallucinations and pareidolias

Previous studies have revealed that visual hallucinations in DLB patients were alleviated by cholinesterase inhibitor treatment (McKeith et al., 2000; Mori et al., 2012, 2006). Therefore, we investigated the effect of donepezil on pareidolias. Significant improvements in the number of hallucinations and pareidolias after administering donepezil suggest that cholinergic insufficiency plays a critical role in promoting these symptoms. The relationship among cholinergic insufficiency, visual hallucinations and visual illusions was previously demonstrated in a classic psychopharmacological study using healthy subjects. Ketchum, Sidell, Crowell, Aghajanian, and (Hayes), (1973) demonstrated that anti-cholinergic agents induced visual hallucinations and visual illusions of people and animals, which are similar to the hallucinations observed in the patients with DLB.

As no significant changes have been observed in visuoperceptual dysfunctions before and after cholinesterase treatment in the DLB patients (Table 3 in the current study) (Mori et al., 2012), acetylcholine may be primarily involved in the non-perceptual mechanisms. The PAD model emphasises the relationship between cholinergic insufficiency and attentional impairment (Collerton et al., 2005). In addition, we argue that cholinergic insufficiency may be associated with abnormal insights or beliefs. For example, several DLB patients treated with cholinesterase inhibitors described that although they had previously believed their hallucinations to be real, they now realised that their experiences were only illusions. The study by Uchiyama et al. (2012) also suggested a relationship between cholinergic insufficiency and delusional beliefs in which the correlation between the scenery pareidolia test and the NPI misidentification scores were lower in patients who received donepezil treatment than in those who did not.

Both this study and the previous studies demonstrated that correlations between pareidolias and visuoperceptual/visuospatial tests changed depending on the donepezil treatment status. However, the patterns of changes were different in the scenery and noise versions of the pareidolia test. In the previous study (Uchiyama et al., 2012), the scenery pareidolia test was not correlated with visuoperceptual/visuospatial test in DLB patients

who did not take donepezil. In contrast, weak correlations were observed between these measures in patients who took donepezil. Conversely, in the current study, correlations between the noise pareidolia test and the visuoperceptual/visuospatial and attention tests were reduced after donepezil administration compared with the baseline. This inconsistency can be explained by the different relative contributions of the perceptual, attentional and insight/belief mechanisms in the scenery and noise pareidolias. Given the importance of insight/belief mechanisms in scenery pareidolias, donepezil administration may increase the relative contribution of visuoperceptual mechanisms by improving the insight/belief abnormalities. In contrast, attentional impairment and visuoperceptual deficits play a larger role in noise pareidolias. According to the PAD model, cholinomimetic drugs alleviate the visual hallucinations by improving attention and enhancing top-down control on bottom-up perception (Collerton et al., 2005). Similarly, donepezil may enhance the attentional top-down control of visual perception, which may decrease the correlations among visuoperceptual/visuospatial deficits, attentional impairment and noise pareidolias and may increase the relative contribution of non-perceptual, non-attentional mechanisms, such as abnormal insights and delusional beliefs.

4.5. Clinical utility of the noise pareidolia test

The specificity of the current clinical diagnostic criteria for DLB is reportedly high, but its sensitivity is low (McKeith et al., 2004; Nelson et al., 2010). Previous authors suggested that the low diagnostic sensitivity may be partly attributable to the difficulty in detecting and assessing two of the three core clinical features, visual hallucinations and cognitive fluctuations (Ballard et al., 2004). Structured interviews or questionnaires, such as the NPI (Cummings et al., 1994) and the North-East Visual Hallucinations Interview (NEVHI) (Mosimann et al., 2008), have been the gold standard for the assessment of visual hallucinations, and these questionnaires have been broadly used in both clinical practice and therapeutic intervention studies (Archibald, Clarke, Mosimann, & Burn, 2011; Mori et al., 2012; Mosimann et al., 2008). However, these proxy- or self-interview methods are not applicable to patients who live alone, lack the insight into their symptoms or have severe memory loss. We believe that adding the pareidolia tests to the evaluation process is beneficial for the differential diagnosis and tracking of therapeutic effects. Comparisons between the current (the noise versions) and previous (the scenery version) pareidolia tests suggest that the former is easier to administer and more highly correlated with the severity of the hallucinations; however, the previous version has higher sensitivity and better discriminatory ability between DLB and AD (Uchiyama et al., 2012). We are currently working on the standardisation of a pareidolia test that combines the two versions.

4.6. Limitations and future directions

Finally, several limitations need to be considered. First, although both the NPI hallucinations scores and illusory responses in the noise pareidolia test were improved after administering donepezil, we failed to demonstrate a significant correlation between the longitudinal differences of these measures. This finding may be associated with the small sample size of the drug intervention section of this study. A larger sample size is required to examine the utility of the noise pareidolia test as a surrogate indicator of visual hallucinations. Second, although substantial interest has been shown in the dopaminergic and prefrontal mechanisms of psychosis (Coltheart, Langdon, & McKay, 2011; Feinberg, 2011; Kapur, 2003), we did not address these issues in the current study. Third, although the results of the current neuropsychological investigations suggest that executive, attentional and visuoperceptual deficits contribute to the development of visual hallucinations and pareidolias, we did not directly address the neuroanatomical bases of these symptoms; however, neuroimaging analyses will provide helpful information on this issue.

Acknowledgments

We thank Kohske Takahashi and an anonymous reviewer for their insightful comments.

This work was supported by a Grant-in-Aid for JSPS Fellows (12J05574 to K.Y.), a Grant-in-Aid for Young Scientists (B) (22791104 to Y.N.) and Grant-in-Aid for Scientific Research (B) (24390278 to E.M.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a grant provided by the Ministry of Health, Labour and Welfare (Research on dementia; H21-Dementia-General-005) for E.M.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2014.01.017.

References

Archibald, N. K., Clarke, M. P., Mosimann, U. P., & Burn, D. J. (2011). Visual symptoms in Parkinson's disease and Parkinson's disease dementia. *Movement Disorders, 26*, 2387–2395.

Ballard, C., McKeith, I., Harrison, R., O'Brien, J., Thompson, P., Lowery, K., Perry, R., & Ince, P. (1997). A detailed phenomenological comparison of complex visual hallucinations in dementia with Lewy bodies and Alzheimer's disease. *International Psychogeriatrics, 9*, 381–388.

Ballard, C., Piggott, M., Johnson, M., Cairns, N., Perry, R., McKeith, I., Jaros, E., O'Brien, J., Holmes, C., & Perry, E. (2000). Delusions associated with elevated muscarinic binding in dementia with Lewy bodies. *Annals of Neurology, 48*, 868–876.

