Longitudinal Changes in Cognition in Parkinson's Disease with and without Dementia

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Key Words

Alzheimer's disease • Parkinson's disease with dementia • Parkinson's disease/parkinsonism • Longitudinal cognitive course • Confirmatory factor analysis

Abstract

Background: The longitudinal cognitive course in Parkinson's disease (PD) with and without dementia remains undefined. We compared cross-sectional models of cognition in PD (both with and without dementia), Alzheimer's disease (AD), and nondemented aging and followed the participants over time. **Method:** Previously validated models of cognitive performance in AD and nondemented aging were extended to individuals with PD (with dementia, $n = 71$; without dementia, $n = 47$). Confirmatory factor analysis and piecewise regression were used to compare the longitudinal course of participants with PD with 191 cognitively healthy subjects and 115 individuals with autopsy-confirmed AD. **Results:** A factor analytic model with one general factor and three specific factors (verbal memory, visuospatial memory, working memory) fit demented and nondemented PD. Longitudinal change indicated that individuals with PD with dementia declined significantly more rapidly on visuospatial and verbal memory tasks than AD alone. Cognitive declines across all

factors in AD and PD dementia accelerated several years prior to clinical dementia diagnosis. **Conclusion:** Both specific and global cognitive changes are witnessed in PD and AD. Longitudinal profiles of cognitive decline in PD and AD differed. PD with or without dementia has a core feature of longitudinal decline in visuospatial abilities.

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Dementia is a recognized sequela of Parkinson's disease (PD), and diagnostic criteria have been outlined [1], but the cognitive phenotype is less clear [2]. A meta-analysis [3] of the course of cognitive decline in initially nondemented individuals with PD identified decline in memory and visuospatial ability as well as on screening instruments such as the Mini Mental State Exam. Additional reports described deficits in working memory, attention, inhibitory control and related abilities [4–7].

This report extends previous work [8, 9] characterizing cognitive ability in normal aging and Alzheimer's disease (AD) to evaluate the cognitive course in PD with (PDD) and without dementia (PDND). First, we determined whether a factor analytic model of general and domain-specific cognitive abilities empirically derived in people with and without AD applied to PDD and PDND.

We then used growth curve analysis to examine the longitudinal course of cognitive abilities in PDD and PDND and compared them to cognitively healthy older adults and those with autopsy-confirmed AD enrolled in the same longitudinal study.

Methods

Participants

Archival data were examined from 4 independent groups of volunteers enrolled in a longitudinal study of healthy aging and dementia at Washington University (table 1). Two PD groups are reported: one in which dementia eventually developed (PDD, $n = 71$), and one who remained without evidence of dementia during longitudinal follow-up (PDND, $n = 47$). The PD participants were derived from two sources. Eighty-four were recruited from the Movement Disorder Center to participate in a study of clinical outcomes in PD [10] and remained active in the longitudinal project. An additional 34 were enrolled in our longitudinal studies of memory and aging as cognitively normal controls but later developed PD. This cohort has been previously described in an evaluation of clinical predictors of PDD [11] ($n = 34$). All PD participants were aged 65 through 85 years, independently ambulatory, and noninstitutionalized. There were no sex or race restrictions. Data from the autopsy-confirmed AD ($n = 115$) and healthy aging ($n = 191$) groups have been previously reported [8] and are included here as reference groups for a comparison with the PD groups. Individuals with disorders that can result in other types of dementia or parkinsonism [e.g. cerebrovascular disease, dementia with Lewy bodies (DLB), frontal lobe syndromes, normal pressure hydrocephalus] were excluded. The Washington University Human Research Protection Office approved all procedures.

Clinical Evaluation

Evaluations were performed by experienced neurologists with expertise in neurodegenerative diseases (e.g. AD, PD, DLB). Detailed information about the clinical assessment and the diagnostic criteria for AD and the nondemented control group was provided in previous reports [9, 12]. The Clinical Dementia Rating (CDR) [13] was used to determine the presence or absence of dementia and, if present, to stage its severity. The CDR is derived from a semistructured interview with the participant and a knowledgeable informant. In addition to the interview, the clinician also collects brief performance measures to assess the patient's cognitive ability including the Mini Mental Status exam [14] (since 1996), the Short Blessed Test [15], abstracting similarities and differences, performing calculations and the Clock Drawing Test [16]. The CDR evaluates cognitive function in each of six categories (memory, orientation, judgment and problem solving, performance in community affairs, home and hobbies, and personal care) without reference to the detailed neuropsychological testing described below or results of previous evaluations. CDR 0 indicates no dementia, and CDR 0.5, 1, 2, and 3 correspond to very mild, mild, moderate, and severe dementia, respectively.

