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Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease

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Abstract

To identify the cognitive characteristics predictive of incident dementia in Parkinson's disease (PD), we examined the baseline neuropsychological profiles of 18 initially non-demented patients with PD who met diagnostic criteria for dementia (PDD) at one-year follow-up. PDD participants' baseline neuropsychological test scores were compared to the baseline performance of 18 patients with PD who did not meet criteria for dementia at one-year follow-up (PDND) and 18 normal controls (NC). The three groups were matched on baseline demographic and disease variables. Relative to the PDND group, the incident PDD participants demonstrated significantly poorer performance on digits backward (Wechsler Memory Scale–Revised), word list learning and recognition (California Verbal Learning Test), and perseverative errors on the Wisconsin Card Sorting Test. Each of these baseline neuropsychological variables exhibited adequate diagnostic classification accuracy in predicting PDD and PDND group membership at follow-up. These results suggest that subtle frontal/executive dysfunction is evident during the immediate PDD prodrome and may be of prognostic value in identifying PD patients at risk for dementia. Accordingly, neuropsychological evaluation may facilitate early identification of PDD and thereby inform appropriate dispositional planning. (*JINS*, 2003, *9*, 17–24.)

Keywords: Parkinson's disease, Dementia, Executive function, Frontal lobe

INTRODUCTION

Dementia occurs in approximately 30% to 50% of patients with Parkinson's disease (PD), although prevalence estimates range from 9% to 93% depending on which diagnostic criteria and sampling methods are used (Jacobs et al., 2000). Annual incidence rates for dementia in PD (PDD) are reported at approximately 15% (e.g., Mayeux et al., 1990). Risk factors for PDD include increasing age, older age at PD onset, longer disease duration, family history of dementia, greater severity of motor symptoms, depression, hypertension, low socioeconomic status, limited educational attainment, and poor medication tolerance evidenced by confusion or psychosis accompanying administration of dopaminergic agents (e.g., Glatt et al., 1996; Hughes et al., 2000; Jacobs et al., 2000; Marder et al., 1995; Salganik & Korczyn, 1990; Stern et al., 1993a; Zhang et al., 1990).

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PD is primarily associated with a disruption of cortical-basal ganglionic-thalamic-cortical circuits secondary to the depletion of dopamine, but PDD likely involves alterations in multiple neurotransmitter systems, including cholinergic projections from the basal forebrain (Dubois & Pillon, 1998; Stern et al., 1993b; Tröster et al., 2000). Clinically, PDD is characterized by the emergence of multiple cognitive deficits and a functional decline from once higher levels. The neuropsychological profile of PDD is often described as revealing of a "subcortical" dementia, a prominent feature of which is impairment in the spontaneous generation and utilization of information processing strategies. Persons with PDD typically exhibit impairment in complex attention, executive functions, information retrieval, procedural memory, visuoconstruction, verbal fluency, and speed of information processing (Cummings & Benson, 1983; Tröster et al., 2000).

Complementing recent efforts linking mild prodromal cognitive impairments to incident Alzheimer's disease (AD) (see Peterson et al., 2001 for review), several investigators have attempted to identify neuropsychological variables

associated with incident PDD. For example, Biggins et al. (1992) reported that incident PDD patients exhibited lower baseline verbal IQ scores and poorer performance on a brief mental status examination as compared to PD participants who were not demented at three-year follow-up. Piccirilli et al. (1989) followed a sample of 30 initially non-demented patients with PD for a period of four years and reported that Lurian frontal tasks (i.e., planning, sequencing, and self-monitoring; Luria, 1966) were sensitive to incident PDD. Jacobs et al. (1995a) found that measures of lexical (CFL and PSV for English and for Spanish-speaking participants, respectively) and semantic fluency (animals, foods, and clothing) were adequate predictors of incident PDD. Most recently, Mahieux et al. (1998) reported that PD participants' performance on the Picture Completion subtest of the Wechsler Adult Intelligence Scale–Revised (WAIS–R; Wechsler, 1981), a Stroop task, and lexical fluency accurately predicted incident PDD.

In general, these prior research findings suggest that subtle frontal/executive dysfunction is noticeable during the prodromal phase of PDD and predicts later conversion to dementia. However, no studies have evaluated the immediate prodrome of incident PDD (test-retest intervals for the above-reviewed investigations were typically three to four years). The present study seeks to delineate the immediate prodromal neurocognitive profile associated with incident PDD and to evaluate the discriminant validity of neuropsychological measures for predicting incident PDD at one-year follow-up. Given that certain demographic and disease characteristics are associated with greater risk for dementia in PD (e.g., Glatt et al., 1996; Stern et al., 1993a), this study examines neuropsychological prediction of dementia after controlling for several of these potentially confounding variables.

METHODS

Research Participants

Participants were recruited through a neurodegenerative disease research program at an urban teaching hospital. The diagnosis of PD was established by the presence of at least two of three cardinal signs of the disease (i.e., tremor, rigidity, and bradykinesia) and a positive response to levodopa. All participants with PD were on anti-parkinsonian agents, but were not taking any other medications known to affect cognition. Exclusionary criteria for the PD group included neurologic disorder other than PD, a history of head injury with loss of consciousness, substance abuse or dependence, developmental disorder, major psychiatric illness (with the exception of mild depression), and medical conditions that might impact cognitive functions (e.g., chronic obstructive pulmonary disease).