Ballard, C. G., Jacoby, R., Del Ser, T., Khan, M. N., Munoz, D. G., Holmes, C., Nagy, Z., Perry, E. K., Joachim, C., & Jaros, E. (2004). Neuropathological substrates of psychiatric symptoms in prospectively studied patients with autopsy-confirmed dementia with Lewy bodies. *American Journal of Psychiatry, 161*, 843–849.

Bar, M. (2004). Visual objects in context. *Nature Reviews: Neuroscience, 5*, 617–629.

Bar, M. (2007). The proactive brain: Using analogies and associations to generate predictions. *Trends in Cognitive Sciences, 11*, 280–289.

Benke, T. (2006). Peduncular hallucinosis: a syndrome of impaired reality monitoring. *Journal of Neurology, 253*, 1561–1571.

Biederman, I., Mezzanotte, R. J., & Rabinowitz, J. C. (1982). Scene perception: Detecting and judging objects undergoing relational violations. *Cognitive Psychology, 14*, 143–177.

Bugelski, B. R., & Alampay, D. A. (1961). The role of frequency in developing perceptual sets. *Canadian Journal of Psychology, 15*, 205–211.

Cagnin, A., Gnoato, F., Jelcic, N., Favaretto, S., Zarantonello, G., Ermani, M., & Dam, M. (2013). Clinical and cognitive correlates of visual hallucinations in dementia with Lewy bodies. *Journal of Neurology, Neurosurgery and Psychiatry, 84*, 505–510.

Cheyne, J. A. (2001). The ominous numinous. sensed presence and 'other' hallucinations. *Journal of Consciousness Studies, 8*, 133–150.

Collerton, D., Burn, D., McKeith, I., & O'Brien, J. (2003). Systematic review and meta-analysis show that dementia with Lewy bodies is a visual-perceptual and attentional-executive dementia. *Dementia and Geriatric Cognitive Disorders, 16*, 229–237.

Collerton, D., Perry, E., & McKeith, I. (2005). Why people see things that are not there: A novel perception and attention deficit model for recurrent complex visual hallucinations. *Behavioral and Brain Sciences, 28*, 737–757 (discussion 757-794).

Coltheart, M., Langdon, R., & McKay, R. (2011). Delusional belief. *Annual Review of Psychology, 62*, 271–298.

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory comprehensive assessment of psychopathology in dementia. *Neurology, 44* (2308-2308).

Ey, H. (1973). *Traité des hallucinations*. Paris: Masson.

Feinberg, T. E. (2011). Neuropathologies of the self: Clinical and anatomical features. *Consciousness and Cognition, 20*, 75–81.

