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# Neuropsychological characteristics of preclinical dementia in Parkinson's disease

D.M. Jacobs, PhD; K. Marder, MD, MPH; L.J. Côté, MD; M. Sano, PhD; Y. Stern, PhD; and R. Mayeux, MD, MSE

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**Article abstract**—The goal of this study was to characterize the changes in cognition associated with the earliest, or preclinical, stages of dementia in Parkinson's disease (PD). We administered a comprehensive neuropsychological test battery to a group of initially nondemented PD patients participating in a longitudinal community-based epidemiologic study. We used Cox proportional hazards models to assess the relative risk of incident dementia associated with baseline scores on the neuropsychological tests. Baseline performance on two verbal fluency tasks (letter fluency and category fluency) was significantly and independently associated with incident dementia. Tests of memory, orientation, abstract reasoning, naming, and constructional skill were less sensitive predictors of subsequent dementia. The neuropsychological pattern characterizing the preclinical stages of dementia in PD differed from that described previously in preclinical Alzheimer's disease. Results suggest that poor performance on tests of verbal fluency may represent a distinct characteristic of the preclinical phase of dementia in PD.

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Recent reports from several prospective longitudinal studies of aging and dementia have indicated that, in healthy older adults who later develop dementia, neuropsychological tests can detect subtle cognitive changes well before the overt clinical signs of dementia are evident. The stage of the degenerative process prior to the clinical diagnosis of dementia, when only subtle or circumscribed cognitive deficits are evident, has been termed the "preclinical phase" of dementing illness.<sup>1</sup> Masur et al<sup>2</sup> followed 317 initially nondemented participants in the Bronx Aging Study for at least 4 years. Using logistic regression, they found that four measures of cognitive function from the baseline assessment identified one subgroup of subjects with an 85% probability of developing dementia during the follow-up period and another group with a 95% probability of remaining dementia-free. Similarly, we examined the associations between baseline neuropsychological test scores and subsequent development of dementia in 443 initially nondemented participants in a community-based, epidemiologic study of dementia in northern Manhattan, NY.<sup>3</sup> Using Cox proportional hazards models, we found that scores on the Boston Naming Test,<sup>4</sup> immediate

recall on the Selective Reminding Test,<sup>5</sup> and the Similarities subtest of the Wechsler Adult Intelligence Scale-Revised<sup>6</sup> were significantly and independently associated with later diagnosis of Alzheimer's disease (AD).

There have been no prospective, longitudinal studies focusing on the neuropsychological manifestations of preclinical dementia in patients with Parkinson's disease (PD). Cross-sectional neuropsychological investigations examining specific domains of cognitive function in PD have indicated that, relative to age-matched normal controls, nondemented patients with PD are impaired on tasks requiring such cognitive abilities as verbal fluency,<sup>7-13</sup> executive functions,<sup>9,14-16</sup> visuospatial skills,<sup>17-19</sup> and recall memory.<sup>20,21</sup> Longitudinal follow-up of these patients would be useful in illuminating whether these relative impairments remain circumscribed to specific cognitive domains or are early manifestations of dementia. To address this issue, we followed a cohort of initially nondemented PD patients for at least 1 year. We then examined the relative risk of incident dementia associated with scores on neuropsychological tests administered at baseline.

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From the Gertrude H. Sergievsky Center (Drs. Jacobs, Marder, Côté, Sano, Stern, and Mayeux) and the Departments of Neurology (Drs. Jacobs, Marder, Côté, Sano, Stern, and Mayeux) and Psychiatry (Drs. Stern and Mayeux), Columbia University College of Physicians and Surgeons; the Center for Alzheimer's Disease Research in the City of New York (Drs. Jacobs, Marder, Côté, Sano, Stern, and Mayeux); and the Division of Epidemiology (Dr. Mayeux), Columbia University School of Public Health, New York, NY.

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Address correspondence and reprint requests to Dr. Diane M. Jacobs, Gertrude H. Sergievsky Center, 630 West 168th Street, New York, NY 10032.

