

Alzheimer's disease pattern of brain atrophy predicts cognitive decline in Parkinson's disease

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Research suggests overlap in brain regions undergoing neurodegeneration in Parkinson's and Alzheimer's disease. To assess the clinical significance of this, we applied a validated Alzheimer's disease-spatial pattern of brain atrophy to patients with Parkinson's disease with a range of cognitive abilities to determine its association with cognitive performance and decline. At baseline, 84 subjects received structural magnetic resonance imaging brain scans and completed the Dementia Rating Scale-2, and new robust and expanded Dementia Rating Scale-2 norms were applied to cognitively classify participants. Fifty-nine non-demented subjects were assessed annually with the Dementia Rating Scale-2 for two additional years. Magnetic resonance imaging scans were quantified using both a region of interest approach and voxel-based morphometry analysis, and a method for quantifying the presence of an Alzheimer's disease spatial pattern of brain atrophy was applied to each scan. In multivariate models, higher Alzheimer's disease pattern of atrophy score was associated with worse global cognitive performance ($\beta = -0.31$, $P = 0.007$), including in non-demented patients ($\beta = -0.28$, $P = 0.05$). In linear mixed model analyses, higher baseline Alzheimer's disease pattern of atrophy score predicted long-term global cognitive decline in non-demented patients [$F(1, 110) = 9.72$, $P = 0.002$], remarkably even in those with normal cognition at baseline [$F(1, 80) = 4.71$, $P = 0.03$]. In contrast, in cross-sectional and longitudinal analyses there was no association between region of interest brain volumes and cognitive performance in patients with Parkinson's disease with normal cognition. These findings support involvement of the hippocampus and parietal-temporal cortex with cognitive impairment and long-term decline in Parkinson's disease. In addition, an Alzheimer's disease pattern of brain atrophy may be a preclinical biomarker of cognitive decline in Parkinson's disease.

Keywords: Alzheimer's disease; dementia; mild cognitive impairment; Parkinson's disease; neurodegeneration

Abbreviations: DRS = Dementia Rating Scale; RAVENS = Regional Analysis of Volumes Examined in Normalized Space; SPARE-AD = Spatial Pattern of Atrophy for Recognition of Alzheimer's Disease; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Patients with Parkinson's disease are at an increased risk of developing dementia, with cumulative prevalence rates up to 80% reported (Aarsland *et al.*, 2003; Hely *et al.*, 2008). In addition, ~25% of non-demented patients with Parkinson's disease meet neuropsychological test criteria for mild cognitive impairment (Aarsland *et al.*, 2010), most of whom eventually convert to Parkinson's disease with dementia (Janvin *et al.*, 2006).

The neural substrate of cognitive decline in Parkinson's disease is a subject of continued debate (Farlow and Cummings, 2008). Parkinson's disease dementia is associated with diffuse subcortical and cortical Lewy body disease pathology, including the transentorhinal and entorhinal cortices, hippocampus, other limbic cortex regions, and neocortex (Galvin *et al.*, 1999; Braak *et al.*, 2005; Beach *et al.*, 2009). However, many patients with Parkinson's disease also have Alzheimer's disease-related neuropathological changes on autopsy (Lieberman, 1997; Sabbagh *et al.*, 2009; Compta *et al.*, 2011), including in the hippocampus (Apaydin *et al.*, 2002). In addition, lower CSF β -amyloid_{1–42} (A β 42) levels have been detected in *de novo* patients with Parkinson's disease (Alves *et al.*, 2010) and decrease further across the stages of cognitive impairment (Compta *et al.*, 2009), are associated with a range of cognitive deficits in non-demented patients with Parkinson's disease (Compta *et al.*, 2009; Alves *et al.*, 2010), and predict long-term cognitive decline (Siderowf *et al.*, 2010). At a minimum there appears to be some overlap in the neurodegenerative process that occurs in Parkinson's disease and Alzheimer's disease, and the pathological processes may even be synergistic (Masliah *et al.*, 2001; Clinton *et al.*, 2010).

Structural brain imaging allows *in vivo* determination of regional neurodegeneration. In Parkinson's disease, studies using a range of imaging analyses have reported diffuse parietal–temporal and prefrontal cortex atrophy in patients with Parkinson's disease with dementia (Camicioli *et al.*, 2003; Burton *et al.*, 2004; Junqué *et al.*, 2005; Tam *et al.*, 2005; Kenny *et al.*, 2008), but most studies have not controlled for possible confounding variables and some have reported an association between regional brain volumes and cognitive performance (Camicioli *et al.*, 2003; Tam *et al.*, 2005; Ibarretxe-Bilbao *et al.*, 2008; Sanchez-Castaneda *et al.*, 2009; Apostolova *et al.*, 2010). In patients with Parkinson's disease who are non-demented or have mild cognitive impairment, varying degrees of atrophy have been reported for the parietal–temporal cortex, prefrontal cortex, hippocampus and amygdala (Brück *et al.*, 2004; Beyer *et al.*, 2007; Ibarretxe-Bilbao *et al.*, 2008; Lyoo *et al.*, 2010; Song *et al.*, 2011), again with mixed evidence for correlation between atrophy and either neuropsychological test performance or conversion to Parkinson's disease with dementia (Brück *et al.*, 2004; Ibarretxe-Bilbao *et al.*, 2008; Aybek *et al.*, 2009; Jokinen *et al.*, 2009; Martin *et al.*, 2009).