The diagnosis of dementia was based upon the criteria proposed by Cummings and Benson (1983). Participants who exhibited impairment in instrumental activities of daily living and who demonstrated deficits in at least three of four cognitive domains (i.e., language, memory, executive, or visuoperceptual functions) were classified as having PDD. Domain-specific impairments were defined by scores falling two or more standard deviations below the mean on at least one of two measures in that area. In the memory domain, the California Verbal Learning Test (CVLT; Delis et al., 1987) Trials 1–5 Total Score and Logical Memory I from the Wechsler Memory Scale–Revised (WMS–R; Wechsler, 1987) were used to define impairment. Total scores from the Controlled Oral Word Association Test (COWAT; Benton et al., 1994) and Boston Naming Test (BNT; Kaplan et al., 1983) were used to determine language impairment. Assessment of executive dysfunction was based upon the total number of categories completed on the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993) and total score on the Conceptualization subtest from the Mattis Dementia Rating Scale (DRS; Mattis, 1988). Finally, visuoperceptual skills were assessed with the WAIS–R Block Design subtest and the Clock Drawing Test. Note that, baseline neuropsychological test data were not used to determine dementia diagnosis at one-year follow-up (Time 2). In an effort to minimize the possibility of including patients with concomitant AD and/or its Lewy body variant, motor symptoms were determined to have clearly predated cognitive changes (although this does not exclude the possibility that patients might subsequently develop co-existing AD).

Healthy elderly control participants (NC) were recruited from the community using advertisements and contacts within local caregiver support groups. Exclusionary criteria for the NC group included history of neurologic or psychiatric illness (except mild depression), dementia, substance abuse or dependence, head injury with loss of consciousness, and current medications or medical conditions known to affect cognition.

Procedure

After providing written informed consent, each participant underwent a comprehensive interview, neurologic examination, and neuropsychological evaluation. All patients with PD and PDD were taking anti-Parkinsonian medications (e.g., levodopa) at the time of evaluation and were tested during their self-reported "on" state. In the event that participants reverted to "off" during testing, the evaluation was temporarily suspended or rescheduled. Participants were administered the following tests in accordance with standardized procedures as part of a larger battery (although not all participants had all tests given occasional scheduling conflicts): North American Adult Reading Test (NAART; Blair & Spreen, 1989), DRS, WAIS–R (seven subtest short-form), WCST, WMS–R (Attention/Concentration Index, Visual Reproduction, and Logical Memory), CVLT, BNT, COWAT, semantic fluency (animal naming), Clock Drawing, and the Beck Depression Inventory (BDI; Beck, 1992).

Of the 118 PD participants without dementia at baseline, a total of 20 met diagnostic criteria for PDD at Time 2

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follow-up, resulting in a 17% annual incidence rate. Two of the incident PDD participants completed only the DRS at baseline, which provided a total of 18 incident PDD participants with sufficient neuropsychological data for inclusion in the current analyses. We individually matched the incident PDD participants to 18 healthy NC and to 18 participants with PD who did not meet criteria for dementia (PDND) at either entry into the study (baseline) or follow-up about one year later. Participants were carefully matched on key demographic and disease variables so as to more precisely examine the neuropsychological characteristics of the prodromal phase of PDD. None of the 14 PDND participants who also completed a two-year follow-up evaluation (Time 3; $M = 27.76$ months, $SD = 2.48$) met diagnostic criteria for dementia. Four of the PDND participants did not complete a Time 3 neuropsychological evaluation as a result of test refusal, scheduling conflicts, or geographic relocation.

Data Analyses

A series of multivariate analyses of variance (MANOVA) with Time 2 diagnosis as the independent factor were conducted to evaluate the hypothesis that incident PDD participants would exhibit poorer performance on measures of frontal/executive functioning at baseline when compared to the PDND or NC groups. Follow-up univariate analyses of variance (ANOVA) were conducted on only those MANOVA results that reached statistical significance ($p < .05$). Similarly, pairwise comparisons were conducted to determine specific between group differences only if the ANOVA was statistically significant. In an effort to control for possible Type I error resultant from multiple analyses, alpha was set at .01 for all *post hoc* comparisons.

It was also hypothesized that the neuropsychological measures discriminating the PDD and PDND groups (as indicated by significant pairwise comparisons) would provide satisfactory diagnostic classification rates and predictive accuracy. Receiver-operating characteristic (ROC) plots were generated from these tests using incident PDD diagnosis as the "gold standard" variable. Predictive values were calculated by identifying cutoff scores based on a review of the ROC plots for test scores that provided the most balanced levels of sensitivity and specificity. To account for the possible interpretive bias of prevalence rates on predictive values (Baldessarini et al., 1983), positive and negative predictive power statistics were also calculated using a conservative 30% dementia prevalence rate based on a recent review of the PD literature (Jacobs et al., 2000). The following formulas proposed by Baldessarini et al. (1983) were used to calculate the prevalence-adjusted predictive values: positive predictive power = (prevalence) $*$ (sensitivity)/(prevalence) $*$ (sensitivity) + (1 − prevalence)(1 − specificity), negative predictive power = (1 − prevalence) $*$ (specificity)/(1 − prevalence) $*$ (specificity) + (1 − prevalence)(1 − sensitivity).