**Methods. Subjects.** Data were obtained from subjects participating in a community-based, epidemiologic study of PD and related disorders in northern Manhattan, NY. Establishment of the cohort has been described in detail elsewhere.<sup>22</sup> Briefly, subjects were identified through the development of a "registry" for PD and related disorders. Sources of patients included regional hospitals, private practitioners, health maintenance organizations, senior centers, government agencies, and newspaper and radio announcements.

Subjects included in the analyses presented here had completed at least one annual follow-up evaluation in addition to the baseline assessment. Because we were interested in defining the neuropsychological characteristics of preclinical dementia in PD, subjects diagnosed as demented at their initial assessment were excluded from these analyses. In addition, subjects with a history of stroke prior to the baseline assessment were excluded.

**Procedures.** Subjects were evaluated annually and received the same standardized neurologic and neuropsychological assessment at each study visit. One of three physicians (K.M., L.J.C., or R.M.) conducted a standardized physical and neurologic examination to confirm the diagnosis of PD and recorded each subject's medical history. Idiopathic PD was defined by clinical and research criteria.<sup>23-25</sup> We excluded patients with secondary parkinsonism resulting from phenothiazines, alpramethyldopa, reserpine, or metaclopramide hydrochloride. Patients with clinical presentations suggestive of progressive supranuclear palsy, essential tremor, Shy-Drager syndrome, presumed striatonigral degeneration, and olivopontocerebellar atrophy were also excluded. Motor signs and symptoms were rated using the Unified Parkinson's Disease Rating Scale (UPDRS).<sup>26</sup> Symptoms of depression were rated using the Hamilton Depression Rating Scale.<sup>27</sup>

The neuropsychological battery was designed to be brief yet also to assess a broad range of cognitive functions. Evaluations were conducted in either English or Spanish, based on the subject's primary language and opinion of which language would yield better performance. To assure comparability of evaluations in English and Spanish, all interview questions, test instructions, and stimuli were translated into Spanish and then translated back to ensure accuracy. Specific cognitive functions assessed and neuropsychological tests administered included the following:

**Word list learning and memory.** The Selective Reminding Test (SRT)<sup>5</sup> was administered to assess verbal memory. Subjects were given six trials to learn a list of 12 unrelated words. To assess long-term retention of the word list, 15-minute delayed free recall was assessed, followed by a multiple-choice recognition task.

**Nonverbal memory.** A multiple-choice version of the Benton Visual Retention Test-Form D (BVRT)<sup>28</sup> was used to assess nonverbal memory. Subjects viewed a geometric design for 10 seconds. It was then removed from view, and the subject was asked to recognize the design in a four-choice multiple-choice array.

**Orientation.** The 10 orientation items from the Mini-Mental State Examination (MMSE)<sup>29</sup> were used to assess orientation to time and place.

**Verbal reasoning.** The Similarities subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R),<sup>6</sup> which requires subjects to identify relevant similarities or superordinate categories for paired items, was administered.

**Nonverbal reasoning.** The Identities and Oddities subtest of the Mattis Dementia Rating Scale<sup>30</sup> was used to assess nonverbal reasoning. In this test, subjects identify

which two of three visually presented stimuli are the same. After all eight triads are completed, the same items are administered again, and the subject is required to identify the one item that is different.

**Naming.** A 15-item version of the Boston Naming Test,<sup>4</sup> a test of visual confrontation naming, was used to assess word-finding ability.

**Letter fluency.** Subjects were instructed to generate as many words as possible in 1 minute that began with a given letter of the alphabet, excluding proper nouns and the same word with different suffixes.<sup>31</sup> English-speaking subjects generated words beginning with the letters C, F, and L, while Spanish-speaking subjects generated words beginning with the letters P, S, and V. Different letters were used for Spanish- and English-speaking subjects to control for word-frequency differences across the two languages.