Voxel-based morphometry analyses aim to identify group differences, but are not suitable for deriving diagnostic biomarkers on an individual patient basis. Therefore, we used a high-dimensional pattern classification methodology developed to classify individual scans as belonging to either healthy controls or patients with

Alzheimer's disease (Fan *et al.*, 2007, 2008a; Davatzikos *et al.*, 2008). The pattern classification method provides an individual-based score called the Spatial Pattern of Abnormalities for Recognition of Alzheimer's disease (SPARE-AD) score, which has been determined via a 'training' database of healthy control subjects and patients with Alzheimer's disease and uses atrophy in the following regions: most of the temporal lobe (especially the hippocampus, entorhinal cortex, inferior temporal cortex and uncus), precuneus, posterior cingulate and peri-hippocampal white matter.

Given the limited understanding of evolution and patterns of neurodegeneration related to cognitive impairment in Parkinson's disease, we report: (i) the relationship between SPARE-AD scores and cognitive performance in a cohort of patients with Parkinson's disease with a range of cognitive abilities; and (ii) the association between baseline SPARE-AD score and long-term cognitive decline in non-demented Parkinson's disease patients, including those with normal cognition.

Materials and methods

Participants

Baseline data ($n = 84$) were obtained as part of the University of Pennsylvania Center of Excellence for Research on Neurodegenerative Diseases (CERN) (<http://cernd.org/>), a cross-sectional study that evaluated individuals at risk for late-life dementia with a range of biomarkers. Based on standardized Dementia Rating Scale (DRS-2) score there were 69 non-demented patients with Parkinson's disease at baseline, and 60 of these participants agreed to enrol in the Penn Udall Center for Parkinson's Research at the University of Pennsylvania (<http://www.med.upenn.edu/udall/>) and were followed longitudinally and administered the DRS-2 annually for at least two additional years (i.e. 2-year follow-up). One of these subjects had a >20% decline in DRS-2 score during this period, was considered an outlier, and was removed from the longitudinal sample. For the remaining 59 non-demented Parkinson's disease subjects followed long-term, none had a >10% increase in DRS-2 score, and only two subjects had a >10% decrease in DRS-2 score from baseline, consistent with what would be expected in a Parkinson's disease population over this time period (Troster *et al.*, 2007).

Disease severity was based on UPDRS (Unified Parkinson's Disease Rating Scale) motor score and Hoehn and Yahr stage (Fahn *et al.*, 1987). Levodopa and dopamine agonist dosages were combined and are presented as levodopa equivalent daily dosage (Hobson *et al.*, 2005). Participants were categorized as having postural instability–gait difficulty subtype (as opposed to non-postural instability–gait difficulty subtype) based on published criteria using UPDRS scores (Jankovic *et al.*, 1990). Psychosis was assessed with the UPDRS Part I 'Thought Disorder' item. Given the small number of participants rated as having psychotic symptoms (i.e. hallucinations or delusions) and the association between vivid dreaming and both psychosis (Arnulf *et al.*, 2000; Forsaa *et al.*, 2010; Goetz *et al.*, 2010) and long-term cognitive decline (Santangelo *et al.*, 2007) in Parkinson's disease, we included presence of 'thought disorder' as a variable, defined as any positive score on the UPDRS Part I thought disorder item (i.e. vivid dreaming, hallucinations or delusions).

Depression severity was assessed with the 15-item Geriatric Depression Scale (GDS-15) (Sheikh and Yesavage, 1986).

Neuropsychological testing and cognitive classification

The DRS-2 (Jurica *et al.*, 2001), a measure of global cognitive performance, has been validated as an assessment instrument for Parkinson's disease with dementia (Llebaria *et al.*, 2008), discriminates between Parkinson's disease with mild cognitive impairment and Parkinson's disease with dementia (Martin *et al.*, 2008), and predicts long-term conversion to Parkinson's disease with dementia (Levy *et al.*, 2002). Cognitive categories were defined on the basis of recommended (Jurica *et al.*, 2001) age-standardized DRS-2 scores using new robust and expanded norms (Pedraza *et al.*, 2010): (i) Parkinson's disease with normal cognition (DRS-2 score of >8 , which corresponds to >28 th percentile); (ii) Parkinson's disease with mild cognitive impairment (DRS-2 score 6–8 inclusive, 6–28th percentile); and (iii) Parkinson's disease with dementia (DRS-2 <6 , <6 th percentile). The DRS-2 total score is constructed from five subscores: memory, attention, initiation/perseveration, construction and conceptualization.

Structural imaging and analyses

Image acquisition

The data sets included standard T_1 -weighted magnetic resonance images acquired sagittally using volumetric 3D magnetization prepared rapid gradient echo with 1.25×1.25 mm in-plane spatial resolution and 1.2 mm thick sagittal slices (8° flip angle) performed on 1.5T scanners.