RESULTS

Table 1 provides a detailed description of participants' demographic and disease characteristics. No significant between-group differences were identified on the basis of age, education, gender, handedness, age at disease onset, Hoehn and Yahr stage, disease duration, self-reported symptoms of depression, or estimated premorbid intelligence (all $p > .05$).

No significant overall differences were identified between the three groups on any DRS variable at baseline (Wilk's $\Lambda = 0.71$, $F[2,51] = 1.73$, $p > .05$). A one-way within-subjects ANOVA revealed significant main effects for time (Wilk's $\Lambda = 0.75$, $F[2,50] = 8.22$, $p < .001$; $\eta^2 = .25$) and diagnosis ($F[2,50] = 12.66$, $p < .001$; $\eta^2 = .34$) on the DRS Total score. Consistent with group definitions, pairwise comparisons indicated that the PDD group demonstrated a significant decline in DRS Total score between their baseline and Time 2 evaluations ($p \leq .001$), whereas the PDND and NC groups did not demonstrate any significant changes on this measure between assessment intervals ($p > .05$) (see Table 1).

Concerning executive functions, an overall multivariate test revealed that the three groups differed with regard to their baseline performance on the WCST (Wilk's $\Lambda = 0.65$, $F[2,49] = 2.13$, $p < .05$; $\eta^2 = .19$). Follow-up analyses of variance indicated significant between-group differences on several WCST indices, including total errors ($F[2,49] = 4.93$, $p < .01$; $\eta^2 = .17$), perseverative errors ($F[2,49] = 8.99$, $p < .001$; $\eta^2 = .27$), and percent conceptual level responses ($F[2,49] = 5.87$, $p < .01$; $\eta^2 = .19$). Subsequent pairwise comparisons disclosed that the PDD participants demonstrated a greater number of perseverative errors as compared to the PDND group ($p < .01$, Cohen's $d = .98$). Significant pairwise differences also emerged between PDD and NC participants on total number of WCST errors ($p < .01$, $d = .95$), total perseverative errors ($p < .001$, $d = 1.36$), and percent conceptual level responses ($p < .01$, $d = 1.09$).

Significant overall differences also emerged on the WMS–R (Logical Memory and Digit Span subtests) (Wilk's $\Lambda = 0.63$, $F[2,50] = 2.36$, $p < .05$; $\eta^2 = .20$). Follow-up univariate analyses of variance revealed significant between-group differences only on the Digits Backward subtest ($F[2,50] = 6.53$, $p < .01$; $\eta^2 = .21$). Pairwise comparisons indicated that participants with PDD demonstrated poorer Digits Backward performance relative to the PDND ($p < .001$, $d = 1.08$) and NC ($p < .001$, $d = 1.21$) groups.

Finally, significant overall differences were identified on the CVLT (Wilk's $\Lambda = 0.40$, $F[2,51] = 2.44$, $p < .01$; $\eta^2 = .37$), specifically for immediate recall across all five learning trials ($F[2,51] = 5.64$, $p < .01$; $\eta^2 = .18$) and an index of recognition discriminability ($F[2,51] = 7.35$, $p < .01$; $\eta^2 = .22$). Follow-up pairwise comparisons indicated that the PDD group displayed poorer performance on total immediate recall as compared to the PDND ($p < .01$, $d = 1.04$) and NC ($p < .01$, $d = 0.92$) samples. Likewise, per-

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Table 1. Baseline demographics, disease characteristics, and neuropsychological variables by group