**Category fluency.** All subjects generated exemplars in the categories animals, foods, and clothing; 60 seconds was allowed for each category. For animal fluency, subjects were instructed to name any type of animal but were provided superordinate categories (animals from the farm, jungle, or ocean, or house pets) to assist retrieval. For clothing and food fluency, subjects were instructed to name essentially anything one can wear or eat, respectively.

**Auditory comprehension.** The first six items of the Complex Ideational Material subtest of the Boston Diagnostic Aphasia Examination<sup>32</sup> were used to assess comprehension of spoken language.

**Repetition.** Subjects were asked to repeat the high-frequency phrases from the Boston Diagnostic Aphasia Examination Repetition of Phrases subtest.<sup>32</sup>

**Visuoconstructional skills.** Subjects copied five designs from the Rosen Drawing Test<sup>33</sup> ranging in difficulty from simple geometric shapes to overlapping, parallel, and three-dimensional figures.

**Visuospatial skills.** Subjects matched a target design to the same design presented simultaneously in a four-choice multiple-choice array containing the target along with three distractors. Target stimuli corresponded to Form C of the original BVRT.<sup>28</sup>

Following each evaluation, medical, historical, and neuropsychological data were reviewed at a diagnostic conference of physicians and neuropsychologists, and a consensus diagnosis of presence or absence of dementia was made. The diagnosis of dementia was based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, revised third edition,<sup>34</sup> and required evidence of cognitive deficit on the neuropsychological battery as well as evidence of impairment in social or occupational function. Neuropsychological test scores were evaluated using a fixed paradigm<sup>35</sup>: criterion scores were applied to each test score, and subjects performing below these scores on two of three aspects of memory testing (ie, immediate verbal, delayed verbal, or visual memory) plus two other cognitive domains (ie, orientation, language, abstract reasoning, or visuospatial skills) were considered to have sufficient cognitive deficit to meet criteria for dementia. Criterion scores were determined previously based upon a review of the performance of 172 patients and controls who had been evaluated in other studies or in our Memory Disorders Clinic. For each test, mean scores and variability in each group were inspected, and the score that best separated nondemented and demented groups was selected as the criterion score.<sup>35</sup>

**Data analysis.** We used Cox proportional hazards models<sup>36</sup> to assess the relative risk (RR) of incident de-

**Table 1. Baseline characteristics of subjects who did and did not become demented**

Mean (SD) variable	Incident dementia (N = 23)	No incident dementia (N = 88)	
Age	75.59 (8.10)	69.21 (11.35)	$t = 2.53; p < 0.02$
Education	10.30 (3.72)	11.44 (5.02)	$t = 1.02; NS$
Sex (% female)	57	43	$\chi^2 = 1.31; NS$
Language (% Spanish)	39	39	$\chi^2 = 0.00; NS$
Duration of Parkinson's disease (yr)*	8.77 (7.38)	6.51 (6.80)	$t = 1.94; NS$
UPDRS	30.83 (13.98)	23.41 (11.99)	$t = 2.55; p < 0.02$
Hamilton	8.13 (6.06)	5.84 (5.07)	$t = 1.85; p < 0.07$
Blessed IMC	5.09 (4.00)	4.05 (3.80)	$t = 1.28; NS$

UPDRS Unified Parkinson's Disease Rating Scale total score (motor portion).  
Hamilton Hamilton Depression Rating Scale total score.  
IMC Information-Memory-Concentration Test.  
NS Not significant.  
\* Duration of Parkinson's disease from first symptom to baseline evaluation.

mentia associated with baseline scores on the neuropsychological tests. Duration of follow-up was used as the timing variable for Cox analyses. For incident dementia cases with more than one follow-up visit, we used duration from baseline to the first follow-up visit at which dementia was diagnosed; for subjects who remained free of dementia, we used duration from baseline to the last available follow-up visit.