The clinical evaluation and diagnosis of PD were performed by a board-certified neurologist according to the United King-

dom Brain Bank criteria [17]. Diagnosis of PD was dependent on the presence of bradykinesia and at least one of the following signs: rigidity, rest tremor and/or postural instability for at least 6 months. Patients with secondary causes of PD including medications that cause extrapyramidal symptoms were excluded. The diagnosis of PDD was based on the development of dementia occurring at least 2 years after the onset of motor symptoms; individuals who developed dementia within a 2-year period of motor symptoms were given a diagnosis of DLB and excluded from this analysis. PDD individuals met DSM-IV criteria for dementia and received a CDR ≥ 0.5 , supporting the presence of at least very mild dementia. At the time of assessment, the current recommended criteria for PDD [1] had not yet been published. Retrospectively, each PDD case would meet these criteria. A diagnosis of PDD, CDR ≥ 0.5 , is supported by the presence of autopsy findings of subcortical, limbic and neocortical Lewy bodies with varying degrees of AD pathology [11]. None of the nondemented PD participants received a diagnosis of dementia or a CDR > 0 at any time of assessment. Standardized motor assessments of PD such as Hoehn and Yahr [18] stages or Unified Parkinson Disease Rating Scale (UPDRS) motor scores [19] were not available for all cases. Therefore, in order to control for bradykinesia, we used Crossing Off [20], a psychometric assessment of simple motor speed, as a gross index of motor slowing across all groups. Although not diagnostic of PD, Crossing Off accurately reflects motor slowing associated with PD (table 1) and was used here as a psychometric (not clinical) control variable.

Neuropsychological Assessment

The psychometric battery (table 2) assesses a broad spectrum of abilities (i.e. semantic memory, episodic memory, working memory, and visuospatial ability) across multiple cognitive domains which were previously described in detail [8]. It was administered annually to all participants approximately 2 weeks after clinical evaluation. Based on a confirmatory factor analysis (CFA) one global factor and three domain-specific factors (verbal memory, working memory, visuospatial memory) were created [8]. Psychometricians were not informed of the results of the clinical evaluation, nor did clinicians use the psychometric data to determine the diagnosis or CDR.

Neuropathology

All brains were examined with a standard protocol [21]. Following fixation in neutral buffered 10% formalin, tissue blocks were taken from 30 brain regions. Sections (6 μm) from paraffin-embedded tissue blocks were stained with hematoxylin-eosin, Gallyas and modified Bielschowsky silver stains and immunohistochemical methods [21]. Histological criteria for AD were based on quantification of diffuse and neuritic amyloid deposition in five cortical regions with 10-mm [2] microscopic fields in each region using modified Khachaturian criteria [22]. These criteria have good agreement with the National Institute on Aging-Reagan [23] intermediate or high probability estimates of AD but also take into account the potential contribution of diffuse amyloid burden on cognitive ability [24–26]. Cases were examined for cortical and nigral Lewy bodies with antibodies to α -synuclein. They were examined for the presence of cortical and subcortical infarcts and hemorrhages and other pathologies that could confound analyses.

Table 1. Characteristics at study entry, time of dementia diagnosis, and last assessment