Feinberg, W. M., & Rapcsak, S. Z. (1989). 'Peduncular hallucinosis' following paramedian thalamic infarction. *Neurology, 39*, 1535–1536.
Fenelon, G., Soulas, T., Cleret de Langavant, L., Trinkler, I., & Bachoud-Levi, A. C. (2011). Feeling of presence in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 82*, 1219–1224.
Field, D. J. (1987). Relations between the statistics of natural images and the response properties of cortical cells. *Journal of the Optical Society of America A: Optics, Image Science, and Vision, 4*, 2379–2394.
Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189–198.
Friston, K. (2005). A theory of cortical responses. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 360*, 815–836.
Frith, C. D., & Done, D. J. (1988). Towards a neuropsychology of schizophrenia. *British Journal of Psychiatry, 153*, 437–443.
Gibby, R. G. (1952). Examiner influence on the Rorschach inquiry. *Journal of Consulting Psychology, 16*, 449.
Halliday, G. (2005). Clarifying Lewy-body parkinsonism with visual hallucinations. *Lancet Neurology, 4*, 588–589.
Harding, A. J., Broe, G. A., & Halliday, G. M. (2002). Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain, 125*, 391–403.
Hirono, N., & Cummings, J. L. (1999). Neuropsychiatric aspects of dementia with Lewy bodies. *Current Psychiatry Reports, 1*, 85–92.
Japan Society for Higher Brain Dysfunction Brain Function Test Commitee. (1997). Visual Perception Test for Agnosia: Shinko Igaku Syuppan.
Johnson, M. H. (2005). Subcortical face processing. *Nature Reviews: Neuroscience, 6*, 766–774.
Kapur, S. (2003). Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. *American Journal of Psychiatry, 160*, 13–23.
Kersten, D., Mamassian, P., & Yuille, A. (2004). Object perception as Bayesian inference. *Annual Review of Psychology, 55*, 271–304.
Ketchum, J. S., Sidell, F. R., Crowell, E. B., , Aghajanian, G. K., & Hayes, A. H., (1973). Atropine, scopolamine, and Ditran: Comparative pharmacology and antagonists in man. *Psychopharmacologia, 28*, 121–145.
Kugo, A., Terada, S., Ata, T., Ido, Y., Kado, Y., Ishihara, T., Hikiji, M., Fujisawa, Y., Sasaki, K., & Kuroda, S. (2007). Japanese version of the Frontal Assessment Battery for dementia. *Psychiatry Research, 153*, 69–75.
Kolmel, H. W. (1991). Peduncular hallucinations. *Journal of Neurology, 238*, 457–459.
Luis, C. A., Barker, W. W., Gajaraj, K., Harwood, D., Petersen, R., Kashuba, A., Waters, C., Jimison, P., Pearl, G., Petito, C., Dickson, D., & Duara, R. (1999). Sensitivity and specificity of three clinical criteria for dementia with Lewy bodies in an autopsy-verified sample. *International Journal of Geriatric Psychiatry, 14*, 526–533.
Macmillan, N. A., & Creelman, C. D. (1990). Response bias: Characteristics of detection theory, threshold theory, and "nonparametric" indexes. *Psychological Bulletin, 107*, 401–413.
McKeith, I. G., Del Ser, T., Spano, P., Emre, M., Wesnes, K., Anand, R., Cicin-Sain, A., Ferrara, R., & Spiegel, R. (2000). Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. *The Lancet, 356*, 2031–2036.
McKeith, I. G., Dickson, D. W., Lowe, J., Emre, M., O'brien, J., Feldman, H., Cummings, J., Duda, J., Lippa, C., & Perry, E. (2005). Diagnosis and management of dementia with Lewy bodies Third report of the DLB consortium. *Neurology, 65*, 1863–1872.
McKeith, I. G., Galasko, D., Kosaka, K., Perry, E. K., Dickson, D. W., Hansen, L. A., Salmon, D. P., Lowe, J., Mirra, S. S., Byrne, E. J., Lennox, G., Quinn, N. P., Edwardson, J. A., Ince, P. G., Bergeron, C., Burns, A., Miller, B. L., Lovestone, S., Collerton, D., Jansen, E. N., Ballard, C., de Vos, R. A., Wilcock, G. K., Jellinger, K. A., & Perry, R. H. (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology, 47*, 1113–1124.
McKeith, I. G., Mintzer, J., Aarsland, D., Burn, D., Chiu, H., Cohen-Mansfield, J., Dickson, D., Dubois, B., Duda, J. E., & Feldman, H. (2004). Dementia with Lewy bodies. *The Lancet Neurology, 3*, 19–28.
McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease Report of the NINCDS–ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34* (939-939).
Mori, E., Ikeda, M., & Kosaka, K. (2012). on behalf of the Donepezil, D. L. B. S. I. (2012). Donepezil for dementia with Lewy bodies: A randomized, placebo-controlled trial. *Annals of Neurology, 72*, 41–52.
Mori, E., Shimomura, T., Fujimori, M., Hirono, N., Imamura, T., Hashimoto, M., Tanimukai, S., Kazui, H., & Hanihara, T. (2000). Visuoperceptual impairment in dementia with Lewy bodies. *Archives of Neurology, 57*, 489–493.
Mori, S., Mori, E., Iseki, E., & Kosaka, K. (2006). Efficacy and safety of donepezil in patients with dementia with Lewy bodies: Preliminary findings from an open-label study. *Psychiatry and Clinical Neurosciences, 60*, 190–195.
Mosimann, U. P., Collerton, D., Dudley, R., Meyer, T. D., Graham, G., Dean, J. L., Bearn, D., Killen, A., Dickinson, L., Clarke, M. P., & McKeith, I. G. (2008). A semi-structured interview to assess visual hallucinations in older people. *International Journal of Geriatric Psychiatry, 23*, 712–718.
Mosimann, U. P., Mather, G., Wesnes, K. A., O'Brien, J. T., Burn, D. J., & McKeith, I. G. (2004). Visual perception in Parkinson disease dementia and dementia with Lewy bodies. *Neurology, 63*, 2091–2096.
Nagahama, Y., Okina, T., Suzuki, N., Matsuda, M., Fukao, K., & Murai, T. (2007). Classification of psychotic symptoms in dementia with Lewy bodies. *American Journal of Geriatric Psychiatry, 15*, 961–967.
Nelson, P. T., Jicha, G. A., Kryscio, R. J., Abner, E. L., Schmitt, F. A., Cooper, G., Xu, L. O., Smith, C. D., & Markesbery, W. R. (2010). Low sensitivity in clinical diagnoses of dementia with Lewy bodies. *Journal of Neurology, 257*, 359–366.
Nishio, Y., Ishii, K., Kazui, H., Hosokai, Y., & Mori, E. (2007). Frontal-lobe syndrome and psychosis after damage to the brainstem dopaminergic nuclei. *Journal of the Neurological Sciences, 260*, 271–274.
Ohayon, S., Freiwald, W. A., & Tsao, D. Y. (2012). What makes a cell face selective? The importance of contrast. *Neuron, 74*, 567–581.
Perry, E. K., Marshall, E., Kerwin, J., Smith, C. J., Jabeen, S., Cheng, A. V., & Perry, R. H. (1990). Evidence of a monoaminergic-cholinergic imbalance related to visual hallucinations in Lewy body dementia. *Journal of Neurochemistry, 55*, 1454–1456.
Riddoch, J., & Humphreys, G. W. (1992). *Birmingham object recognition battery*. Lawrence Erlbaum.
Rorschach, H. (1942). *Psychodiagnostics*
Ruderman, D. L. (1994). The statistics of natural images. *Network: Computation in neural systems, 5*, 517–548.
Sarbin, T. R. (1939). Rorschach patterns under hypnosis. *American Journal of Orthopsychiatry, 9*, 315–318.
Stanislaw, H., & Todorov, N. (1999). Calculation of signal detection theory measures. *Behavior Research Methods, Instruments, & Computers, 31*, 137–149.
Sugishita, M. (2001). *The Japanese version of Wechesler Memory Scale-Revised*. Tokyo: Nihon bunka Kagakusha.
Uchiyama, M., Nishio, Y., Yokoi, K., Hirayama, K., Imamura, T., Shimomura, T., & Mori, E. (2012). Pareidolias: Complex visual illusions in dementia with Lewy bodies. *Brain, 135*, 2458–2469.
Warrington, E. K., & James, M. (1991). *The visual object and space perception battery*. Thames Valley Test Company Bury St Edmunds.
Yanovski, A., & Fogel, M. L. (1978). Effects of instructions for visual-imagery on Rorschach responses. *Perceptual and Motor Skills, 47*, 1323–1335.

PLOS | ONE

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

Yumiko Shoji[1], Yoshiyuki Nishio[1]*, Toru Baba[1], Makoto Uchiyama[1,2], Kayoko Yokoi[1], Toshiyuki Ishioka[3], Yoshiyuki Hosokai[4], Kazumi Hirayama[1,5], Hiroshi Fukuda[6], Masashi Aoki[7], Takafumi Hasegawa[7], Atsushi Takeda[8], Etsuro Mori[1]

1 Department of Behavioral Neurology and Cognitive Neuroscience, Tohoku University School of Medicine, Sendai, Japan, **2** Department of Speech, Language and Hearing Sciences, Niigata University of Health and Welfare, Niigata, Japan, **3** Department of Occupational Therapy, Saitama Prefectural University, Koshigaya, Japan, **4** Department of Diagnostic Image Analysis, Tohoku University School of Medicine, Sendai, Japan, **5** Department of Occupational Therapy, Yamagata Prefectural University of Health Science, Yamagata, Japan, **6** Department of Radiology and Nuclear Medicine, Institute of Development, Aging, and Cancer, Tohoku University, Sendai, Japan, **7** Department of Neurology, Tohoku University School of Medicine, Sendai, Japan, **8** Department of Neurology, Sendai Nishitaga Hospital, Sendai, Japan

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.