We conducted both exploratory and confirmatory Cox analyses. First, to reduce the large number of candidate variables in the neuropsychological test battery, we performed an exploratory analysis using stepwise Cox regression with backward stepping. Fourteen scores from the baseline neuropsychological assessment competed for retention in the model. The outcome was incident dementia, and the criterion for removal from the model was  $p > 0.05$ . The following variables were included in this initial analysis: total immediate recall, delayed recall, and delayed recognition from the SRT<sup>5</sup>; age-corrected scaled score from the WAIS-R Similarities subtest<sup>6</sup>; total number of words generated across three trials each of letter<sup>31</sup> and category fluency; and total correct on the Identities and Oddities subtest of the Mattis Dementia Rating Scale,<sup>30</sup> Rosen Drawing Test,<sup>33</sup> Benton Visual Retention Test<sup>28</sup> Matching and Recognition Memory, Boston Naming Test,<sup>4</sup> Repetition and Auditory Comprehension from the Boston Diagnostic Aphasia Examination,<sup>32</sup> and the MMSE orientation items.<sup>29</sup>

We then confirmed the usefulness of the variables retained in the stepwise analysis by reexamining them in a Cox regression with simultaneous entry of variates and covariates. In addition to the neuropsychological test scores, age, education, sex, and duration of PD symptoms were included as covariates. Because our previous investigations have shown that severity of motor signs and depression are significant predictors of incident dementia in PD,<sup>37</sup> baseline scores on the Hamilton Depression Rating Scale and UPDRS also were included as covariates. All variables were entered into the model simultaneously; thus, the RR associated with each variable was independent of all other variates and covariates.

**Results.** One hundred twenty-two PD patients who were not demented at the time of their initial assessment had completed at least one follow-up

evaluation. Eleven of these patients were excluded from the current analysis because they were missing baseline data for one or more of the following variables: letter fluency ( $n = 7$ ), category fluency ( $n = 7$ ), Hamilton Depression Rating Scale ( $n = 6$ ), and UPDRS ( $n = 1$ ). The remaining 111 subjects were included in the Cox models. Twenty-three of the 111 initially nondemented subjects were diagnosed with dementia at follow-up. The average duration of follow-up was 2.70 ( $\pm 1.03$ ) years.

Baseline characteristics of subjects who did and did not become demented are presented in table 1. Subjects who subsequently became demented were older, had more severe motor symptoms, and had more symptoms of depression at baseline than those who did not become demented. The two groups did not differ significantly in education, sex, language spoken, or disease duration. Of note, no significant difference was observed on baseline scores on the Blessed Information-Memory-Concentration Test,<sup>38</sup> indicating that the two groups were comparable in terms of overall level of cognitive function at the time of initial assessment. The percentage of patients receiving dopamine agonists (83% incident dementia, 75% no dementia) and anticholinergics (22% incident dementia, 17% no dementia) for treatment of PD did not differ between those who did or did not become demented.

Four of the 14 neuropsychological variables in the stepwise Cox regression were retained after backward stepping: total immediate recall on the SRT, category fluency, letter fluency, and Mattis Identities and Oddities. When these four variables were entered simultaneously in a Cox regression along with the covariates (age, education, sex, Hamilton, and UPDRS), the RR of incident dementia associated with baseline scores on letter fluency and category fluency remained significant. Total immediate recall on the SRT and Mattis Identities and Oddities did not contribute significantly to the model that included the covariates. In the final model, letter and category fluency were retained along with the co-

**Table 2. Risk ratios for incident dementia derived from a Cox proportional hazards model with simultaneous entry of variables\***

Variable	Adjusted risk ratio	95% Confidence interval	p Value<
Age	1.06	1.01-1.11	0.02
Education	1.01	0.91-1.12	NS
Sex (female)	0.73	0.30-1.82	NS
Duration of Parkinson's disease (yr)	1.01	0.95-1.08	NS
UPDRS total score	1.04	1.01-1.09	0.03
Hamilton total score	1.11	1.02-1.21	0.03
Letter fluency (score below median)	3.31	1.01-10.83	0.05
Category fluency (score below median)	6.01	1.25-28.84	0.03

\* The risk ratio for each variable represents its associated relative risk independent of all other variables in the model.