	Nondemented		Demented	
	controls (n = 191)	PD (n = 47)	AD (n = 115)	PD (n = 71)
Number of assessments	785	205	462	365
Age at first assessment, years	74.1 (9.4)	71.1 (8.0)	78.3 (10.2)	72.4 (7.8)
Age at dementia diagnosis, years	–	–	79.1 (10.8)	74.4 (7.8)
Age at last assessment, years	78.4 (9.3)	75.3 (8.2)	81.5 (10.4)	77.2 (8.0)
Age at death (autopsied individuals only), years	–	74.6 (6.5)	85.4 (9.9)	79.5 (8.4)
Gender, % male	39	75	47	75
Education, years	14.7 (3.0)	13.6 (2.9)	13.9 (3.4)	14.7 (3.2)
Depression at first assessment, %	7	13	10	18
Depression at dementia diagnosis, %	–	–	13	18
Depression at last assessment, %	6	15	12	26
Crossing Off ^a at entry	161.3 (35.9)	134.6 (32.9)	134.8 (37.7)	129.7 (36.9)
Crossing Off ^a at dementia diagnosis	–	–	131.2 (38.8)	121.9 (33.4)
Crossing Off ^a at last assessment	159.2 (35.0)	130.9 (31.1)	118.7 (36.1)	111.3 (35.1)
SBT ^b score at entry	1.4 (2.1)	1.9 (2.4)	7.1 (6.2)	3.9 (5.5)
SBT ^b score at dementia diagnosis	–	–	8.2 (5.9)	4.8 (5.8)
SBT ^b score at last assessment	1.2 (2.1)	2.4 (4.2)	12.0 (8.1)	7.6 (6.9)
CDR-SB ^c at entry	0.1 (0.2)	0.4 (0.9)	2.6 (2.3)	2.1 (1.6)
CDR-SB ^c at dementia diagnosis	–	–	3.2 (2.0)	2.5 (1.9)
CDR-SB ^c at last assessment	0.1 (0.1)	0.4 (1.6)	4.4 (2.9)	3.5 (2.5)

Values indicate means ($\pm$ SD) unless otherwise stated.

SBT = Short Blessed Test; CDR-SB = clinical dementia rating sum of boxes.

^a Score is the reciprocal of the number of seconds to complete, multiplied by 100; higher scores indicate better performance. ^b Scores range from 0 (no impairment) to 28 (maximal impairment). ^c CDR-SB is a quantitative expansion of the clinical dementia rating. Scores range from 0 (no impairment) to 18 (maximal impairment).

Table 2. Comparison of clinical diagnoses and pathologic findings at autopsy

Clinical diagnoses	Pathologic diagnoses			
	AD	DLB	AD+DLB	PD
AD	115	0	0	0
PDD	9	8	13	0
PDND	0	5	0	6

Statistical Analyses

The current paper combines cross-sectional and longitudinal methods detailed in two previous reports on AD and healthy aging [8, 9]. Models were initially built to determine the underlying structure of cognitive ability in healthy, cognitively intact controls and then used to test for differences in AD. Here we extend these analyses to examine the underlying structure of PDD and PDND and how they differ from healthy aging and AD. Cross-sectional analyses used either the first assessment for the healthy

aging and PDND groups or the first assessment where dementia was diagnosed for the patient groups (PDD and AD; either last available CDR 0.5 or first CDR 1 rating). This selection strategy was chosen to exemplify the cognitive strengths and weaknesses of each of the 4 groups in subsequent between-group contrasts using CFA. CFA is based on the aggregation of common variance across multiple subtests resulting in more sensitive and specific estimates of true score ability. For example, when the variance common among subtests such as Trails A, Block Design, Benton Visual Retention Test, and Digit Symbol are aggregated, the resultant index of visuospatial ability is a more reliable and efficient statistic. We conducted cross-sectional multigroup CFA tests of invariance (TOI; AMOS v 16.0, SPSS, Chicago, Ill., USA) using full information maximum likelihood [27]. TOI is a nested comparison procedure that uses a series of increasingly restrictive models to investigate how groups differ in factor structure and variance-covariance patterns [28]. Lower nested models must be accepted before subsequent higher-order solutions can be interpreted. The level at which the model fails to fit defines how the groups differ. Trailmaking A was reverse-scored so that a high score on all variables indicated good performance and all psychometric measures were standardized across the 4 groups. Three TOIs compared the fit of the validated model across the 4 groups

with and without PD and dementia. Model evaluation was based on differences in the root mean square error of approximation (RMSEA) [29, 30]; values closer to 0 indicate better fit (preferred values <0.09) [8].

