Relationships Between Extrapyramidal Signs and Cognitive Function in a Community-Dwelling Cohort of Patients with Parkinson's Disease and Normal Elderly Individuals

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The relationship between extrapyramidal sign (EPS) severity and cognitive function was investigated in 184 patients with idiopathic Parkinson's disease (PD) and 301 normal elderly individuals from a community-dwelling cohort in northern Manhattan, New York City. Fifty-six of the patients with PD met criteria for dementia of the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised, and of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association. EPS were rated according to the Unified Parkinson's Disease Rating Scale. Cognitive function was assessed by neuropsychological tests of memory, orientation, abstract reasoning, language, construction, and psychomotor speed. Significant associations were found between EPS and neuropsychological performance in PD patients without dementia. Yet EPS severity was unable to account for the pronounced cognitive impairment in PD dementia. Individuals in the normal group with subtle EPS, but without overt idiopathic PD, showed widespread cognitive changes, including impairment in most of the tests that differentiated PD patients from normal subjects. Prospective follow-up of these individuals will determine whether this represents a preclinical stage of PD or constitutes an early manifestation of dementia.

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Cognitive changes, including impairments in memory and in visuomotor and executive function, that accompany the motor signs of Parkinson's disease (PD) are well known [1–4]. Several studies have shown positive relationships between the severity of extrapyramidal signs (EPS) in patients with PD and the degree of cognitive impairment [5–9]. Accordingly, this impairment has been linked to degeneration in the nigrostriatal system and to consequent impaired function of the "complex" caudatofugal pathway. This view is based on the assumption that EPS and cognitive changes in patients with PD share a common pathophysiological basis, most likely that of dopamine depletion. The present study critically examined the association between EPS and neuropsychological function in nondemented patients with PD and tested 2 predictions that follow from it, i.e., (1) cognitive impairment is positively and specifically associated with EPS severity in nondemented patients with PD, but that EPS activity cannot account for the severe cognitive impairment in patients with PD meeting clinical criteria for dementia; and (2) similar (albeit milder) patterns of cognitive impairment to those found in patients with PD can be identified in normal individuals with subtle EPS, but without overt PD. Several studies have documented EPS in normal elderly individuals [10–12], but the relationship of these signs to cognitive function has not been investigated.

The present study addressed these issues using a population-based cohort of normal elderly individuals and PD patients with and without dementia in the Washington Heights-Inwood community of New York City.

Subjects

All subjects were drawn from the Washington Heights-Inwood Columbia Aging Project, a community-based prospective investigation of dementias in a geographically de-

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fined district of New York City. Methods of PD patient recruitment have been described in detail [13]. In brief, patients with PD were identified through the development of a community registry for PD that used records of all patients seen at the Columbia Presbyterian Medical Center, contact with practitioners in the area unaffiliated with the center, and information from regional health insurance providers and the health resources association in the area. In addition, announcements were placed in every local newspaper and were carried on television and radio programs during the recruitment period. Complete case ascertainment was assumed and prevalence of the condition was reported [13]. A random sample survey is presently underway to determine the completeness of the registry. Normal elderly volunteers from the community were recruited through similar means. All subjects gave informed consent.

Three subject groups were defined for statistical analysis.

Nondemented Patients with PD (PD-ND)

All patients had idiopathic PD. Patients were required to have at least 2 of the following cardinal features of PD on examination or mentioned in the medical records: resting tremor, shuffling gait, bradykinesia, or muscular rigidity. Patients with dementia (see below) and patients who developed memory loss before the motor signs of PD were excluded.

Patients with Dementia (PD-D)

The determination of dementia was made according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised [14] and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association [15] and is described in detail elsewhere [16]. Patients with any other primary degenerative dementia, any secondary dementia (toxic, metabolic or traumatic), or dementia or memory loss before the development of motor signs were excluded.

Normal Elderly (NE)

No individuals in this group had dementia or a diagnosed neurological disorder that might affect cognitive functioning.

For all subjects, essential tremor, stroke, and any other major neurological disorder were grounds for exclusion.

Methods

Neurological

For patients with PD, the neurological examination was conducted by one of three attending neurologists (L.C., K.M., R.M.), each with extensive experience in movement disorders. EPS were recorded using the Unified Parkinson's Disease Rating Scale (UPDRS) [17]. Interrater reliability of the UPDRS was assessed on a random sample of 24 patients with PD. Each patient was double-rated by two of the above neurologists, with rater combination counterbalanced. Intraclass correlation coefficients and their significance levels were calculated using equation ICC(2,1) [18]. ICCs for rigidity, bradykinesia, posture, and postural stability were in the 0.5 to 0.6 range ($p < 0.01$) and ICCs for all other signs except speech and facial mobility were in the 0.6 to 0.9 range ($p < 0.001$). ICCs for the latter two signs were not significant.