Image analysis

CERND MRI analysis was based on an image processing protocol developed at the Section of Biomedical Image Analysis (SBIA) of the Department of Radiology at the University of Pennsylvania and previously described in detail (Goldszal *et al.*, 1998). Global volumes were obtained via an automated segmentation technique that labels the brain into white matter, grey matter, CSF and ventricles, after a sequence of preprocessing steps that remove extracranial material and aligns each scan with the anterior–posterior commissure plane. Quantification of regional brain volumes is performed through an elastic atlas warping algorithm that coregisters a template of brain anatomy with each individual scan (Shen and Davatzikos, 2002). The template has 97 regions of interest based on the Montreal Neurological Institute (MNI) template, which are transferred to individual scans, so that regional volumetric and functional measurements can be obtained. These regions of interest were then collapsed into 14 larger regions of interest. To limit the number of variables presented, we calculated the average of the right and left volumes for each region of interest and present grey matter volumes only (hippocampus, medial temporal lobe, temporal lobe, parietal lobe, occipital lobe, frontal lobe, insula, anterior cingulate and posterior cingulate).

In order to further characterize local atrophy in the brain, a voxel-based morphometry analysis, named Regional Analysis of Volumes Examined in Normalized Space (RAVENS) (Shen and Davatzikos, 2003), was performed. This approach computes grey matter, white matter and ventricle tissue density maps separately in a common coordinate system after spatial normalization. The RAVENS approach bears similarities with the 'optimized voxel-based

morphometry' approach, except it uses a high-dimensional image warping algorithm termed HAMMER (Shen and Davatzikos, 2002, 2003). Moreover, it uses tissue-preserving transformations, which ensure that image warping absolutely preserves the amount of grey matter, white matter and CSF tissue present in an individual's scan. Thus, the RAVENS value in a certain region in the reference space is directly proportional to the amount of tissue present in the respective anatomical region of a subject's scan. Voxel dimensions were $2.0 \times 2.0 \times 2.0$ mm.

Pattern classification

Although voxel-based morphometry analysis aims to identify group differences, it is not suitable for deriving diagnostic biomarkers on an individual patient basis. Therefore, we applied to our Parkinson's disease sample a high-dimensional pattern classification approach that was generated using healthy controls and patients with Alzheimer's disease, called COMPARE (Classification of Morphological Patterns Using Adaptive Regional Elements) (Fan *et al.*, 2007, 2008a; Davatzikos *et al.*, 2008). This approach considers all brain regions jointly, and identifies a minimal set of regions whose volumes jointly maximally differentiate the two groups under consideration, on an individual scan basis. Leave-one-out cross-validation is used to test this classification scheme on data sets not used for training, and obtain a relatively unbiased estimate of the generalization power of the classifier to new patients. The pattern classification method provides an individually calculated score, called the SPARE-AD score. For a classifier constructed from healthy controls and patients with Alzheimer's disease, a positive SPARE-AD score implies Alzheimer's disease-like pattern of cerebral atrophy, while a negative score reflects a brain structure associated with normal structure (Fig. 1). The software used to generate SPARE-AD scores is available through the Section of Biomedical Image Analysis at the University of Pennsylvania (<http://www.rad.upenn.edu/sbia>).

Statistical analysis

Chi-square tests, t -tests (with Levene's test for equality of variances), non-parametric tests to compare medians and ANOVA with *post hoc* analyses (Tukey's test) were used for between-group comparisons on clinical, demographic, neuropsychological and imaging variables. To determine the association between SPARE-AD score or regions of interest and cognitive performance, all clinical and demographic variables of interest (i.e. those previously associated with cognitive impairment in Parkinson's disease) that were associated with global cognitive performance on bivariate analysis were entered into linear regression models.

Linear mixed model analysis (Laird and Ware, 1982) was used to determine if baseline SPARE-AD score and other baseline demographic and clinical variables predicted cognitive decline over a 2-year period in non-demented patients with Parkinson's disease and patients with Parkinson's disease with normal cognition, and all relevant clinical, demographic and imaging variables that might be associated with long-term cognitive decline were included as covariates. The mixed model procedure accounts for the correlations that are due to the repeated measurements of DRS-2 over time in the same patients. In our implementation of the mixed model, the intercept and the regression coefficient for the follow-up time (visit) were treated as random effects such that each subject has a unique intercept and regression coefficient for the follow-up time. The population mean coefficient for the follow-up time was obtained by averaging across the subject