Longitudinal analyses applied factor score weights generated from the cross-sectional TOIs across all available repeatedly measured psychometric test scores. In the event of missing data (less than 3% of longitudinal sample), we prorated factor scores based on all available data and changed the denominator to accommodate a differential number of contributing items. A procedure identical to our previous report [9] compared linear, quadratic, and piecewise change models across the 4 groups for each cognitive domain using random coefficients analyses [31] (SAS v9.1.3; PROC MIXED). The piecewise change model allows a point of inflection and tests to determine if the rate of change is significantly different before and after that point. An initial point of inflection in the piecewise models was defined as the time of the first clinical diagnosis of dementia in the 2 demented groups, but an optimized placement of the bend was determined after comparing inflection placement along a range of time of assessments (from 3 years prior to 3 years after the time of the first clinical diagnosis of dementia). Because these models are nested for increasing complexity, we used χ^2 goodness of fit tests for $-2 \log$ likelihoods. We then used best unbiased linear predictors from each time of assessment to calculate latent difference scores (LDS) for each person. The LDS equal the difference between the predicted values at two adjacent times of assessments ($\hat{Y}_{T1} - \hat{Y}_{T2}$, $\hat{Y}_{T2} - \hat{Y}_{T3}$, $\hat{Y}_{T3} - \hat{Y}_{T4}$, and so forth) beginning with the difference of the predicted value at the optimized inflection point ($\hat{Y}_{T1}$) and the next assessment thereafter ($\hat{Y}_{T2}$). Finally, we tested a linear mixed model to determine if the slope of the LDS values (i.e. the slope of the slopes) accelerated over time in the dementia groups [9].

All analyses reported here included the covariates of age, education, and simple psychomotor speed (Crossing Off) [20]. The longitudinal analyses were based on all times of assessment for the 2 nondemented groups. Longitudinal data for the 2 demented groups included all available assessments from study entry through mild stage dementia (CDR 1); people in later stages of dementia (CDR ≥ 2) have extensive missing data because they are unable to complete many of the tests. Pair-wise comparisons used Bonferroni correction for multiple tests.

Results

Sample Characteristics

At study entry, the autopsy-confirmed AD group (mean age = 78.3 ± 10.2 years) was oldest and the PDND group (mean age = 71.1 ± 8 years) was youngest (table 1). Both PD groups were predominantly men (75%). The healthy aging and AD groups were predominantly women (61 and 53%). People with AD and PDND were less well-educated than people with PDD and the healthy controls [$F(3, 421) = 3.04$; $p < 0.05$]. Though simple motor speed at first assessment in the PDND sample was markedly slowed compared with the healthy aging group ($t = 2.12$; $p < 0.001$), absolute levels of simple motor speed

performance were largely preserved in nondemented samples throughout the study ($t = 0.54$; $p > 0.05$). In contrast both AD and PDD simple motor speed worsened over time ($t > 6.16$; $p < 0.001$), but PDD was not significantly different from AD either cross-sectionally or longitudinally (all $ts < 1.04$).

Autopsy Findings

All 115 AD participants met histological criteria and there were no other causes for their dementia. A total of 41 PD cases came to autopsy (PDND = 11, PDD = 30, table 2). All PD cases had nigral neuronal loss and nigral Lewy bodies. None of the PDND cases met criteria for AD but 3 cases had sufficient cortical Lewy body pathology (Braak stages 5–6) to meet DLB criteria [32] while 2 cases had limbic Lewy bodies (Braak stage 4). Of the 30 PDD participants who came to autopsy, 21 cases had neocortical Lewy bodies (Braak stages 5–6) sufficient to meet pathological criteria for DLB; 8 cases had pure DLB while 13 cases had mixed pathology. Nine cases had subcortical Lewy bodies (Braak stages 2–3) but no limbic or cortical Lewy bodies; instead these cases had AD pathology (diffuse and neuritic plaques and neurofibrillary tangles) sufficient to meet Washington University criteria for AD [21] with most cases meeting intermediate probability by National Institute on Aging-Reagan criteria. These findings are consistent with reports that cortical Lewy body pathology accounts for most cases of PDD; however, AD pathology may explain up to a third of cases [6, 11].

Neuropsychological Testing

Performance on neuropsychological testing (table 3) for the 4 groups from the cross-sectional time of assessment (PDND and healthy aging at first assessment; PDD and AD at first time CDR > 0) show that individuals with dementia performed more poorly on all subtests compared with nondemented individuals (PDD vs. PDND and healthy controls vs. AD; all $ts > 2.4$). The average number of years for participant follow-up was 5.3 (range = 1–19) in the healthy aging group and 5.1 years (range = 1–20) in the PDND group. The mean number of years for participant follow-up was 4.1 years (range 1–21) in the AD group and 5.7 years (range 1–20) in the PDD group. All participants spoke English and lived in the greater St. Louis metropolitan area; 24 were African-American, and the remainder was Caucasian.