UPDRS Unified Parkinson's Disease Rating Scale (motor portion).

Hamilton Hamilton Depression Rating Scale.

variables. To aid in the interpretation of RR values, we dichotomized baseline test performance on each of the fluency tasks into scores above and below the median, and then examined the RR associated with obtaining a score below the median. The median total score for letter fluency was 27 words; for category fluency the median total was 42 items. RR values are presented in table 2. Letter fluency, category fluency, age, degree of depressive symptomatology, and severity of extrapyramidal signs were significantly and independently associated with incident dementia. Education, sex, and duration of PD were not significantly associated with incident dementia.

**Discussion.** The current results suggest that impaired performance on tests of verbal fluency in PD may represent a harbinger of more global and severe cognitive impairment. Although letter and category fluency tests were originally developed to assess fluency in aphasic patients, we hypothesize that the poor performance of PD patients on these tasks does not reflect a primary impairment of language but is a sign of executive dysfunction associated with the incipient stages of dementia. To generate words efficiently on these tasks, subjects must plan and initiate a systematic search of semantic memory.<sup>39,40</sup>

There is discrepancy across previous cross-sectional studies as to the relative impairment on tests of letter versus category fluency in PD patients. While some investigators report impairment on tests of both letter and category fluency in PD patients,<sup>12</sup> others report impairment only on letter fluency tasks,<sup>8</sup> while still others report impairment on category but not letter fluency.<sup>11,13</sup> In the current study, we found that both letter and category fluency tests were sensitive to the subtle cognitive changes associated with preclinical dementia in PD.

Relative to age-referenced normative data, PD patients who subsequently became demented scored, on average, at the 15th percentile on category fluency and the 20th percentile on letter fluency, while those who remained nondemented scored at the 44th percentile on both fluency tasks. Thus, there appears to be a nonspecific impairment on tests of verbal fluency in nondemented PD patients who later develop clinically significant dementia.

The discrepant findings of previous cross-sectional studies comparing letter and category fluency tests in PD patients and normal control subjects may be due to differences in task demands or instructions across studies. Although specific instructions seldom are described in research articles, the studies probably used different stimuli (ie, letters and categories) and instructions. Letters differ with regard to their frequency of occurrence as the initial letter of words, and categories differ with regard to the number of possible exemplars, so the difficulty level of fluency tasks can vary depending upon the letters and categories used. Similarly, test instructions can alter the difficulty of a task. For example, the difficulty of the category fluency test can be modified based on whether or not the instructions provide superordinate categories as retrieval cues. The benefit provided by these more explicit instructions may be particularly pronounced for PD patients, because these patients often have difficulty initiating cognitive strategies for retrieving stored information. Randolph et al<sup>39</sup> reported significant impairment in PD patients relative to normal control subjects on an uncued category fluency task; however, the performance of PD patients was normalized when retrieval cues were provided. Subjects in the current study were provided with superordinate categories to assist retrieval; thus, scores may have been relatively higher than if an uncued fluency task had been administered. Nevertheless, performance on the cued category fluency task was a good predictor of incident dementia.

The neuropsychological pattern characterizing the preclinical stages of dementia in PD differs from that reported in our earlier work describing the neuropsychological characteristics of preclinical AD in nondemented healthy elderly subjects.<sup>3</sup> Verbal fluency scores did not predict incident AD in healthy elders. Instead, the neuropsychological characteristics of preclinical AD were poor immediate recall on the SRT,<sup>5</sup> visual confrontation naming (Boston Naming Test),<sup>4</sup> and verbal abstract reasoning (WAIS-R Similarities subtest).<sup>6</sup> The PD incident dementia patients described here, and the incident AD patients described previously, scored comparably on a mental status screening examination<sup>38</sup> administered at baseline; thus, this disparate result between these two subject groups does not appear to be attributable to a difference in overall severity of cognitive impairment.