Variable	NC	PDND	PDD
Age (years)	68.76 (6.44)	69.39 (5.80)	69.67 (6.78)
Education (years)	14.18 (2.30)	14.44 (2.57)	14.44 (2.84)
Gender			
Male	12 (67%)	12 (67%)	12 (67%)
Female	6 (33%)	6 (33%)	6 (33%)
Handedness			
Right	16 (90%)	17 (94%)	16 (90%)
Left	2 (10%)	1 (6%)	2 (10%)
Age at disease onset (years)	—	63.89 (6.19)	63.33 (8.15)
Duration of disease (years)	—	5.50 (3.35)	6.33 (5.36)
Hoehn & Yahr Stage (median)	—	2	2
Stage 1	—	3 (17%)	0 (0%)
Stage 2	—	12 (67%)	16 (89%)
Stage 3	—	3 (17%)	1 (6%)
Stage 4	—	0 (0%)	1 (6%)
Mean test-retest interval (months)	15.03 (4.79)	15.01 (3.94)	16.29 (3.80)
Beck Depression Inventory (of 63)	4.22 (3.46)	7.28 (4.46)	7.67 (5.78)
NAART estimated Full Scale IQ	107.76 (11.73)	113.11 (6.99)	111.11 (5.94)
Mattis Dementia Rating Scale			
Attention (of 37)	34.67 (2.89)	35.94 (1.26)	35.28 (1.32)
Initiation/Perseveration (of 37)	36.44 (1.15)	34.89 (3.23)	33.61 (3.66)
Construction (of 6)	5.89 (0.32)	5.89 (0.32)	6.00 (0.00)
Conceptualization (of 39)	35.33 (4.05)	34.89 (2.61)	33.44 (4.05)
Memory (of 25)	23.50 (2.81)	23.06 (1.76)	23.50 (1.50)
Total (of 144)	136.17 (5.31)	134.67 (3.96)	131.83 (6.09)
Time 2 Total score (of 144)	135.53 (6.07)	137.72 (4.65)	121.33 (16.52)**††
Letter fluency (FAS)	37.11 (16.20)	39.33 (13.17)	31.65 (9.75)
Category fluency (animals)	18.17 (4.15)	17.61 (3.76)	16.18 (3.97)
Boston Naming Test (of 60)	54.50 (5.01)	55.00 (2.85)	53.88 (4.47)
Wisconsin Card Sorting Test			
Categories (of 6)	4.61 (1.72)	4.59 (1.91)	2.88 (2.12)
Trials to 1st category	14.67 (6.91)	18.94 (28.44)	29.82 (37.95)
Total errors	32.50 (20.47)	36.24 (19.14)	54.18 (25.09)†
Perseverative errors	16.28 (10.62)	20.53 (11.55)	33.24 (14.36)*††
Conceptual responses (%)	64.44 (20.44)	59.17 (21.90)	39.06 (26.32)†
Wechsler Memory Scale–Revised			
Logical Memory I (of 50)	24.56 (6.07)	22.17 (6.49)	19.65 (5.49)
Logical Memory II (of 50)	20.78 (7.06)	17.22 (6.66)	13.82 (5.84)
LM % Retention	83.68 (13.81)	77.12 (14.19)	68.72 (15.28)
Digit Span Forward	7.89 (1.86)	8.56 (2.31)	7.29 (1.86)
Digit Span Backward	6.94 (1.43)	7.44 (2.71)	5.12 (1.58)**††
California Verbal Learning Test			
Total Trials 1–5 (T-score)	42.44 (10.71)	41.35 (6.18)	32.83 (10.21)*†
List B	4.78 (1.83)	2.41 (3.00)	5.78 (4.12)
Short delay free (of 16)	8.17 (3.59)	7.29 (2.34)	6.22 (2.69)
Short delay free vs. List A (%)	−21.37 (20.74)	−25.58 (27.77)	−28.28 (17.67)
Long delay free (of 16)	8.28 (3.68)	8.41 (2.35)	6.00 (3.51)
Semantic clustering	1.30 (0.46)	1.73 (0.81)	1.31 (0.69)
Intrusions	3.94 (3.13)	3.47 (4.06)	6.39 (7.00)
Perseverations	5.00 (5.11)	3.18 (2.72)	4.61 (6.66)
Discriminability (%)	91.11 (5.07)	90.12 (6.85)	81.56 (11.64)*††

Note. Data are presented as the mean ± standard deviation in parentheses. NC = normal controls; PDND = Parkinson's disease–nondemented; PDD = Parkinson's disease–incident dementia.
*$p \leq .01$. **$p \leq .001$. (pairwise comparisons between PDD and PDND).
†$p \leq .01$. ††$p \leq .001$. (pairwise comparisons between PDD and NC).

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sons with incident PDD exhibited poorer word list recognition discriminability relative to participants in the PDND ($p < .01$, $d = 0.93$) and NC ($p < .001$, $d = 1.14$) groups.

There were no significant between-group differences identified on the language measures considered as a group, including confrontational naming, letter fluency, and animal naming (Wilk's $\Lambda = 0.92$, $F[2,50] = 0.73$, $p > .05$).

Classification Accuracy

ROC curves and predictive values were generated for CVLT Trials 1–5 and Recognition Discriminability, WCST Perseverative Errors, and WMS-R Digits Backward to determine the clinical utility of the neuropsychological variables that discriminated between PDD and PDND (see Table 2). In an effort to evaluate relative risk of incident PDD based on multiple measures impaired, we also assessed the diagnostic efficiency of a summary impairment index using these four test scores. The summary index was calculated as the total number of scores in the impaired range (as determined by the ROC plots) for each participant. Index scores ranged from zero to four.

Each of the predictor variables and the summary index performed significantly better than chance in correctly classifying the PDD and PDND groups (all $p < .05$). CVLT Trials 1–5 proved to be the most sensitive individual measure, with 89% of PDD patients exhibiting baseline T-scores less than 40. Similarly, 89% of patients with PDD displayed impaired test scores on two or more of the predictor variables included in the summary index. Specificity (i.e., the percentage of PDND participants with scores above cutoff) was comparable for each of the measures, and ranged between 65% (WCST Perseverative Errors) and 72% (CVLT Trials 1–5, CVLT Recognition Discriminability, and WMS-R Digits Backward). Overall predictive power (i.e., ratio of all true positive and true negative instances to the total number of test scores) was satisfactory, with values ranging from 68% (WCST Perseverative Errors) to 81% (CVLT Trials 1–5). The summary index provided the greatest positive predictive power (i.e., the ratio of all true positive instances to all test positives), with the PDD group accounting for 85% of all summary index scores falling in the impaired range (≥ 2 of 4 tests impaired). Although negative predictive values (i.e., the ratio of all true negative instances to all test negatives) remained relatively unchanged when corrected for prevalence rates, estimates of positive predictive power were slightly lower, ranging from 51% (CVLT Recognition Discriminability) to 67% (WCST Perseverative Errors).