Citation: Shoji Y, Nishio Y, Baba T, Uchiyama M, Yokoi K, et al. (2014) Neural Substrates of Cognitive Subtypes in Parkinson's Disease: A 3-Year Longitudinal Study. PLoS ONE 9(10): e110547. doi:10.1371/journal.pone.0110547

Editor: Stephen D. Ginsberg, Nathan Kline Institute and New York University School of Medicine, United States of America

Received July 7, 2014; **Accepted** September 15, 2014; **Published** October 20, 2014

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

Funding: This work was supported by a Grant-in-Aid for Scientific Research (B) (24390278 to EM) and a Grant-in-Aid for Scientific Research for Young Scientists (90451591 to YN). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Email: nishiou@med.tohoku.ac.jp

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

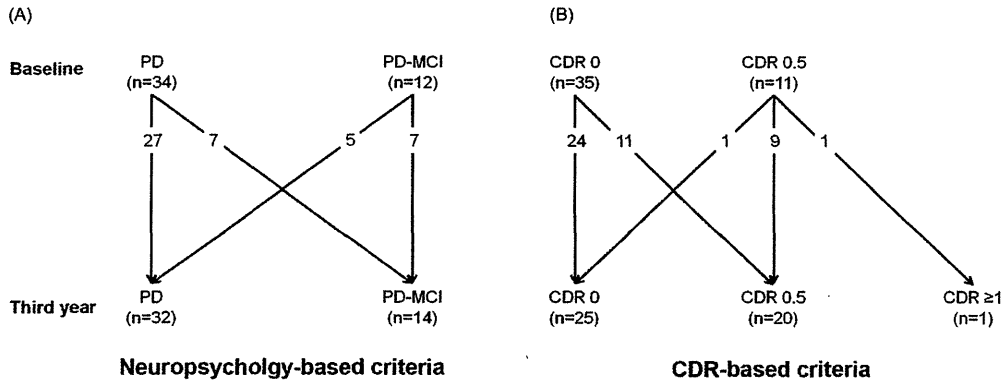

Figure 1. Diagrams of the 3-year cognitive changes observed in patients. In (A), the patients were classified as having Parkinson's disease without cognitive impairment (PD) or PD with mild cognitive impairment (PD-MCI) based on neuropsychological tests. (B) shows the results based on the Clinical Dementia Rating (CDR)-based patient classification.
doi:10.1371/journal.pone.0110547.g001

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.

doi:10.1371/journal.pone.0110547.t001

Table 2. Demographic and clinical profiles of patients with a Clinical Dementia Rating of 0.5 or more at baseline.

		Baseline memory-only (N=8)		Baseline memory-plus (N=6)		Differences between groups
Age at baseline (years)		69.0±6.6		66.2±5.5		
Gender (male/female)		6/2		6/0		
Education (years)		12.3±2.3		14.3±2.7		
Test-retest interval (days)		1115.3±107.1		1096.7±54.7		
Disease duration at baseline (years)		6.8±3.3		9.7±6.8		
Age at onset (years)		62.4±6.6		56.6±8.0		
Levodopa equivalent dose at baseline (mg/day)		453.6±163.1		658.6±337.9		
UPDRS part III	Baseline	27.1±5.4		23.8±6.6		
	Progression rate (/years)	−0.7±3.3		4.6±5.0		Baseline memory-plus>Baseline memory-only[a]
UPDRS tremor¶	Baseline	0.7±0.5		0.4±0.6		
	Third year	0.3±0.2		0.4±0.7		Main effect of non-tremor score: Baseline memory-plus> Baseline memory-only[a]
UPDRS non-tremor¶	Baseline	1.2±0.2		1.0±0.1		
	Third year	1.1±0.2		1.7±0.7		
CDR sum of boxes	Baseline	0.5		2.1±1.3		NE
	Third year	1.4±1.2		5.3±4.1		NE
MMSE	Baseline (/30)	27.0±3.0		27.0±2.2		
	Progression rate (/years)	−0.3±0.7		−1.1±2.7		
ADAS word recall†	Baseline (/30)	17.9±4.1		14.3±5.4		
	Progression rate (/years)	−0.1±1.4		−0.3±1.2		
Overlapping figure‡	Baseline (/40)	29.6±4.1		29.4±6.2		
	Progression rate (/years)	0.1±1.1		−2.4±3.1		
Backward digit-span§	Baseline	3.6±1.0		3.8±0.5		NE
	Progression rate (/years)	−0.1±0.1		−0.3±0.3		NE
# of patients below −1 SD at baseline and at third year	ADAS word recall†	4/8	3/8	5/6	5/6	NE
	Overlapping figure‡	3/8	4/8	2/5	5/5	NE
	Backward digit-span§	3/7	4/7	1/4	2/4	NE

Two-sample *t*-tests were used for group-wise comparisons of baseline scores and progression rates except for the UPDRS tremor/non-tremor scores. A two-way analysis of variance was used for the UPDRS tremor/non-tremor scores. No group-wise comparisons were performed for the backward digit-span owing to the small number of subjects. 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 6 baseline memory-only and 6 baseline memory-plus patients.

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

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

§The mean score of controls (n=20, 65.5±4.8 years) is 4.8±1.0. [49]; a statistical comparison was not performed owing to an insufficient number of subjects.

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.

doi:10.1371/journal.pone.0110547.t002

memory-only patients (**Figures 2E and 3E**). These findings can be interpreted in two ways: the posterior neocortical hypometabolism found in these patients may represent pathological changes in Braak stages 5–6, or they may represent a pathological progression pattern that does not conform to Braak's scheme. [7] The latter was suggested by the following clinical and neuroimaging findings. First, the severity of motor symptoms at baseline was equivalent in the memory-plus converters, non-converters and memory-only converters, suggesting that the three groups had similar degrees of midbrain pathology. In other words,