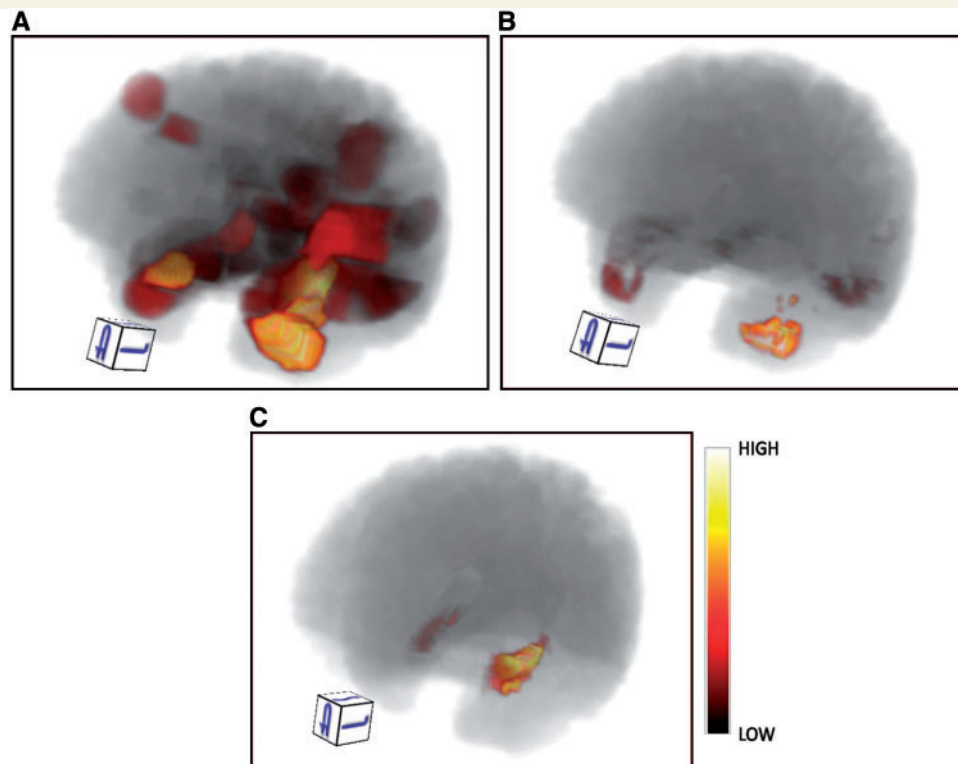


Figure 1 3D rendering of the brain COMPARE maps used to generate SPARE-AD scores that distinguish healthy controls from patients with Alzheimer's disease. (A) Entire brain, (B) medial temporal lobe and (C) hippocampus. The colour scale is graded (low to high) based on significance for that region/pattern in the COMPARE classification.

specific regression coefficients for the follow-up time. This population mean coefficient estimated the average yearly change for DRS-2 score. The following covariates were adjusted in the mixed-effect models and their regression coefficients were treated as fixed effects: baseline DRS-2 score, SPARE-AD score, age, Hoehn and Yahr stage (entered as a dichotomous variable based on the median score due to significant skewing toward mild disease in the longitudinal sample), Parkinson's disease duration, and postural instability–gait difficulty subtype in the primary models. In an additional model, sex, education, total levodopa equivalent daily dosage, Geriatric Depression Scale-15 score and presence of thought disorder were also added as covariates, either individually or as a group. The predictive ability of baseline SPARE-AD and other demographic and clinical variables on cognitive decline was examined through their interactions with follow-up time.

Normality assumptions were checked whenever the tests required normality assumption. All statistical tests were two-sided. Statistical significance was set at $P \leq 0.05$. All analyses were conducted using the PASW Statistics (version 18.0) software.

Results

Participant characteristics

At baseline, the mean (SD; range) DRS-2 score for the entire sample was 134.2 (12.5; 74–144), and using recommended age-corrected cut-off scores, 51 patients (60.7%) were classified

as having Parkinson's disease with normal cognition, 18 (21.4%) as Parkinson's disease with mild cognitive impairment and 15 (17.9%) as Parkinson's disease with dementia. For the 59 non-demented patients with Parkinson's disease (i.e. combination of Parkinson's disease with normal cognition and Parkinson's disease with mild cognitive impairment) followed longitudinally, the average standardized DRS-2 score at baseline was approximately the 50th percentile; for the subset of 43 patients with Parkinson's disease with normal cognition followed longitudinally, the average standardized DRS-2 score was approximately the 65th percentile. Baseline demographic and clinical characteristics for the cross-sectional ($n = 84$) and longitudinal ($n = 59$) cohorts of patients are presented in Table 1.

Cross-sectional analyses

SPARE-AD score as correlate of cognitive impairment in entire cohort

On bivariate analysis, increasing age, increasing Parkinson's disease duration, higher Hoehn and Yahr stage, higher UPDRS motor score, and postural instability–gait difficulty subtype were associated with worse total DRS-2 score, so these variables were included as covariates in subsequent linear regression models. There was no association between cognitive performance and intracranial volume, sex, education, total levodopa equivalent daily dosage, Geriatric Depression Scale-15 score and presence

Table 1 Subject characteristics at baseline

Variable [mean (SD), % or median]	Cross-sectional cohort (n = 84)	Longitudinal cohort (n = 59)
Clinical and demographic		
Age [mean (SD) years]	70.6 (6.5)	70.0 (6.4)
Sex (% male)	66.7%	62.7%
Education [mean (SD) years]	15.7 (2.7)	16.1 (2.3)
PD duration [mean (SD) years]	7.7 (4.8)	7.4 (4.1)
Hoehn and Yahr stage [median (interquartile range)]	2.0 (2.0–2.5)	2.0 (2.0–2.0)
Total LEDD [mean (SD) mg/day]	554 (379) ^a	525 (373)
UPDRS motor score [mean (SD)]	22.0 (10.2)	20.3 (9.2)
PIGD subtype (% yes)	69.9 ^b	58.6 ^c
Thought disorder (% yes)	25.9 ^d	27.1
GDS-15 [mean (SD)]	2.5 (2.5) ^e	2.3 (2.5)
DRS-2		
Total raw score [mean (SD)]	134.2 (12.5)	138.6 (3.9)
Age-adjusted standardized score [mean (SD)]	9.2 (3.9)	10.4 (2.8)
PD-NC (% of sample)	60.7	72.9
PD-MCI (%)	21.4	27.1
PDD (%)	17.9	–

a n = 83.

b n = 83.

c n = 58.

d n = 81.

e n = 79.