For the normal elderly controls, a shortened version of the UPDRS was administered by a physician. This scale allowed the rating of speech, facial immobility, resting tremor, rigidity, posture, and bradykinesia. Interrater reliability of this brief scale has been established for demented patients [19].

For all subjects, the short version of the Blessed Memory Information and Concentration Test [20] was administered as a brief index of mental status. Higher scores on this test represent greater impairment.

Functional

Functional capacity was rated by a physician, using Part 1 (Sections A and B) of the Blessed Dementia Rating Scale (BDRS) [21], the Barthel scale [22], and the Schwab and England Activities of Daily Living Scale (ADL) [23].

Neuropsychological

All tests were administered by trained examiners and testing was conducted in English or Spanish, according to the preference of the subject. Verbal memory was assessed by the Selective Reminding Test (SRT) [24]. The multiple choice recognition version of the Benton Visual Retention Test (BVRT) [25] was used to assess nonverbal memory. The first 10 items of the Mini-Mental State Examination [26] allowed an assessment of orientation to time and place. Visuospatial ability was measured by the matching-to-sample version of the BVRT and by 5 selected items from the Rosen Drawing Test [27]. Language tests consisted of 15 selected items from the Boston Naming Test [28], 2 verbal fluency tests (the Controlled Oral Word Association Test [COWAT] [29] and Category Naming, where the subject was allowed 1 minute each for 3 categories, i.e., Animals, Food, and Clothing), the first 6 items of the Complex Ideational Material (Comprehension) subtest of the Boston Diagnostic Aphasia Examination (BDAE) [30] and the high probability Repetition items of the BDAE. Abstract reasoning was assessed by the Similarities subtest of the revised Wechsler Adult Intelligence Scale [31] and by the Identities and Oddities subtest of the Mattis Dementia Rating Scale [32]. Finally, a cancellation task [33] (using a diamond shape as target and triangles, circles, and squares as distractors) was used to assess attention and speeded performance.

Results

Using the above inclusion and exclusion criteria, 130 PD-ND patients (62 men, 68 women), 56 PD-D patients (28 men, 28 women), and 307 NE individuals (67 men, 234 women) were retained for analysis. Eight subjects (6 from the NE group, 2 from the PD-ND group) were taking antipsychotic medication that can evoke EPS. These subjects were eliminated. Demographic and clinical characteristics of the remaining subjects, including disease duration and current medications for the patients in the PD groups, are shown in Table 1.

Factor Analysis of the UPDRS

Factor analysis was used to reduce the many items of the UPDRS to a smaller number of summary variables

Table 1. Group Demographic and Clinical Characteristics

	NE	PD-ND	PD-D
n	301 (SD)	128 (SD)	56 (SD)
Age (yr)	75.6 (7.7)	70.6 (10.2)	78.8 (7.6)
Education (yr)	8.1 (4.3)	10.5 (4.7)	9.4 (4.9)
BDRS	1.67 (1.96)	2.55 (2.31)	7.42 (4.24)
Barthel	1.04 (2.0)	2.16 (2.63)	6.07 (2.69)
Schwab ADL (%)	83.7 (18.6)	76.7 (17.9)	44.5 (23.3)
Short Blessed	4.7 (4.2)	4.9 (4.3)	14.7 (7.9)
PD duration (yr)	. . .	6.6 (6.8)	6.6 (5.8)
Sinemet (% taking)	. . .	69.9	73.6
DA agonist (% taking)	. . .	34.7	24.0
Anticholinergic (% taking)	. . .	21.4	16.3

NE = normal elderly; PD-ND = nondemented patients with Parkinson's disease; PD-D = demented patients with Parkinson's disease; BDRS = Blessed Dementia Rating Scale; ADL = Activities of Daily Living Scale; DA = dopamine.

to simplify correlational analyses between particular EPS and neuropsychological performance. This was performed on UPDRS scores for the PD-ND and PD-D groups combined, using principal components analysis. The Kaiser–Meyer–Olkin measure of sampling adequacy [34] was 0.91 (rated as "marvelous" [34]). Three factors were extracted, accounting for 72.4% of the total variance. These were then subjected to oblimin rotation with Kaiser normalization. The resultant factor matrix is shown in Table 2.

Factor 1 reflects balance and stability and also includes gait, posture, and bradykinesia. With the exception of bradykinesia, this factor clearly corresponds to the postural instability and gait difficulty (PIGD) factor identified by Zetusky and colleagues [35]. Leg agility showed a moderate loading on this factor. Factor 2 consists of speeded movements (rapid alternating movements, hand movements, and leg agility), rigidity, speech, and facial expression. Rigidity may be a common denominator across these signs. Although interrater reliability for speech and facial mobility was low, both these signs showed high loadings on this factor. Factors 1 and 2 were highly correlated ($r = -0.66$). Factor 3 clearly represents tremor and did not correlate with either factors 1 or 2. These three factors correspond, to some extent, to the classic triad of bradykinesia, rigidity, and tremor, although in the present case, bradykinesia was associated with instability and gait difficulty.