The distinct neuropsychological manifestation of preclinical dementia in PD patients and healthy elderly subjects suggests differences in the onset and

progression of dementia in PD compared with AD. Different pathologic substrates may be accounting for the differences in test performance between these subject groups. Results similar to those reported here were observed when we compared nondemented and demented PD patients with AD patients<sup>41</sup>; nondemented and demented PD patients performed worse than AD patients on verbal fluency and visuospatial tasks, even after the PD and AD groups were equated for overall level of cognitive function. We hypothesize that when dementia occurs in PD, worsening memory is superimposed on cognitive changes that already exist in nondemented patients, but that the dementing process is not due to concomitant AD. As speculated previously,<sup>39</sup> the difficulties with initiating retrieval of information (eg, category exemplars) and generating responses exhibited by PD patients may be due to striatal dysfunction, while the memory, naming, and verbal abstract reasoning deficits in AD patients likely reflect cortical degeneration. There are several possible causes of dementia in PD, however, such as dopamine depletion, cortical Lewy bodies, and cortical cholinergic deficiency with or without AD pathology. As we have not yet obtained post-mortem analyses on the participants in this study, we can conclude only that diminished verbal fluency might be a precursor of any of these conditions.

A potential limitation of the current study is that the tasks within our neuropsychological test battery are not comparable for overall level of difficulty. Thus, variations in test sensitivity may have contributed to the specific profile of deficits that emerged as being predictive of incident dementia. Further, our test battery does not include formal measures of "executive function" on which nondemented patients with PD often perform poorly, such as the Wisconsin Card Sorting Test,<sup>42</sup> the Stroop Test,<sup>43</sup> or the Trail Making Test.<sup>44</sup> These tests might have detected additional subtle cognitive changes in our nondemented PD patients who subsequently became demented and might have provided a further independent contribution to the prediction of incident dementia. As noted above, we hypothesize that the poor performance of some PD patients on our tests of verbal fluency reflects executive dysfunction.

In summary, the current study provides evidence of a preclinical phase in the dementia of PD and suggests that the neuropsychological characteristics of predementia in PD are distinct from those previously reported to be associated with preclinical AD. The divergent cognitive profiles between PD and AD patients may reflect different pathologic substrates for the dementia syndromes associated with these two diseases.

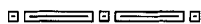
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# Emotional facial imagery, perception, and expression in Parkinson's disease

Daniel H. Jacobs, MD; Jeffrey Shuren, MD; Dawn Bowers, PhD; and Kenneth M. Heilman, MD

**Article abstract**—Patients with Parkinson's disease (PD) may be impaired at expressing emotional faces and perceiving emotional facial affect. We tested the hypothesis that patients with PD may be impaired at imaging emotional faces. We first compared 12 patients with PD and 30 control subjects on perceptual and imagery tasks. Patients were significantly impaired on a task of emotional facial imagery but not on a control task of object imagery. Patients were also impaired on a task of perceiving emotional faces. Subsequently, we found that PD patients were impaired relative to controls on making emotional faces. Performance on both the perceptual and motor tasks of facial expression significantly correlated with performance on the emotional facial imagery task. We suggest that the basal ganglia, together with the right hemisphere, are part of a neural network subserving emotional facial tasks.

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The formation of mental images is assumed to depend upon accessing long-term memory stores from visual cortical representations.<sup>1,2</sup> Initially, Farah<sup>1</sup>

proposed that visual representations, used both for imagery and for perception, were housed in the posterior left hemisphere. However, dissociations

From the Department of Neurology, University of Florida College of Medicine, and the Veterans Administration Medical Center, Gainesville, FL.

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Address correspondence and reprint requests to Dr. Daniel H. Jacobs, Department of Neurology, New England Medical Center, 750 Washington Street, Boston, MA 02111.

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## Neuropsychological characteristics of preclinical dementia in Parkinson's disease

D. M. Jacobs, K. Marder, L. J. Cote, et al.

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