GDS = Geriatric Depression Scale; LEDD = levodopa equivalent daily dosage; PD = Parkinson's disease; PDD = Parkinson's disease with dementia; PD-MCI = Parkinson's disease with mild cognitive impairment; PDNC = Parkinson's disease with normal cognition; PIGD = postural instability–gait difficulty.

Table 2 SPARE-AD score and global cognitive performance^a

Models	Unstandardized coefficients		Standardized coefficients Beta	t	P-value
	B	Std. Error			
Model 1^b					
Age	–0.102	0.207	–0.054	–0.495	0.62
PD duration	–0.516	0.267	–0.199	–1.935	0.06
Hoehn and Yahr stage	–4.851	1.824	–0.288	–2.659	0.01
PIGD subtype	–0.633	2.638	–0.023	–0.240	0.81
SPARE-AD score	–4.841	1.748	–0.310	–2.769	0.007
Model 2^c					
Age	–0.068	0.213	–0.036	–0.320	0.75
PD duration	–0.625	0.263	–0.241	–2.380	0.02
UPDRS motor score	–0.285	0.127	–0.233	–2.242	0.03
PIGD subtype	–1.562	2.649	–0.058	–0.590	0.56
SPARE-AD score	–5.454	1.721	–0.350	–3.169	0.002

a Total raw DRS-2 score.

b Linear regression model with baseline DRS-2 score as dependent variable and Hoehn and Yahr stage as measure of disease severity [$F = 8.53$ ($df = 5,77$), $P < 0.001$].c Linear regression model with baseline DRS-2 score as dependent variable and UPDRS motor score as measure of disease severity [$F = 7.95$ ($df = 5,77$), $P < 0.001$].

PD = Parkinson's disease; PIGD = postural instability–gait difficulty.

of thought disorder. As Hoehn and Yahr stage and UPDRS motor score are both measures of disease severity and were highly correlated, only one of these variables was entered into a given model, with Hoehn and Yahr stage used preferentially.

In a linear regression model including SPARE-AD score and the aforementioned covariates, higher SPARE-AD score ($\beta = -0.31$, $P = 0.007$) and increasing Hoehn and Yahr stage ($\beta = -0.29$, $P = 0.01$) were independent predictors of worse

total DRS-2 score (Table 2, Model 1). In a model that substituted UPDRS motor score for Hoehn and Yahr stage, higher SPARE-AD score ($\beta = -0.35$, $P = 0.002$), higher UPDRS motor score ($\beta = -0.23$, $P = 0.03$), and longer Parkinson's disease duration ($\beta = -0.24$, $P = 0.02$) predicted worse global cognition (Table 2, Model 2).

Substituting DRS-2 subtest scores for DRS-2 total score in the original model, only higher SPARE-AD score ($\beta = -0.32$,

$P = 0.007$) was associated with worse memory. Higher SPARE-AD score ($\beta = -0.38$, $P = 0.004$) and longer Parkinson's disease duration ($\beta = -0.23$, $P = 0.04$) predicted worse conceptualization performance, and higher SPARE-AD score ($\beta = -0.25$, $P = 0.04$) and increasing Hoehn and Yahr stage ($\beta = -0.23$, $P = 0.05$) predicted worse initiation/perseveration performance. Only increasing Hoehn and Yahr stage predicted worse construction ($\beta = -0.32$, $P = 0.01$) and attention scores ($\beta = -0.41$, $P = 0.001$).

SPARE-AD score across cognitive categories

SPARE-AD scores increased across patients with Parkinson's disease with normal cognition, Parkinson's disease with mild cognitive impairment and patients with Parkinson's disease with dementia [$F = 3.56$ ($df = 2,81$), $P = 0.03$] with a significant difference between patients with Parkinson's disease with dementia and Parkinson's disease with normal cognition ($P = 0.03$) (Fig. 2).

Including only non-demented patients with Parkinson's disease in a multivariate model, only higher SPARE-AD score ($\beta = -0.28$, $P = 0.05$) predicted worse global cognitive performance (Table 3). Including patients with Parkinson's disease with normal cognition only, there was a suggestion only for higher SPARE-AD score ($\beta = -0.29$, $P = 0.06$) predicting lower DRS-2 score.

Substituting regions of interest individually into the model for SPARE-AD score, smaller hippocampal ($\beta = 0.28$, $P = 0.03$), medial temporal lobe ($\beta = 0.25$, $P = 0.04$), and temporal lobe ($\beta = 0.27$, $P = 0.03$) volumes predicted worse DRS-2 score in non-demented patients with Parkinson's disease, but no individual region of interest predicted DRS-2 performance in patients with Parkinson's disease with normal cognition (Table 3).