Cross-Sectional Model Fit in PD

TOI results indicated that these 4 groups were equivalent at the level of strong factorial invariance (RMSEA =

Table 3. Performance on cognitive testing used in confirmatory factor analysis

	Nondemented at first assessment		Demented at first dementia diagnosis	
	healthy older adults	PD	AD	PD
Information [42]	20.4 (4.3)	20.2 (4.7)	14.7 (5.8)	18.2 (5.2)
Associate learning [43]	13.86 (3.4)	12.6 (3.2)	8.7 (3.5)	10.8 (4.2)
Boston naming [44]	54.3 (5.3)	53.9 (5.3)	43.3 (11.6)	50.3 (9.7)
Logical memory [43]	8.7 (2.9)	6.7 (2.9)	3.7 (2.8)	5.9 (3.1)
Benton (copy) [45]	9.7 (0.8)	9.4 (0.8)	8.8 (1.9)	8.6 (2.0)
Digit symbol [42]	45.2 (10.0)	38.8 (13.3)	26.4 (14.1)	26.4 (13.5)
Trailmaking A [46], s ^a	42.0 (20.1)	56.8 (25.6)	78.9 (43.7)	81.2 (43.9)
Block design [42]	29.2 (8.9)	27.5 (9.9)	18.9 (10.7)	18.8 (10.3)
Word fluency (S & P) [47]	29.3 (9.8)	26.4 (10.7)	21.0 (9.6)	22.5 (12.2)
Mental control [43]	7.2 (1.7)	7.3 (1.7)	5.5 (2.4)	6.5 (2.1)
Digit forward [43]	6.4 (1.3)	6.8 (1.3)	5.9 (1.3)	6.4 (1.2)
Digit backward [43]	4.6 (1.2)	4.7 (1.4)	3.8 (1.3)	4.1 (1.3)

Values indicate mean scores ($\pm$ SD) unless otherwise stated.

^a Higher scores indicate poorer performance.

Table 4. -2LL values for each factor for each model and significant maximum likelihood deviance tests ($\Delta\chi^2$)

Model	d.f.	Global -2LL ($\Delta\chi^2$)	Verbal memory -2LL ($\Delta\chi^2$)	Visuospatial -2LL ($\Delta\chi^2$)	Working memory -2LL ($\Delta\chi^2$)
<i>AD</i>					
Simple linear	9	1,473.5	1,690.0	3,562.8	1,895.9
Quadratic	10	1,475.2 (+2.3)	1,690.0 (0)	3,562.8 (0)	1,895.9 (0)
Piecewise linear					
At diagnosis	10	1,425.6 (-47.9)	1,686.9 (-3.1)	n.c.	1,889.8 (-6.1)
Optimized	10	1,279.2 (-194.3)	1,531.3 (-158.7)	3,222.0 (-340.8)	1,732.3 (-163.6)
<i>PD</i>					
Simple linear	9	1,115.5	975.5	2,459.2	846.2
Quadratic	10	1,219.3 (+103.8)	975.5 (0)	2,459.2 (0)	846.2 (0)
Piecewise linear					
At diagnosis	10	1,084.5 (-31.0)	n.c.	2,409.9 (-49.7)	814.5 (-31.7)
Optimized	10	1,008.6 (-106.9)	928.0 (-47.5)	2,256.7 (-202.5)	796.9 (-49.3)

1 d.f. for deviance tests. Smaller -2LL values indicate better fit. n.c. = Model did not converge indicating poor fit.

0.03; 90% CI 0.02–0.04). Higher levels of invariance failed to improve fit [factor means (RMSEA = 0.05; 90% CI 0.05–0.06) and variances (RMSEA = 0.06; 90% CI 0.06–0.07)]. Overall, this latent model of cognition fit these 4 groups well. The psychometric tests contributed to the construct validity of the latent model in a similar fashion across groups (equivalent factor loadings and measurement intercepts); however, groups differed in the absolute level and variability of performance in spe-

cific combinations of these factors. Across all domains, variability was marked in both dementia groups and their standard errors were about 2–3 times as large as in healthy controls. Even with objectively large differences in mean scores, the standard error of dementia scores attenuated sensitivity for between-group *t* tests. Although *t* tests failed to reveal between-group differences factor-by-factor, the TOIs are the omnibus tests that indicate that groups differ. Factor loadings for the AD and

healthy aging groups are similar to those reported previously [8]. Slight differences in loadings between these 2 studies are due to the inclusion of additional PD groups, which slightly shifted factor structure. Resultant weights represent a unique contrast between individuals with and without PD. Because the PDND group was small, estimates from this cross-sectional moment are included (because of their clinical relevance) but no tests conducted.