DISCUSSION

To elucidate the prodromal cognitive characteristics of incident dementia in PD, we retrospectively examined the baseline neuropsychological profiles of PD patients who were diagnosed with incident dementia at one-year follow-up (PDD) as compared to demographically similar nondemented patients with PD (PDND) and normal controls (NC). Relative to NC participants, the PDD sample demonstrated impairment on measures of executive functioning, working memory, and verbal memory. When compared to the PDND group, incident PDD participants exhibited a greater number of perseverative errors on the WCST, poorer digits backward performance, and less efficient immediate auditory-verbal list learning and recognition discriminability (CVLT). Effect sizes (Cohen's *d*) derived from differences between the PDND and PDD samples' neuropsychological test scores at baseline were large, as values ranged from 0.93 (CVLT Recognition Discriminability) to 1.08 (Digits Backward).

While statistically discrepant neuropsychological performance between groups is important, such findings are of limited utility in diagnostic decision-making dilemmas in the individual case. Follow-up diagnostic efficiency statistics revealed that scores on CVLT Trials 1–5 and Recognition Discriminability, WCST Perseverative Errors, and WMS–R Digits Backward efficiently classified individuals within the PDD and PDND groups. Overall predictive power estimates for these measures fell between 68% (WCST Perseverative Errors) and 81% (CVLT Trials 1–5). A summary index comprised of the four predictor variables was highly sensitive to incident PDD (89%) and provided excellent positive predictive rates (85%) using a cutoff score of two or more measures impaired.

Table 2. Classification accuracy of neuropsychological measures and a summary index for predicting incident PDD

Variable	ROC	Sens.	Spec.	PPP	NPP	OPP	PPP-p	NPP-p
CVLT Trials 1–5 (< 40T)	0.798**	0.89	0.72	0.76	0.87	0.81	0.58	0.87
CVLT Rec. Discrim. (< 88%)	0.728*	0.67	0.72	0.71	0.68	0.69	0.51	0.69
WCST Persev. Errors (> 28)	0.768**	0.71	0.65	0.67	0.69	0.68	0.67	0.69
Digits Backward (< 6)	0.766**	0.71	0.72	0.71	0.72	0.71	0.52	0.71
Summary Index (≥ 2/4 tests impaired)	0.849***	0.89	0.67	0.85	0.70	0.75	0.53	0.86

Note. Classification accuracy statistics were calculated between the PDD and PDND groups. ROC = Total area under the receiver-operating curve; Sens. = sensitivity; Spec. = specificity; PPP = positive predictive power; NPP = negative predictive power; OPP = overall predictive power. PPP-p and NPP-p reflect positive and negative predictive values adjusted for an estimated 30% PDD prevalence rate.
*$p < .05$, **$p < .01$, ***$p < .001$

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The neuropsychological findings observed in incident PDD are unlikely to be secondary to generalized cognitive deficits as no significant group differences emerged on the baseline DRS. Discrepant neuropsychological performance between PDD and PDND cannot be explained by the effects of depression, demographics, or disease characteristics given that these variables were controlled for by matching. Although Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1997) Motor section scores may have allowed for more stringent control of disease severity, the Hoehn and Yahr ratings utilized in this study consistently show high correlations with the UPDRS (e.g., Martinez-Martin et al., 1994; Stebbins & Goetz, 1998).

Overall, the neuropsychological findings are consistent with the initial research hypotheses and prior investigations indicating that subtle frontal/executive dysfunction is evident during the immediate prodromal phase of dementia in PD (e.g., Jacobs et al., 1995a; Mahieux et al., 1998). Considering the known pathophysiology of PD, the current neuropsychological findings are interpreted to reflect a disruption of prefrontal-subcortical circuitry, with particular involvement of the basal ganglionic-thalamic-cortical loops associated with the dorsolateral (DLPFC) and anterior (APFC) prefrontal cortex. Digits backward, for example, is often characterized as a measure of working memory and is associated with activation of the DLPFC and APFC (Fletcher & Henson, 2001). Although the WCST is typically identified as a complex measure of executive functioning that is sensitive to a variety of cerebral pathologies (Spreen & Strauss, 1998), perseverative errors on this measure are consistently linked to dysfunction in the DLPFC (e.g., Lombardi et al., 1999).

At issue is whether verbal memory deficits observed in this study are also attributable to executive dysfunction and frontal pathophysiology. Memory deficits in PDD have traditionally been attributed to retrieval inefficiency (for reviews see Tröster et al., 2000; Tröster & Fields, 1995), yet recent research has highlighted the heterogeneity of PD memory profiles, and thus, in the cognitive mechanisms presumed to underlie memory deficits in PD (Filoteo et al., 1997; Stern et al., 1993b). Given the pattern of CVLT differences evident between the PDD and PDND groups in this study (specifically in immediate recall and recognition of a word list) one might hypothesize that an encoding or consolidation (rather than an executive) deficit is operative in PDD. Among these two possible mechanisms, the consolidation hypothesis is less attractive given the absence of significant differences among the NC, PD, and PDD groups' forgetting rates (contrasting short- and long-delay free recall on the CVLT, and percent retained for Logical Memory). Certainly, encoding has been reported to be deficient in PD (e.g., Buytenhuijs et al., 1994), and a contribution of temporal lobe dysfunction to deficient encoding cannot be excluded given evidence of reciprocal connections between temporal lobe and basal ganglia (see Middleton & Strick, 1996). Present clinical test data do not, however, permit disentanglement of "pure" encoding deficits from deficient *executive control* over encoding and retrieval processes. Given that functional neuroimaging research reveals that both encoding and retrieval are associated with activation of the prefrontal cortex (see Fletcher & Henson, 2001 for review), and because other functional neuroimaging and psychometric research supports the role of executive functions and prefrontal-subcortical circuitry in learning, recall and recognition of word lists (Johnson et al., 2001; Ricker et al., 2001; Spreen & Strauss, 1998; Stuss et al., 1994; Tremont et al., 2000; Vanderploeg et al., 1994), the idea that executive control mechanisms over encoding are deficient has merit. This explanation also has parsimony with the overall neuropsychological profile of PDD revealed in this study.