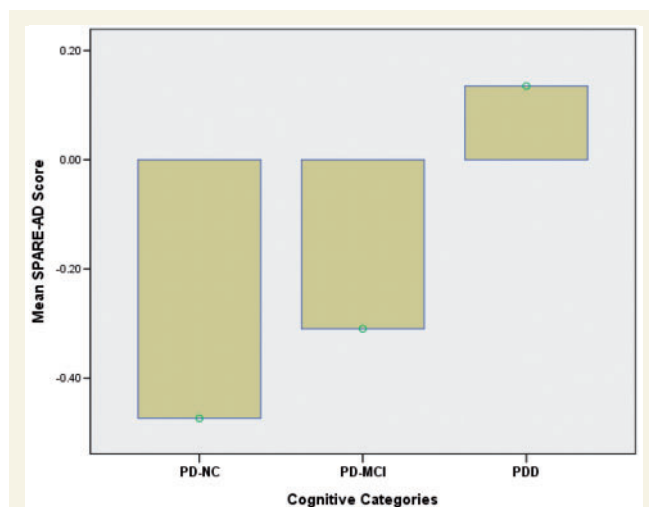


Figure 2 Means plot SPARE-AD score. PDD = Parkinson's disease with dementia; PD-MCI = Parkinson's disease with mild cognitive impairment; PD-NC = Parkinson's disease with normal cognition.

Longitudinal analyses

SPARE-AD score as predictor of long-term cognitive decline in non-demented patients

DRS-2 scores decreased significantly from baseline [mean (SD) = 138.6 (3.9)] to the end of Year 2 [135.6 (7.2); $F = 22.1$ (1,117), $P < 0.001$] in non-demented Parkinson's disease patients. In the linear mixed model analysis with the primary covariates entered, higher baseline SPARE-AD score [$F(1, 110) = 9.72$, $P = 0.002$], increasing age [$F(1, 110) = 9.59$, $P = 0.002$], and postural instability–gait difficulty subtype [$F(1, 110) = 4.84$, $P = 0.03$] predicted long-term decline in DRS-2 score (Table 4, Model 1).

Entering other covariates of interest, either as a group (Table 4, Model 2) or individually (data not shown), only higher baseline SPARE-AD score [$F(1, 105) = 7.69$, $P = 0.007$], increasing age [$F(1, 105) = 5.96$, $P = 0.02$], and postural instability–gait difficulty subtype [$F(1, 105) = 5.62$, $P = 0.02$] predicted long-term cognitive decline. Serially substituting all regions of interest into the model for SPARE-AD score, no baseline region of interest volume predicted decline in DRS-2 score over time (data not shown).

SPARE-AD score as predictor of long-term cognitive decline in patients with Parkinson's disease with normal cognition

In mixed model analyses that included only patients with Parkinson's disease with normal cognition ($n = 43$) and the primary covariates (i.e. age, Hoehn and Yahr stage, Parkinson's disease duration, postural instability–gait difficulty subtype and SPARE-AD score), only higher baseline SPARE-AD score [$F(1, 80) = 4.71$, $P = 0.03$] and increasing age [$F(1, 80) = 6.85$, $P = 0.01$] predicted worsening global cognitive performance over time. Serially substituting all regions of interest into the model for SPARE-AD score, no baseline region of interest volume predicted decline in DRS-2 score over time in patients with Parkinson's disease with normal cognition (data not shown).

Discussion

The specific physiological, biochemical and anatomical changes that underlie the development of cognitive impairment in Parkinson's disease are not well understood. Diffuse Lewy body deposition (Aarsland *et al.*, 2005), brain atrophy (Song *et al.*, 2011) and metabolic deficits (Peppard *et al.*, 1992) are the most commonly documented correlates of Parkinson's disease with dementia. However, over half of patients with Parkinson's disease with dementia also have significant Alzheimer's disease-related plaques and neurofibrillary tangles on autopsy (Lieberman, 1997; Sabbagh *et al.*, 2009), with a positive correlation between amount of Alzheimer's disease pathology and severity of Parkinson's disease with dementia (Jellinger *et al.*, 2002), and some patients with Parkinson's disease with dementia are

Table 3 Association between SPARE-AD score and cognitive performance in non-demented Parkinson's disease patients

	PD-MCI + PD-NC (n = 69)			PD-NC only (n = 51)		
	Standardized coefficients (Beta)	t	P-value	Standardized coefficients (Beta)	t	P-value
SPARE-AD models^a						
Age	−0.155	−1.168	0.25	−0.213	−1.467	0.15
PD duration	−0.053	−0.415	0.68	0.079	0.545	0.59
Hoehn and Yahr stage	−0.069	−0.533	0.60	−0.185	−1.262	0.59
PIGD subtype	0.010	0.081	0.94	0.199	1.44	0.16
SPARE-AD	−0.279	−1.997	0.05	−0.287	−1.971	0.06
Hippocampus models^b						
Age	−0.152	−1.162	0.25	−0.270	−1.817	0.08
PD duration	0.005	0.040	0.97	0.141	0.968	0.34
Hoehn and Yahr stage	−0.124	−1.013	0.32	−0.249	−1.693	0.10
PIGD subtype	0.028	0.224	0.82	0.210	1.462	0.15
Hippocampal volume	0.283	2.211	0.03	0.116	0.808	0.42

a Linear regression models with baseline DRS-2 score as dependent variable and SPARE-AD score as measure of atrophy.

b Linear regression models with baseline DRS-2 score as dependent variable and hippocampal volume as measure of atrophy.