The AD group had the lowest general factor score (−2.04 Z-score lower than in the nondemented group; fig. 1) followed by the PDD group (−1.49). Verbal means were lower in AD (−0.72) than in the PDD group (−0.44). Visuospatial means were lower in PDD (−1.33) than for the AD group (−0.59). Working memory means were slightly lower in PDD (−0.17) than for the AD group (−0.29). Overall, this pattern of scores indicated AD affects verbal memory more than other domains and PDD affects visuospatial memory. A striking finding unique to PD was an attenuated correlation among the three specific factors in both nondemented and demented individuals. In both groups the correlations associated with the working memory factor were lower (0.29 and 0.26) than in non-PD samples (0.64 and 0.66). Further, the PDD group showed an attenuated correlation between the visuospatial and verbal memory factors (0.11) versus their PDND counterparts (0.55). Overall the pattern of PD and AD intercorrelations among factors was very dissimilar between groups.

Longitudinal Analyses Piecewise Change Regressions

The longitudinal cognitive data for each of the domains were best fit by a simple linear regression (no inflection) for the 2 nondemented groups (a more than 5-year follow-up in these groups afforded sufficient power for longitudinal tests, even in PDND; tables 4, 5). Data from the 2 demented groups were best fit by two-segment piecewise linear regressions joined by a single inflection point (fig. 2a–d), indicating that slopes before and after diagnosis differed significantly. Fit was improved by moving the inflection point prior to diagnosis ($p < 0.001$). For the global factor the PDD group's inflection was 3 years before diagnosis and in AD, 2 years before. For the domain-specific factors in both PDD and AD the optimal inflection point was 2 years prior to clinical diagnosis. The AD group showed an inflection point for all four factors at 2 years prior to diagnosis of dementia. Differences between these inflection points and our previous report [8] are due to methods and sample (see legend of fig. 2).

Table 5. Estimated slopes and rates of acceleration (standard errors) for four factors

Group	Inflection point	Before inflection slope	After inflection	
			slope	acceleration
<i>Global</i>				
Control	–	+0.04 (0.02) ^a		
PDND	–	–0.01 (0.03) ^b		
PDD	–3	–0.05 (0.05) ^b	–0.17 (0.03) ^a	–0.03 (0.01) ^a
AD	–2	–0.10 (0.04) ^{c, #}	–0.28 (0.03) ^b	–0.04 (0.01) ^a
<i>Verbal memory</i>				
Control	–	–0.03 (0.03) ^a		
PDND	–	–0.02 (0.05) ^a		
PDD	–2	–0.04 (0.07) ^a	–0.43 (0.05) ^a	–0.09 (0.02) ^a
AD	–2	–0.12 (0.06) ^{b, #}	–0.21 (0.04) ^b	–0.04 (0.01) ^b
<i>Visuospatial</i>				
Control	–	–0.04 (0.02) ^a		
PDND	–	–0.17 (0.05) ^{b, #}		
PDD	–2	–0.20 (0.06) ^{b, #}	–0.68 (0.05) ^a	–0.10 (0.02) ^a
AD	–2	–0.04 (0.06) ^a	–0.23 (0.05) ^b	–0.06 (0.01) ^a
<i>Working memory</i>				
Control	–	–0.01 (0.01) ^a		
PDND	–	–0.06 (0.02) ^{b, #}		
PDD	–2	–0.05 (0.03) ^{b, #}	–0.11 (0.02) ^a	–0.02 (0.00) ^a
AD	–2	–0.02 (0.03) ^a	–0.14 (0.02) ^a	–0.04 (0.00) ^a

Slope coefficients estimated by piecewise change model of raw data. Acceleration coefficients estimated by LDS regression.

[#] $p < 0.05$ that slope is different than zero.

^{a–c} Within factor and diagnostic epoch, entries with the same subscript letter are not significantly different from each other. All changes in slope and acceleration coefficients are significant after inflection for that progress to dementia (all $p < 0.001$).