The present findings are generally consonant with those of previous studies of incident PDD (e.g., Jacobs et al., 1995a; Mahieux et al., 1998; Piccirilli et al., 1989); however, the insignificant verbal fluency results differ from earlier investigations and warrant further consideration. The absence of verbal fluency differences is surprising, particularly since this task requires the initiation and persistence of retrieval strategies and is often associated with frontal/executive functions (Spreen & Strauss, 1998). Furthermore, several cross-sectional studies have described letter and category fluency deficits in PD with dementia, but not in patients without dementia (e.g., Testa et al., 1998; Tröster et al., 1998). In the present sample, however, the three groups performed similarly on animal naming and letter fluency (all $p \geq .10$). Despite conflicting with the work of Jacobs et al. (1995a) who reported adequate predictive values for verbal fluency, these results are consonant with the work of Mahieux et al. (1998) who found only a trend for letter fluency and non-significant results for category fluency in predicting incident PDD. Further longitudinal research is needed to reconcile these inconsistent verbal fluency findings, which are likely related to several factors, including differences in methodology, sample size and composition, global cognitive ability, and/or task complexity (Piatt et al., 1999a). Measures of action (verb) fluency might be useful to this end considering this instruments' sensitivity to PDD and its convergent validity with other measures of frontostriatal functions (Piatt et al., 1999a, 1999b).

Certain limitations to the current findings deserve mention. The PD and NC samples consisted primarily of highly educated Caucasian males, which raises concerns regarding generalizability. Although the one year interval between baseline and follow-up neuropsychological evaluations provides a clearer picture of the cognitive deficits immediately prior to the formal diagnosis of dementia, one cannot confidently assert that the neuropsychological tests revealing dysfunction at baseline represent *prodromal* PDD rather than the early stages of PDD itself. Additionally, without neuropathological confirmation one cannot rule out the possibility that the incident PDD participants developed concomitant AD or another dementing process rather than a PD-related dementia. Yet participants with suspected comorbid dementia other than PDD were excluded on the basis of compre-

hensive clinical evaluations at baseline and follow-up. Furthermore, the profile of frontal/executive dysfunction described above differs from the neuropsychological profile associated with incident AD, which, in addition to a rapid rate of forgetting, typically includes deficits in semantic memory, object naming, and verbal abstract reasoning (e.g., Jacobs et al., 1995b; Peterson et al., 2001). In the absence of specific treatments for different dementias, the most salient clinical issue remains prediction of dementia in the patient with PD, rather than the prediction of the neuropathologically confirmed etiology of the decline.

In summary, results from this study indicate that subtle frontal/executive dysfunction is apparent during the immediate PDD prodrome (that is, at least one year prior to formal diagnosis) and is useful in identifying those patients who are at greatest risk for incident dementia. Early identification of PDD is of clinical importance because dementia in PD is commonly associated with increased mortality (Marder et al., 1991), caregiver distress (Aarsland et al., 1999), poorer quality of life (Schrag et al., 2000), greater medical costs due to nursing home placement (Aarsland et al., 2000), and poorer treatment outcomes (Fields & Tröster, 2000; Jacobs et al., 2000; Marder, et al., 1991). Comprehensive neuropsychological evaluation may facilitate early identification of incident PDD and subsequently inform appropriate therapeutic regimens, caregiver preparations, as well as legal and financial planning. When coupled with appropriate medical and psychosocial management, early identification of PDD may ultimately serve to improve patients quality of life by delaying the onset and/or impact of this debilitating disorder, thereby also potentially curbing direct and indirect clinical expenditures associated with PDD (Peterson et al., 2001).

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REFERENCES

Aarsland, D., Larsen, J.P., Karlsen, K., Lim, N.G., & Tandberg, E. (1999). Mental symptoms in Parkinson's disease are important contributors to caregiver distress. *International Journal of Geriatric Psychiatry*, *14*, 866–874.

Aarsland, D., Larsen, J.P., Tandberg, E., & Laake, K. (2000). Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study. *Journal of the American Geriatric Society*, *48*, 938–942.

Baldessarini, E.J., Finklestein, S., & Arana, G.W. (1983). The predictive power of diagnostic tests and the effect of prevalence of illness. *Archives of General Psychiatry*, *40*, 569–573.

Beck, A.T. (1992). *Beck depression inventory*. Manual. San Antonio TX: Psychological Corporation.

Benton, A.L., Hamsher. K., & Sivan, A.B. (1994). *Multilingual aphasia examination* (3rd ed.). Iowa City, IA: AJA Associates.

Biggins, C.A., Boyd, J.L., Harrop, F.M., Madeley, P., Mindham, R.H.S., Randall, J.I., & Spokes, E.G.S. (1992). A controlled, longitudinal study of dementia in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*, 566–571.