PD = Parkinson's disease; PD-MCI = Parkinson's disease with mild cognitive impairment; PD-NC = Parkinson's disease with normal cognition; PIGD = postural instability–gait difficulty.

Table 4 Baseline predictors of long-term cognitive decline in patients with Parkinson's disease without dementia

Model	Regression coefficient	df	F	P-value
Model 1^a				
Age	−0.152	1, 110	9.585	0.002
Hoehn and Yahr stage	−1.046	1, 110	1.696	0.20
PD duration	−0.073	1, 110	0.869	0.35
PIGD subtype	1.318	1, 110	4.837	0.03
SPARE-AD score	−1.424	1, 110	9.717	0.002
Model 2^b				
Age	−0.154	1, 105	5.962	0.02
Hoehn and Yahr stage	1.372	1, 105	2.715	0.10
PD duration	−0.073	1, 105	1.273	0.26
PIGD subtype	1.458	1, 105	5.616	0.02
SPARE-AD score	−1.456	1, 105	7.690	0.007
Sex	1.108	1, 105	3.362	0.07
Education	−0.070	1, 105	0.072	0.79
Total LEDD	< −0.001	1, 105	0.080	0.78
GDS-15 score	−0.084	1, 105	0.395	0.53
Presence of thought disorder	0.881	1, 105	1.114	0.29

a Type III tests in the mixed model with repeated measures of DRS-2 score as dependent variable, and visit, baseline DRS-2 score, age, Hoehn and Yahr stage (high versus low based on median cut-off), Parkinson's disease duration, postural instability–gait difficulty subtype, SPARE-AD score, age × visit interaction, Hoehn and Yahr stage × visit interaction, Parkinson's disease duration × visit interaction, postural instability–gait difficulty subtype × visit interaction and SPARE-AD × visit interaction entered as covariates. The intercept and the regression coefficients for the follow-up time (visit) were treated as random effects such that each subject has a unique intercept and regression coefficient for the follow-up time. Results for age, Hoehn and Yahr stage, Parkinson's disease duration, postural instability–gait difficulty subtype and SPARE-AD score are for variable × visit interaction term.

b Results for age, Hoehn and Yahr stage (high versus low based on median cut-off), Parkinson's disease duration, postural instability–gait difficulty subtype, SPARE-AD score, sex, education, total levodopa equivalent daily dosage, Geriatric Depression Scale-15 score and presence of thought disorder are for variable × visit interaction term. LEDD = levodopa equivalent daily dosage; PD = Parkinson's disease; PIGD = postural instability–gait difficulty.

reported to have increased β -amyloid using Pittsburgh Compound B (PiB) PET imaging (Gomperts *et al.*, 2008; Maetzler *et al.*, 2009). Even less is known about biomarkers of preclinical cognitive impairment or at the stage of Parkinson's disease with mild cognitive impairment.

Using multivariable analyses to control for possible confounding variables and applying a validated Alzheimer's disease-pattern of brain atrophy to the MRI scans of patients with Parkinson's disease, we found that this pattern also predicts global cognitive performance in patients with Parkinson's disease across a range

of cognitive abilities. The results indicate that the overall pattern of brain neurodegeneration that occurs in Alzheimer's disease, as summarized by SPARE-AD score (i.e. weighted toward hippocampal, medial temporal lobe and parietal–temporal cortex atrophy), is also associated with progression of cognitive decline in Parkinson's disease. This association between neurodegeneration in medial temporal lobe structures and cognitive performance is also consistent with recent research highlighting that memory impairment is relatively common in Parkinson's disease, even at the stage of mild cognitive impairment. Whether this neurodegeneration is due primarily to Parkinson's disease pathology, Alzheimer's disease pathology, some combination of the two, or even represents a compensatory mechanism remains to be determined. Our finding that both an Alzheimer's disease pattern of neurodegeneration and increasing Parkinson's disease severity were independent contributors to cognitive performance raises the possibility that both Alzheimer's disease and Parkinson's disease pathology contribute to cognitive decline in Parkinson's disease, which is supported by a recent clinicopathological study (Compta *et al.*, 2011).

Of significance was that the Alzheimer's disease pattern of atrophy predicted cognitive performance even in patients with Parkinson's disease without dementia-level severity of cognitive impairment, remarkably even in those with normal cognition based on robust and expanded normative data. There was no association between region of interest volumes, including the hippocampus and medial temporal lobe, and cognitive performance in patients with normal cognition. This suggests that applying a dementia pattern of atrophy that differentially weighs brain regions may be more sensitive to cognitive decline in Parkinson's disease than a region of interest approach, and may even be a preclinical (i.e. present in patients with normal cognition) biomarker.