Before Inflection. For the global cognitive factor, the healthy aging group exhibited a slight upward trajectory that appeared to differ from the slight negative slopes in both PD groups (−0.01 and −0.05) and the steeper negative slope in AD (−0.10). Although it is tempting to interpret these between-group differences as evidence for a practice effect in healthy controls and preclinical decline in AD, the omnibus test equal for all slopes (before inflection) failed to differ from zero ($t = 0.13$). This pattern of performance was repeated in the verbal memory domain; all slopes failed to differ significantly ($t = 0.44$). PD slopes differed significantly from non-PD slopes in the visuospatial domain ($t = 3.32$; $p < 0.001$).

After Inflection. Demented groups (AD and PDD) showed a consistent and accelerating decline in postin-

flection cognitive scores across all domains (all t s >2.32). In the verbal memory and visuospatial domains the PDD group performance declined faster than AD. PDD and AD were equivalent in working memory, and AD declined more rapidly in the global cognitive domain.

Discussion

We used methods from previous cross-sectional and longitudinal reports about the cognitive structure in healthy brain aging and AD [8, 9] and applied them to a model of cognition in PDD and PDND. Cross-sectional results indicated that this cognitive model is also robust for PDND and PDD; however, in PDD specific cognitive factors were significantly less intercorrelated. Figure 1 shows how PDD uniquely affected the cognitive model's subcomponents and that failing subcomponents resulted in more variance (larger standard errors). When the factor structure was applied to longitudinal data, piecewise regressions showed that PDD was similar to AD in that an accelerating cognitive decline across these four cognitive domains begins at least 2 years prior to the clinical diagnosis (fig. 2); however, they significantly differed from AD in that there was a unique pattern to longitudinal decline that was pronounced in the specific factors. The PDD group performed most poorly on the visuospatial factor, even after controlling for the motor slowing characteristic of PD. Their precipitous decline on this factor is the most pronounced feature of the PDD cognitive phenotype. The visuospatial decline was also observed in the PDND group, which agrees with a meta-analysis [33] that concluded that PD takes a heavy toll on visuospatial abilities, regardless of the status in other cognitive domains. Finally, these longitudinal data converge with the

prevalent finding that age is a significant moderating factor in cognitive decline in PDD [11, 34, 35]. These findings expand a recent report [36] demonstrating a nonlinear cognitive decline in PD using the Mini Mental State Examination.

Both the PDND group and the PDD group before clinical diagnosis of dementia (preclinical PDD) showed constant and equivalent visuospatial decline through time. These data suggest that PD is a dementing illness with early visuospatial features and that nearly all individuals may develop dementia if they live long enough. Longitudinal follow-up will be necessary to determine if this is true; however, these analyses support epidemiological studies that report that the cumulative prevalence of dementia in PD is very high with at least 75% of PD patients who survive for more than 10 years developing dementia [37]. Finally, the PDD group declined 3 times faster than the AD group on the verbal memory factor. One possible explanation is the coexistence of AD pathology in a large proportion of autopsied PDD cases; alternatively, hippocampal atrophy and neuronal degeneration may be greater in PDD due to Lewy-related pathology. It seems likely that 2 diseases may act synergistically for verbal and visuospatial deficits in PDD similar to what has been reported in DLB [38]. This was least true in working memory where AD and PDD were largely equivalent. Both AD and PDD patients experienced significant working memory deficits, rendering this domain not differentially diagnostic using this psychometric battery.

Our PDD participants who came to autopsy were heterogeneous in their pathological findings. While 70% had limbic and neocortical Lewy bodies sufficient to diagnose DLB, 73% also had Alzheimer-type changes at death (73% of autopsied sample), reflecting the presence of two brain diseases. The presence of two pathologies (AD and Lewy body) may be interactive and explain why PDD model intercorrelations were so low and longitudinal trajectories steeper in verbal and visuospatial memory compared to the other 3 groups. If the two pathologies are interactive, then one would expect that as the disease burden worsens, whole brain integrity needed for coordinated complex cognition and behavior is disrupted and subcomponent cognitive processes become more independent. Empirically, this results in lower correlations between component processes with higher standard errors due to increased disease-related variability. These ideas are similar to process-specific declines reported by others [39–41] but they are more starkly pronounced in this clinical sample. Overall, the burden level appears to be best reflected by the global factor which was the most