Blair, J.R. & Spreen, O. (1989). Predicting premorbid IQ: A revision of the national adult reading test. *The Clinical Neuropsychologist*, *3*, 129–136.

Buytenhuijs, E.L., Berger, H.J.C., VanSpaendonck, K.P.M., Horstink, W.I.M., Borm, G.F., & Cools, A.R. (1994). Memory and learning strategies in patients with Parkinson's disease. *Neuropsychologia*, *32*, 335–342.

Cummings, J.L. & Benson, D.F. (1983). *Dementia: A clinical approach*. Boston: Butterworths.

Delis, D.C., Kramer, J.H., Kaplan, E., & Ober, B.A. (1987). *California verbal learning test: Adult version*. San Antonio, TX: The Psychological Corporation.

Dubois, B. & Pillon, B. (1998). Cognitive and behavioral aspects of movement disorders. In J. Jankovic & E. Tolosa (Eds.), *Parkinson's disease and movement disorders* (3rd ed.). (pp. 837–858). Baltimore, MD: Williams & Wilkins.

Fahn, S., Elton, R.L., & Members of the UPDRS Development Committee. (1987). The Unified Parkinson's Disease Rating Scale. In: S. Fahn, S.D. Marden, D.B. Calne, & M. Goldstein (Eds.), *Recent developments in Parkinson's disease*, Vol. 2 (pp. 153–163). Florham Park, NJ: Macmillan Healthcare.

Fields, J.A. & Tröster, A.I. (2000). Cognitive outcomes after deep brain stimulation for Parkinson's disease: A review of initial studies and recommendations for future research. *Brain and Cognition*, *42*, 268–293.

Filoteo, J.V., Rilling, L.M., Cole, B., Williams, B.J., Davis, J.D., & Roberts, J.W. (1997). Variable memory profiles in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*, *19*, 878–888.

Fletcher, P.C. & Henson, R.N. (2001). Frontal lobes and human memory: Insights from functional neuroimaging. *Brain*, *124*, 849–881.

Glatt, S.L., Hubble, J.P., Lyons, K., Paolo, A., Tröster, A.I., Hassanein, R.E.S., & Koller, W.C. (1996). Risk factors for dementia in Parkinson's disease: Effect of education. *Neuroepidemiology*, *15*, 20–25.

Heaton, R.K., Chelune, G.J., Talley, J.L., Kay, G.G., & Curtis, G. (1993). *Wisconsin card sorting test manual—revised and expanded*. Odessa, FL: Psychological Assessment Resources.

Hughes, T.A., Ross, H.F., Musa, S., Bhattacherjee, S., Nathan, R.N., Mindham, R.H.S., & Spokes, E.G.S. (2000). A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. *Neurology*, *54*, 1596–1602.

Jacobs, D.M., Marder, K., Cote, L.J., Sano, M., Stern, Y., & Mayeux, R. (1995a). Neuropsychological characteristics of preclinical dementia in Parkinson's disease. *Neurology*, *45*, 1691–1696.

Jacobs, D.M., Sano, M., Dooneief, G., Marder, K., Bell, K.L., & Stern, Y. (1995b). Neuropsychological detection and characterization of preclinical Alzheimer's disease. *Neurology*, *45*, 957–962.

Jacobs, D.M., Stern, Y., & Mayeux, R. (2000). Dementia in Parkinson's disease, Huntington's disease, and other degenerative conditions. In M.J. Farah & T.E. Feinberg (Eds.), *Patient-based approaches to cognitive neuroscience* (pp. 375–384). Cambridge, MA: MIT Press.

Johnson, S.C., Saykin, A.J., Flashman, L.A., McAllister, T.W., & Sparling, M.B. (2001). Brain activation on fMRI and verbal memory ability: Functional neuroanatomic correlates of CVLT

performance. *Journal of the International Neuropsychological Society*, *7*, 55–62.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *Boston naming test*. Philadelphia: Lea & Febiger.

Lombardi, W.J., Andreason, P.J., Sirocco, K.Y., Rio, D.E., Gross, R.E., Umhau, J.C., & Hommer, D.W. (1999). Wisconsin card sorting test performance following head injury: Dorsolateral fronto-striatal circuit activity predicts perseveration. *Journal of Clinical and Experimental Neuropsychology*, *21*, 2–16.

Luria, A.R. (1966). *Higher cortical functions in man*. London: Tavistock.

Mahieux, F., Fenelon, G., Flahault, A., Manifacier, M.J., Michelet, D., & Boller, F. (1998). Neuropsychological prediction of dementia in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *64*, 178–183.

Marder, K., Leung, D., Tang, M., Bell, K., Dooneief, G., Cote, L., Stern, Y., & Mayeux, R. (1991). Are demented patients with Parkinson's disease accurately reflected in prevalence surveys? A survival analysis. *Neurology*, *41*, 1240–1243.

Marder, K., Tang, M.X., Cote, L., Stern, Y., & Mayeux, R. (1995). The frequency and associated risk factors for dementia in patients with Parkinson's disease. *Archives of Neurology*, *52*, 695–701.

Martinez-Martin, P., Gil-Nagel, A., Gracia, L.M., Gomez, J.B., Martinez-Sarries, J., & Bermejo, F. (1994). Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. *Movement Disorders*, *9*, 76–83.