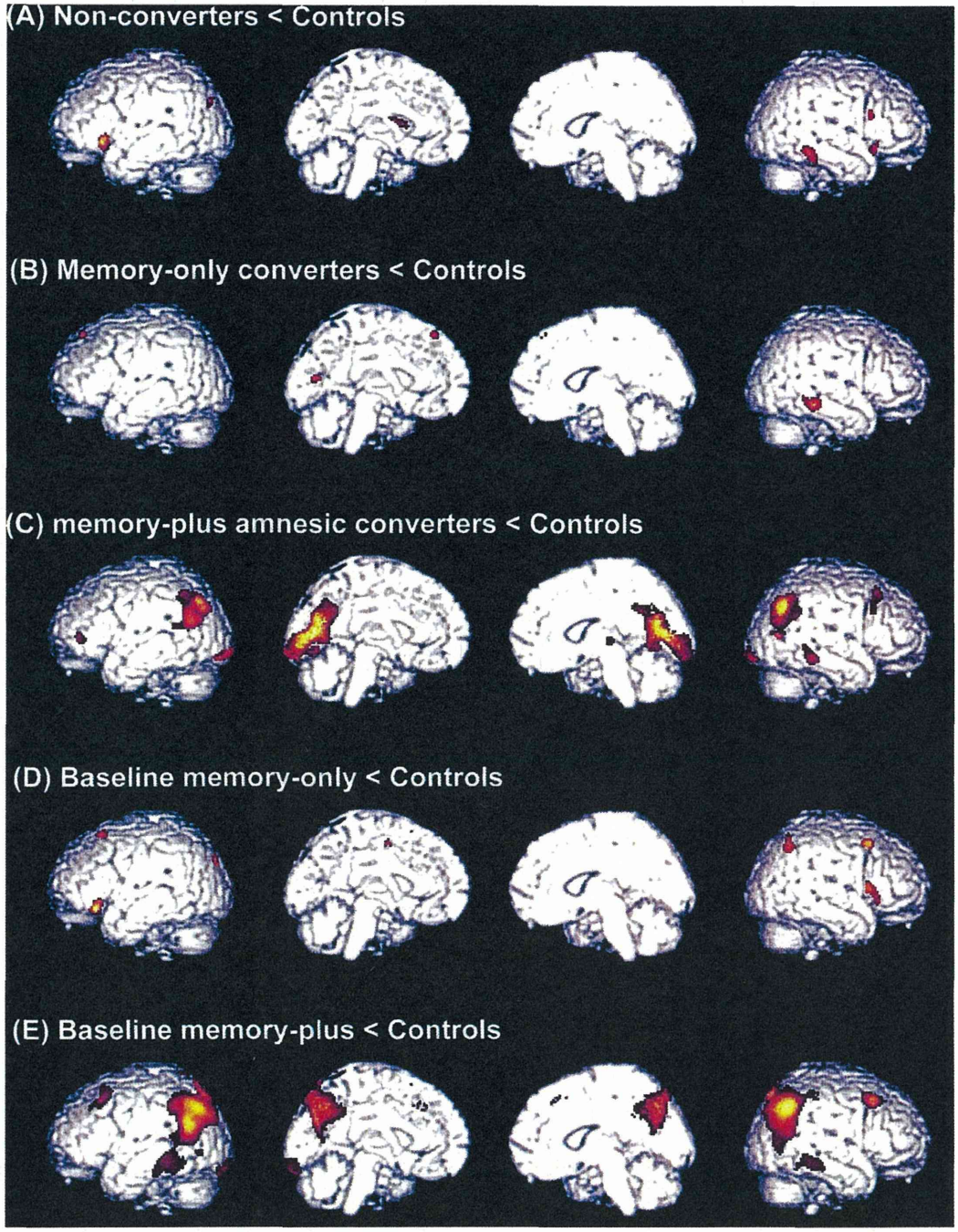

Figure 2. Areas of relative reduction in regional cerebral glucose metabolism in the patient groups compared with controls. Rendered images are shown in the order of the left lateral, left medial, right medial and right lateral.
doi:10.1371/journal.pone.0110547.g002

if the memory-plus converters represented a more advanced stage of the disease than did the other groups, they would not present with an equivalent severity of motor symptoms. Second, a comparison of metabolic patterns between the baseline memory-only and the baseline memory-plus patients showed a double dissociation in which posterior neocortical hypometabolism was more severe in the baseline memory-plus patients, whereas hypometabolism in the medial temporal lobe was more severe in the baseline memory-only patients (**Figures 3D and 3E**). These findings suggest that the brainstem and neocortex may be affected nearly simultaneously without marked limbic involvement in the memory-plus converters and the baseline memory-plus patients. A parallel finding was reported in a population-based cohort study in which incidental Lewy-related pathology was found in the

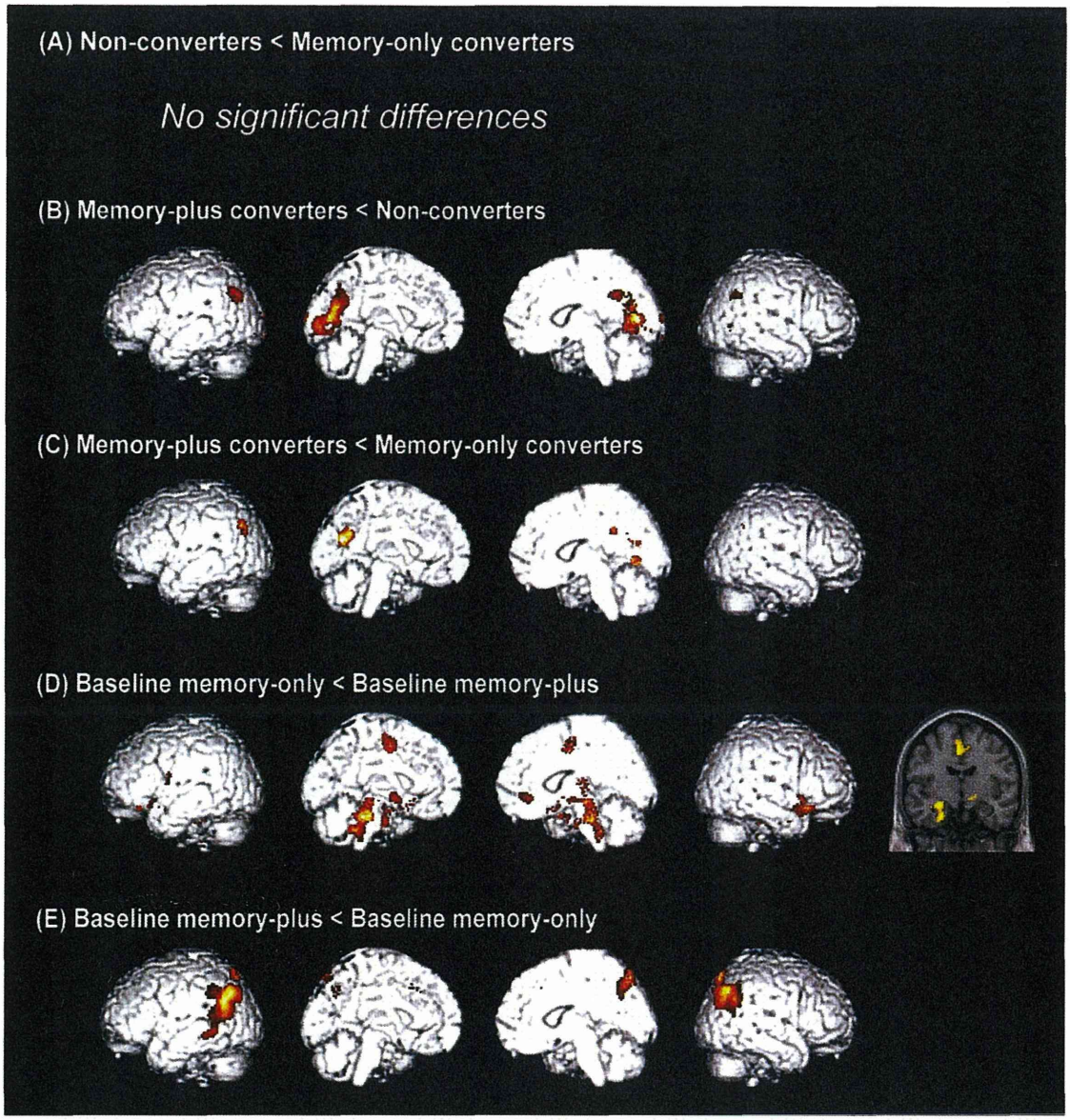

Figure 3. Group comparisons of regional cerebral glucose metabolism at baseline. (A) to (C) show the results of comparisons between patient groups with baseline Clinical Dementia Rating (CDR) 0, and (D) and (E) show the results of comparisons between groups with baseline CDR 0.5. Rendered images are shown in the order of the left lateral, left medial, right medial and right lateral. The left side of a coronal section corresponds to the left side of the brain.
doi:10.1371/journal.pone.0110547.g003

brainstem and neocortex but not in the limbic structures (medial temporal and cingulate cortices) in 3% of cases. [36].