Fig. 1. Results of between-group test of the model at the level of strong factorial invariance. Between-group TOI. Relative fit of four models to describe the underlying cognitive structure in control subjects, AD, PDD and PDND. Bold values represent factor means and standard deviations, values associated with single-headed arrows represent subtest measurement intercepts, and values associated with double-headed arrows represent factor correlations. INFO = Information; PA = paired associate learning; BNT = Boston Naming Test; LM = logical memory; BVRT = Benton Visual Retention Test; DSym = digit symbol; TRA = trailmaking A; BD = block design; WF = word fluency; MC = mental control; DS-B = digit span backward; DS-F = digit span forward. ^a $p < 0.05$ vs. control group; ^b $p < 0.05$ vs. AD group.

Fig. 2. Longitudinal change in global and domain-specific factor scores. Longitudinal course of cognitive abilities. The longitudinal cognitive course for participants with PD (grey triangles) and without (black dots) in the general (a), across verbal memory (b), visuospatial (c) and working memory (d) factor scores. Times of assessment before and after diagnosis of dementia (DX) are shown. Solid lines represent individuals who remained free of dementia (ND) throughout study. All available data were used for analysis, but the plotted values for the stable and progressed groups include at least 25 observations per time point per group. Optimized points of inflection are circled. In the current project, inflection points for the specific factors differ by 1 year from those

previously reported in the transition from health to AD [8] (general = T-2, verbal memory = T-1, visuospatial = T-3, and working memory = T-1). The inclusion of simple motor speed as a longitudinal covariate resulted in a shift in the inflection point for visuospatial factor which relies heavily on speeded tests. Equating PDD and AD for simple motor speed offsets the visuospatial decline by 1 assessment as compared to previous analyses. The shift in verbal and working memory domains differed slightly from our previous report due to the inclusion of an additional dementia group (PDD) in the CFA. These individuals insured that more weight would be given to the specific factors in the overall group solution and thus increased the sensitivity of the specific domains.

sensitive cognitive marker in both PDD and AD; however, visuospatial changes clearly represent a very early and sensitive marker, especially when Lewy body pathology and AD are mixed. Interestingly, 9/30 cases had only AD changes in the cortex (in addition to nigral Lewy bodies) that could explain their dementia. Thus, of the 30 cases, we describe a spectrum of possible pathologies that

could explain PDD: DLB alone (27%), DLB mixed with AD (43%), and in 30% of cases AD with nigral Lewy bodies.

Our study has limitations. Due to the observational nature of our research project, we do not prescribe medications either for cognitive or motor function. Although all PD patients received some form of dopaminergic ther-

apy, we are not able to account fully for possible medication efforts nor do we have information regarding on/off state. We also do not have information on disease duration. An additional limitation is the absence of UPDRS scores for the older cases. To overcome these limitations, we instead attempted to control for bradykinesia, the motor symptoms that were most likely to impact neuropsychological testing with the Crossing-Off test, a psychometric measure of pure motor speed without a cognitive component.

The strengths of the study include the use of well-characterized longitudinal samples of participants with and without dementia as well as with and without PD to explore the underlying structure of cognitive abilities in PD and PDD. The nondemented samples represent older adults who remained dementia free for at least two follow-up assessments, lessening the possibility of preclinical states of dementia or cognitive impairment. Likewise the entire AD and a proportion of the PD samples were drawn from individuals who were clinically diagnosed in life and confirmed by autopsy. The long follow-up periods of the PD sample allow us to now implicate decline in visuospatial abilities as the hallmark cognitive feature of PDD and PDND. The magnitude of the rates of decline is highly dependent on the sensitivities of the measures chosen to assess the various domains. Some of the measures included here were selected at the beginning of our longitudinal study more than 30 years ago; more sophisticated tests of executive ability and attention were not available for these analyses.

This is one of the first studies to demonstrate a preclinical PDD state that begins with acceleration of global cognitive abilities 3 years prior to clinical detection of dementia. AD and PDD cognitive abilities declined across all domains, accelerating precipitously 2 years prior to clinical diagnosis. Notably, this change point would otherwise be undetectable using either informants or published test norms. The model allows us now to explore the longitudinal cognitive performance across diverse clinical samples, eliminates the necessity of allowing unique factor structures for people with and without dementia, and permits direct comparison of cognitive abilities between AD and PD using a common neuropsychological battery.

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Disclosure Statement

The authors report no conflicts of interest.

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