Mattis, S. (1988). *Dementia rating scale: Professional manual*. Odessa FL: Psychological Assessment Resources.

Mayeux, R., Chen, J., Mirabello, E., Marder, K., Bell, K., Dooneief, G., Cote, L., & Stern, Y. (1990). An estimate of the incidence of dementia in idiopathic Parkinson's disease. *Neurology*, *40*, 1513–1517.

Middleton, F.A. & Strick, P.L. (1996). The temporal lobe is a target of output from the basal ganglia. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 8683–8687.

Peterson, R.C., Stevens, J.C., Ganguli, M., Tangalos, E.G., Cummings, J.L., & DeKosky, S.T. (2001). Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, *56*, 1133–1142.

Piatt, A.L., Fields, J.A., Paolo, A.M., Koller, W.C., & Tröster, A.I. (1999a). Lexical, semantic, and action verbal fluency in Parkinson's disease with and without dementia. *Journal of Clinical and Experimental Neuropsychology*, *21*, 435–443.

Piatt, A.L., Fields, J.A., Paolo, A.M., & Tröster, A.I. (1999b). Action (verb naming) fluency as an executive function measure: Convergent and divergent evidence of validity. *Neuropsychologia*, *37*, 1499–1503.

Piccirilli, M., D'Alessandro, P., Finali, G., Piccinin, G.L., & Agostini, L. (1989). Frontal lobe dysfunction in Parkinson's disease: Prognostic value for dementia? *European Neurology*, *29*, 71–76.

Ricker, J.H., Muller, R.A., Zafonte, R.D., Black, K.M., Millis, S.R., & Chugani, H. (2001). Verbal recall and recognition following traumatic brain injury: A [0-15]-water positron emission tomography study. *Journal of Clinical and Experimental Neuropsychology*, *23*, 196–206.

Salganik, I. & Korczyn, A. (1990). Risk factors for dementia in Parkinson's disease. *Advances in Neurology*, *53*, 343–347.

Schrag, A., Jahanshahi, M., & Quinn, N. (2000). What contributes to quality of life in patients with Parkinson's disease? *Journal of Neurology, Neurosurgery, and Psychiatry*, *69*, 308–312.

Spreen, O. & Strauss, E. (1998). *A compendium of neuropsychological tests: Administration, norms, and commentary* (2nd ed.). New York: Oxford University Press.

Stebbins, G.T. & Goetz, C.G. (1998). Factor structure of the Unified Parkinson's Disease Rating Scale: Motor Examination section. *Movement Disorders*, *13*, 633–636.

Stern, Y., Marder, K., Tang, M.X., & Mayeux, R. (1993a). Antecedent clinical features associated with dementia in Parkinson's disease. *Neurology*, *43*, 1690–1692.

Stern, Y., Richards, M., Sano, M., & Mayeux, R. (1993b). Comparison of cognitive changes in patients with Alzheimer's and Parkinson's disease. *Archives of Neurology*, *50*, 1040–1045.

Stuss, D.T., Alexander, M.P., Palumbo, C.L., Buckle, L., Sayer, I., & Pogue, J. (1994). Organizational strategies of patients with unilateral or bilateral frontal lobe injury on word list learning tasks. *Neuropsychology*, *8*, 355–373.

Testa, J.A., Tröster, A.I., Fields, J.A., Gleason, A.C., Salmon, D.P., & Beatty, W.W. (1998). Semantic fluency performance of patients with cortical and subcortical neurodegenerative diseases. *Aging, Neuropsychology, and Cognition*, *5*, 203–214.

Tremont, G., Halpert, S., Javorsky, D., & Stern, R.A. (2000). Differential impact of executive dysfunction on verbal list learning and story recall. *The Clinical Neuropsychologist*, *14*, 295–302.

Tröster, A.I. & Fields, J.A. (1995). Frontal cognitive function and memory in Parkinson's disease: Toward a distinction between prospective and declarative memory impairments. *Behavioural Neurology*, *8*, 59–74.

Tröster, A.I., Fields, J.A., Testa, J.A., Paul, R.H., Blanco, C.R., Hames, K.A., Salmon, D.P., & Beatty, W.W. (1998). Cortical and subcortical influences on clustering and switching in the performance of verbal fluency tasks. *Neuropsychologia*, *36*, 295–304.

Tröster, A.I., Fields, J.A., & Koller, W.C. (2000). Parkinson's disease and parkinsonism. In C.E. Coffey, & J.L. Cummings (Eds.), *The American Psychiatric Press textbook of geriatric neuropsychiatry* (2nd ed.). (pp. 559–600). Washington, DC: American Psychiatric Press, Inc.

Vanderploeg, R.D., Schinka, J.A., & Retzlaff, P. (1994). Relationship between measures of auditory verbal learning and executive functioning. *Journal of Clinical and Experimental Neuropsychology*, *16*, 243–252.

Wechsler, D. (1981). *Wechsler adult intelligence scale–revised*. San Antonio: The Psychological Corporation.

Wechsler, D. (1987). *Wechsler memory scale–revised. Manual*. San Antonio: The Psychological Corporation.

Zhang, Z.X., Anderson, D.W., & Mantel, N. (1990). Geographic patterns of parkinsonism-dementia complex on Guam. *Archives of Neurology*, *47*, 1069–1074.