From the viewpoint of prediction and early intervention, it is critical to establish the cognitive and neuroimaging features that are associated with rapid symptomatic deterioration and the future development of dementia. [2] In the current study, the memory-plus converters exhibited clinical features that are consistent with those of the clinical subtype associated with the rapid progression of motor symptoms and/or dementia, including rapid declines in the CDR sum of boxes and the UPDRS part III scores, and non-tremor dominant motor features (**Table 1**). [4,5,6] They had impaired performance on the overlapping-figure test (**Table 1**) and posterior cortical hypometabolism at baseline (**Figures 2C, 3B and 3C**), suggesting that early visuoperceptual impairment and posterior neocortical involvement may be risk factors for rapid symptomatic deterioration and the future development of dementia. The predictive value of visuoperceptual impairment for the future development of dementia in PD has been demonstrated in 3 of the 4 previous longitudinal neuropsychological studies with a follow-up of 2 years or more. [37,38,39,40] Similarly, a recent study demonstrated that patients with non-amnestic multi-domain MCI that had visuoperceptual deficits were associated with bradykinesia and gait disturbance (non-tremor-dominant motor features), suggesting a link to the rapidly progressive, dementia-

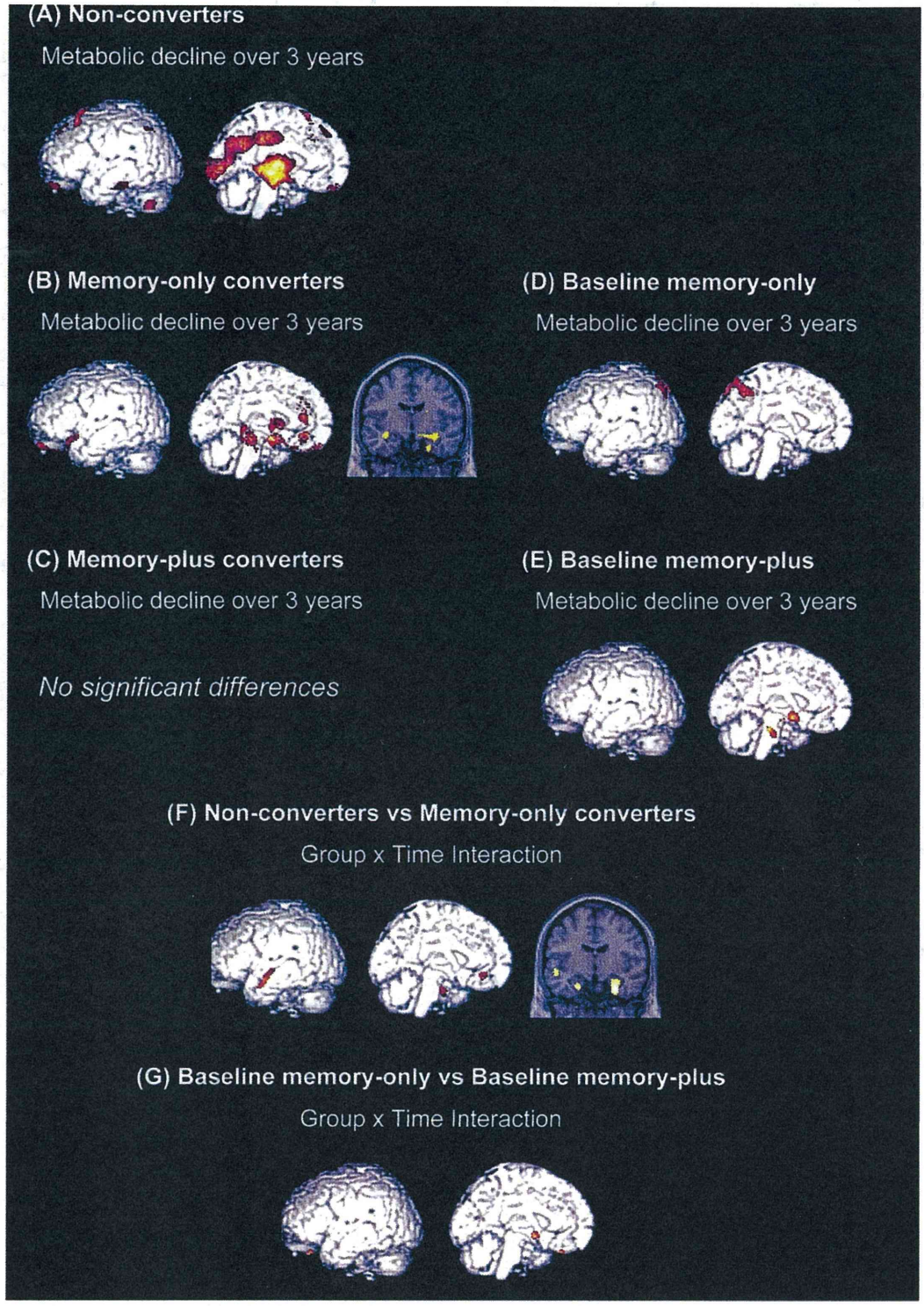

Figure 4. Longitudinal changes in regional cerebral glucose metabolism. (A) to (E) show 3-year metabolic declines in the individual patient groups. (F) and (G) show group x time interactions between the non-converters and the memory-only converters and between the baseline memory-only patients and the baseline memory-plus patients, respectively. Rendered images show the left hemisphere. The left sides of coronal sections correspond to the left side of the brain.
doi:10.1371/journal.pone.0110547.g004

related clinico-pathological subtype. [41] Although there is no neuropathological evidence for the relationship between lesions in the particular cortical regions and rapid symptomatic progression and dementia in PD, a previous longitudinal FDG-PET study demonstrated that parieto-occipital hypometabolism preceded the development of dementia. [42].