Demographic and clinical correlates or risk factors for cognitive decline and development of dementia in Parkinson's disease include increasing age, male sex, lower level of education, increasing severity and longer duration of Parkinson's disease, postural instability–gait difficulty subtype and hallucinations (Aarsland *et al.*, 1996, 2001; Green *et al.*, 2002; Ramirez-Ruiz *et al.*, 2007; Williams-Gray *et al.*, 2007). In addition, dopamine replacement therapy may impair cognition, depending on dosage, cognitive domain assessed, disease severity and genetic factors (Kehagia *et al.*, 2010). Including those variables associated with cognitive performance in our sample as covariates in linear regression models, an Alzheimer's disease pattern of brain atrophy, as well as increasing disease severity and duration, predicted current cognitive performance in the entire sample. In non-demented patients, no demographic or clinical variables were associated with cognitive performance when controlling for severity of brain atrophy, suggesting that some clinical and demographic variables reported to be associated with cognitive decline in Parkinson's disease are confounded by their association with brain atrophy. It is also possible that the relatively low frequency of thought disorder, including psychotic symptoms, and lack of a correlation between thought disorder and cognition was due to the use of the UPDRS Part I thought disorder item, which has limited sensitivity to detect psychosis in Parkinson's disease (Starkstein and Merello, 2007).

In addition to the cross-sectional findings, an Alzheimer's disease-like pattern of brain atrophy also predicted 2-year decline in cognitive performance in non-demented patients with Parkinson's disease, including the subset of patients with normal cognition at baseline. Even when entering into the models numerous other demographic and clinical covariates associated with cognitive impairment in Parkinson's disease, an Alzheimer's disease-like pattern of brain atrophy continued to predict long-term cognitive decline. Other baseline variables that independently predicted cognitive decline were increasing age and postural instability–gait difficulty subtype, raising the possibility that the neuropathological underpinnings of cognitive decline in Parkinson's disease are varied and complex [i.e. potentially a mix of Parkinson's disease-related, Alzheimer's disease-related and vascular changes (Compta *et al.*, 2011)], which has implications for clinical course and management, as well as the design of intervention studies for cognitive impairment in Parkinson's disease. Overall, the longitudinal results are similar to those reported for patients with mild cognitive impairment in the general population, a population in which higher SPARE-AD scores predicted long-term declines in Mini-Mental State Examination score (Fan *et al.*, 2008a) and conversion to Alzheimer's disease (Misra *et al.*, 2009). Also consistent with our results, a recent analysis in cognitively normal elderly found that higher SPARE-AD scores were associated with worse memory performance (Davatzikos *et al.*, 2009).

Impairment in the neural circuits connecting the basal ganglia and cortical regions, including the prefrontal cortex, are thought to contribute to cognitive impairment in Parkinson's disease (Dubois and Pillon, 1997; Burn and O'Brien, 2003; Carbon *et al.*, 2004). Some studies have reported that prefrontal cortical atrophy occurs early in the process of cognitive decline in Parkinson's disease (Song *et al.*, 2011) and that executive impairment in non-demented patients predicts long-term development of Parkinson's disease with dementia (Mahieux *et al.*, 1998; Janvin *et al.*, 2005; Santangelo *et al.*, 2007), while others suggest that prefrontal cortex deficits may occur early in the disease course, be stable and not predict future cognitive decline (Williams-Gray *et al.*, 2009; Kehagia *et al.*, 2010). Our finding that an Alzheimer's disease pattern of brain atrophy, characterized by hippocampal and medial temporal lobe atrophy, predicts long-term cognitive decline in non-demented patients with Parkinson's disease is consistent with prospective research in an incident Parkinson's disease cohort that posterior cortical cognitive impairments predict long-term development of dementia (Williams-Gray *et al.*, 2009).

Limitations of this research include lack of formal diagnostic criteria for MCI and dementia, a sample of patients with primarily mild to moderate stage Parkinson's disease, lack of a validated rating scale to assess psychotic symptoms, and longitudinal data limited to 2 years. However, the mean age of our cohort is when Parkinson's disease dementia typically has its onset (Reid *et al.*, 2011), making our sample vulnerable to cognitive decline over a relatively short time period. Future studies need to enrol larger samples, have longer follow-up periods, use formal mild cognitive impairment and Parkinson's disease with dementia diagnostic criteria to document change in clinical status over time, include multiple biomarkers for comparison or combination e.g. both

molecular and structural imaging (Fan *et al.*, 2008b), and corticometry (cortical thickness) versus traditional voxel-based morphometry analyses (Jubault *et al.*, 2011), include clinicopathological correlation and incorporate specific Alzheimer's disease biomarkers, the latter to determine the extent that Alzheimer's disease-specific pathophysiological changes contribute to cognitive decline in Parkinson's disease.

For Alzheimer's disease, a model of dynamic biomarkers of pathological cascade has been proposed, starting with evidence for β -amyloidosis at a presymptomatic stage, followed by neuronal dysfunction and neurodegeneration at the time of clinical manifestation of cognitive impairment (Jack *et al.*, 2010), and a pattern of neuronal dysfunction (i.e. altered perfusion using fluorodeoxyglucose-PET) that is associated with cognitive performance has been reported in patients with Parkinson's disease with mild cognitive impairment (Huang *et al.*, 2008). Our findings suggest at least overlap in the regions undergoing neurodegeneration with cognitive decline in the two disease states, and raise the possibility that use of a pattern classification method to detect brain atrophy in Parkinson's disease may allow preclinical detection of patients at imminent risk of cognitive decline.

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