Memory impairment and its predictive value for future development of dementia in PD

Recent studies have demonstrated that memory impairment is the most common cognitive deficit in non-demented PD. [43,44] In agreement with these findings, positive scores on the memory subdomain were the most commonly observed CDR findings and baseline impairment in the ADAS-word recall test was found in 45% of the patients in the current study (**Tables 1 and 2**). However, the results of the previous longitudinal neuropsychological studies were split regarding the predictive value of memory impairment for dementia in PD. [37,38,39,40] One of the possible factors associated with this inconsistency is the variability of memory tests. The materials to be remembered (words, stories or figures) and the duration of retention (immediate or delayed) vary from test to test. Another possible factor which contribute to the low predictive value of memory impairment for dementia is the variability of the neural substrates of memory impairment in PD. Memory impairment in PD is associated with both dysexecutive retrieval deficits due to fronto-striatal dopaminergic insufficiency and mnemonic dysfunction due to hippocampal degeneration. [45] In the current study, baseline impairment on the backward digit-span observed in the memory-only converters suggests the possible contribution of executive/working memory deficits to memory complaints in PD (**Table 1**), whereas the relative medial temporal hypometabolism in the memory-only converters and the baseline memory-only patients suggested the role for hippocampal/medial temporal dysfunction (**Figures 3D, 4B and 4F**). Furthermore, a third mechanism of memory impairment is indicated by the findings of the current study; the memory-plus converters and the baseline memory-plus patients did not show significant hypometabolism in the medial temporal lobe despite their obvious memory problems, but they instead showed temporo-parietal and medial parietal hypometabolism (**Figures 2C, 2E, 3B, 3C and 3E**). The involvement of the parietal lobe in memory tasks has been documented in functional neuroimaging studies, but its functional role has been a matter of debate. [46].

Limitations

There are a number of limitations in the current study. First, although we claim that the memory-plus converters represent the rapidly progressive clinical subtype, no significant metabolic changes over 3 years were observed in this patient group. The following reasons can be suggested for this negative finding: (1) the small sample size may have result in a low statistical power; and (2) diffuse metabolic decline across the entire cerebral cortex may have obscured by the proportional scaling in the PET analysis. Consistent with the latter, a supplementary PET analysis in which a cerebellar reference was used instead of the proportional scaling demonstrated a CMRglc reduction over 3 years in the prefrontal cortex in the memory-plus converters (**Figure S1**).

Second, there were substantial inconsistencies between the CDR-based criteria and performance on the individual neuropsychological tests. Although patients with a CDR of 0 were defined as cognitively normal' according to our criteria, some were impaired in one or more neuropsychological tests. This inconsistency is most likely due to the insensitivity of the CDR to slight cognitive impairment, particularly in the executive and visuoperceptual domains. By contrast, neuropsychological tests failed to detect cognitive declines over time in the memory-only converters and memory-plus converters, despite the obvious cognitive deterioration documented by the CDR (**Table 1**). Measuring longitudinal cognitive changes using neuropsychological tests is contaminated by spurious improvement associated with practice effects. [20,21,22,23] Although the neuropsychological tests were administered twice with a relatively long interval of 3 years in the current study, previous studies demonstrated that practice effects persist over 5 years and are strongest between the first and second administrations. [20,47,48] Furthermore, the impact of dopaminergic therapy on cognition and mood should be taken into account in PD patients. A formal definitions of clinically meaningful cognitive decline' in PD should be established in future studies. [29] In addition, the criteria for at-risk state for dementia or PD-MCI should be not only sensitive but also specific. Insensitive criteria would lead to the oversight of at-risk patients of dementia, whereas an overly sensitive and insufficiently specific ones would make every PD patient an at-risk one because almost every PD patient is impaired in some of highly-demanded cognitive tasks.

Third, we separately analyzed the patient groups with a baseline CDR of 0 and those with a CDR of 0.5 and integrated the results obtained from these separate analyses to discuss long-term (more than 3 years) cognitive changes. Our findings and discussion should be examined by studies with longer follow-up periods.

Finally, the reduction in glucose metabolism may reflect not only neurodegeneration itself but also the remote effects of lesions in distant neural structures. In addition, because FDG-PET is unable to differentiate between Alzheimer's disease-related and Lewy-related pathologies, further studies utilizing amyloid-PET and other neuroimaging techniques are necessary to examine these issues.

Supporting Information

Figure S1 The results of a cerebellar-referenced PET analysis for the patient groups with baseline CDR 0 (non-converters, memory-only converters and memory-plus converters). A two-way repeated-measures ANOVA with variables of no interest of age, sex and UPDRS part III score was used. The statistical threshold was set at an uncorrected $p<0.001$ at the voxel level and at 20 voxels at the cluster level.
(TIF)

Author Contributions

Conceived and designed the experiments: YS YN TB EM. Performed the experiments: YN TB MU KY TI YH KH AT. Analyzed the data: YS YN. Contributed reagents/materials/analysis tools: HF MA TH EM. Contributed to the writing of the manuscript: YS YN.

References

1. Kehagia AA, Barker RA, Robbins TW (2010) Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol 9: 1200–1213.
2. Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, et al. (2011) MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord 26: 1814–1824.

3. Baba T, Kikuchi A, Hirayama K, Nishio Y, Hosokai Y, et al. (2012) Severe olfactory dysfunction is a prodromal symptom of dementia associated with Parkinson's disease: a 3 year longitudinal study. Brain 135: 161–169.
4. Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, et al. (2006) Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 77: 585–589.
5. Lewis SJ, Foltynie T, Blackwell AD, Robbins TW, Owen AM, et al. (2005) Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. J Neurol Neurosurg Psychiatry 76: 343–348.
6. van Rooden SM, Colas F, Martinez-Martin P, Visser M, Verbaan D, et al. (2011) Clinical subtypes of Parkinson's disease. Mov Disord 26: 51–58.
7. Halliday GM, Holton JL, Revesz T, Dickson DW (2011) Neuropathology underlying clinical variability in patients with synucleinopathies. Acta Neuropathol 122: 187–204.
8. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT (2004) Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 127: 791–800.
9. Hosokai Y, Nishio Y, Hirayama K, Takeda A, Ishioka T, et al. (2009) Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment. Mov Disord 24: 854–862.
10. Huang C, Mattis P, Tang C, Perrine K, Carbon M, et al. (2007) Metabolic brain networks associated with cognitive function in Parkinson's disease. Neuroimage 34: 714–723.
11. Nagano-Saito A, Washimi Y, Arahata Y, Kachi T, Lerch JP, et al. (2005) Cerebral atrophy and its relation to cognitive impairment in Parkinson disease. Neurology 64: 224–229.
12. Summerfield C, Junque C, Tolosa E, Salgado-Pineda P, Gomez-Anson B, et al. (2005) Structural brain changes in Parkinson disease with dementia: a voxel-based morphometry study. Arch Neurol 62: 281–285.
13. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C (2005) Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Ann Neurol 58: 773–776.
14. Compta Y, Parkkinen L, O'Sullivan SS, Vandrovcova J, Holton JL, et al. (2011) Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain 134: 1493–1505.
15. Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, et al. (2009) A clinico-pathological study of subtypes in Parkinson's disease. Brain 132: 2947–2957.
16. Bohnen NI, Muller ML (2013) In vivo neurochemical imaging of olfactory dysfunction in Parkinson's disease. J Neural Transm 120: 571–576.
17. Nishio Y, Hirayama K, Takeda A, Hosokai Y, Ishioka T, et al. (2010) Corticolimbic gray matter loss in Parkinson's disease without dementia. Eur J Neurol 17: 1090–1097.
18. Amrerical Psychiatric Association. (1987) Diagnostic and Statistical Manual of Mental Disorders. 3rd, revised.
19. Morris JC (1997) Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 9 Suppl 1: 173–176; discussion 177–178.
20. Abner EL, Dennis BC, Mathews MJ, Mendiondo MS, Caban-Holt A, et al. (2012) Practice effects in a longitudinal, multi-center Alzheimer's disease prevention clinical trial. Trials 13: 217.
21. Duff K, Beglinger LJ, Schultz SK, Moser DJ, McCaffrey RJ, et al. (2007) Practice effects in the prediction of long-term cognitive outcome in three patient samples: a novel prognostic index. Arch Clin Neuropsychol 22: 15–24.
22. Machulda MM, Pankratz VS, Christianson TJ, Ivnik RJ, Mielke MM, et al. (2013) Practice Effects and Longitudinal Cognitive Change in Normal Aging vs. Incident Mild Cognitive Impairment and Dementia in The Mayo Clinic Study of Aging. Clin Neuropsychol 27: 1247–1264.
23. Mathews M, Abner E, Caban-Holt A, Kryscio R, Schmitt F (2013) CERAD practice effects and attrition bias in a dementia prevention trial. Int Psychogeriatr 25: 1115–1123.
24. Mathews M, Abner E, Kryscio R, Jicha G, Cooper G, et al. (2014) Diagnostic accuracy and practice effects in the National Alzheimer's Coordinating Center Uniform Data Set neuropsychological battery. Alzheimers Dement. doi: 10.1016/j.jalz.2013.11.007.
25. Doody RS, Ferris SH, Salloway S, Sun Y, Goldman R, et al. (2009) Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurology 72: 1555–1561.
26. Dubois B, Tolosa E, Katzenschlager R, Emre M, Lees AJ, et al. (2012) Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. Mov Disord 27: 1230–1238.
27. Mori E, Ikeda M, Kosaka K (2012) Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. Ann Neurol 72: 41–52.
28. Rogers SL (1998) Perspectives in the management of Alzheimer's disease: clinical profile of donepezil. Dement Geriatr Cogn Disord 9 Suppl 3: 29–42.
29. Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D, et al. (2012) Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 27: 349–356.
30. Folstein MF, Robins LN, Helzer JE (1983) The Mini-Mental State Examination. Arch Gen Psychiatry 40: 812.
31. Mohs RC, Rosen WG, Davis KL (1983) The Alzheimer's disease assessment scale: an instrument for assessing treatment efficacy. Psychopharmacol Bull 19: 448–450.
32. Ishioka T, Hirayama K, Hosokai Y, Takeda A, Suzuki K, et al. (2011) Illusory misidentifications and cortical hypometabolism in Parkinson's disease. Mov Disord 26: 837–843.
33. Schrag A, Dodel R, Spottke A, Bornschein B, Siebert U, et al. (2007) Rate of clinical progression in Parkinson's disease. A prospective study. Mov Disord 22: 938–945.
34. Reijnders JS, Ehrt U, Lousberg R, Aarsland D, Leentjens AF (2009) The association between motor subtypes and psychopathology in Parkinson's disease. Parkinsonism Relat Disord 15: 379–382.
35. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, et al. (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24: 197–211.
36. Zaccai J, Brayne C, McKeith I, Matthews F, Ince PG (2008) Patterns and stages of alpha-synucleinopathy: Relevance in a population-based cohort. Neurology 70: 1042–1048.
37. Janvin CC, Larsen JP, Aarsland D, Hugdahl K (2006) Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Mov Disord 21: 1343–1349.
38. Levy G, Jacobs DM, Tang MX, Cote LJ, Louis ED, et al. (2002) Memory and executive function impairment predict dementia in Parkinson's disease. Mov Disord 17: 1221–1226.
39. Mahieux F, Fenelon G, Flahault A, Manifacier MJ, Michelet D, et al. (1998) Neuropsychological prediction of dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 64: 178–183.
40. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA (2007) Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 130: 1787–1798.
41. Goldman JG, Weis H, Stebbins G, Bernard B, Goetz CG (2012) Clinical differences among mild cognitive impairment subtypes in Parkinson's disease. Mov Disord 27: 1129–1136.
42. Bohnen NI, Koeppe RA, Minoshima S, Giordani B, Albin RL, et al. (2011) Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study. J Nucl Med 52: 848–855.
43. Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, et al. (2010) Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. Neurology 75: 1062–1069.
44. Hanna-Pladdy B, Jones K, Cabanban R, Pahwa R, Lyons KE (2013) Predictors of mild cognitive impairment in early-stage Parkinson's disease. Dement Geriatr Cogn Dis Extra 3: 168–178.
45. Aarsland D, Bronnick K, Fladby T (2011) Mild cognitive impairment in Parkinson's disease. Curr Neurol Neurosci Rep 11: 371–378.
46. Wagner AD, Shannon BJ, Kahn I, Buckner RL (2005) Parietal lobe contributions to episodic memory retrieval. Trends Cogn Sci 9: 445–453.
47. Rabbitt P, Lunn M, Ibrahim S, McInnes L (2009) Further analyses of the effects of practice, dropout, sex, socio-economic advantage, and recruitment cohort differences during the University of Manchester longitudinal study of cognitive change in old age. Q J Exp Psychol (Hove) 62: 1859–1872.
48. Rabbitt P, Lunn M, Wong D, Cobain M (2008) Age and ability affect practice gains in longitudinal studies of cognitive change. J Gerontol B Psychol Sci Soc Sci 63: P235–P240.
49. Abe N, Fujii T, Hirayama K, Takeda A, Hosokai Y, et al. (2009) Do parkinsonian patients have trouble telling lies? The neurobiological basis of deceptive behaviour. Brain 132: 1386–1395.