Items from the UPDRS were then grouped according to these factors. To compare factor scores between the PD-ND and PD-D groups, the three factors were subjected to multivariate analysis of covariance (MANCOVA) [36], with group (PD-ND and PD-D) as a between-groups factor and age as a covariate. Hotelling's T^2 test revealed a significant group effect ($p < 0.001$). Univariate F tests revealed that PD-D patients had greater factor 1 and factor 2 scores than PD-ND patients (both, $p < 0.001$), an increase that could not be explained by the greater age of the patients with dementia.

Table 2. Factor Loadings for the UPDRS

	Factor 1	Factor 2	Factor 3
Postural stability	1.01	0.14	−0.11
Gait	0.95	0.04	−0.04
Arising from chair	0.80	−0.08	0.04
Bradykinesia	0.73	−0.15	0.04
Posture	0.66	−0.26	0.06
Facial mobility	−0.04	−0.86	−0.12
Speech	−0.03	−0.79	−0.18
Rapid alternating movements	0.12	−0.76	0.15
Hand movements	0.13	−0.74	0.10
Rigidity	0.09	−0.64	0.26
Leg agility	0.43	−0.47	0.12
Resting tremor	0.00	0.01	0.85
Action tremor	−0.07	0.05	0.83

UPDRS = Unified Parkinson's Disease Rating Scale.

Relationships Between EPS and Neuropsychological Performance: PD-ND Group

CORRELATIONS BETWEEN TOTAL EPS SEVERITY AND NEUROPSYCHOLOGICAL TEST SCORES. All UPDRS items were summed to obtain a total EPS score for the two PD groups. This score was correlated with each neuropsychological test score, with coefficients adjusted for age. These are shown in Table 3.

Modest correlations were found between EPS and memory (verbal and nonverbal), orientation, verbal fluency (category naming), verbal comprehension, drawing-to-copy (Rosen), and cancellation time. In all cases, the higher the EPS score, the poorer the neuro-

Table 3. Pearson Correlation Coefficients Between EPS and Neuropsychological Measures for the PD Groups

Test	PD-ND	PD-D
SRT		
Immediate recall	−0.29	−0.55
Delay recall	−0.18	−0.10
BVRT recognition	−0.28	−0.57
Orientation	−0.34	−0.65
Similarities (age scaled)	−0.05	−0.20
Identities/Oddities	−0.15	−0.51
Boston Naming	−0.04	−0.52
COWAT (mean)	−0.20	−0.53
Category (mean)	−0.29	−0.19
Repetition	−0.06	−0.23
Comprehension	−0.26	−0.43
Rosen Drawing	−0.27	−0.09
BVRT matching	−0.15	−0.40
Cancellation time	0.43	0.30
Cancellation errors	0.09	0.21

EPS = extrapyramidal signs; PD = Parkinson's disease; PD-ND = nondemented patients with PD; PD-D = demented patients with PD; SRT = Selective Reminding Test; BVRT = Benton Visual Retention Test; COWAT = Controlled Oral Word Association Test.

psychological performance. It can be seen that EPS showed little correspondence with tests of abstract reasoning, naming, repetition, and visual matching-to-sample.

RELATIONSHIPS BETWEEN UPDRS FACTORS, DEMOGRAPHIC VARIABLES, AND NEUROPSYCHOLOGICAL TEST SCORES. The three UPDRS total factor scores, along with age, education, PD duration, and the language in which neuropsychological tests were administered (English/non-English), were entered into a multiple linear regression analysis, with each neuropsychological test score in turn as dependent variables. A stepwise procedure was used throughout. Results are summarized in Table 4.

EPS were retained in the regression model for most neuropsychological variables. In all cases, it was factor 2 (rigidity/motor speed) that entered into the model. Factor 3 (tremor) showed a relationship with only 1 test (positive for BVRT recognition) and factor 1 (stability/posture/bradykinesia) showed no significant relationships with any of the tests. None of the UPDRS factors entered into the model for tests of abstract reasoning, naming, repetition, and visual matching.

COMPARISON OF NEUROPSYCHOLOGICAL TEST PERFORMANCE BETWEEN NE AND PD-ND GROUPS. *t*-tests revealed that the NE group was significantly older ($p < 0.001$) and less educated ($p < 0.001$) than the PD-ND group. Group differences in neuropsychological performance between the normal elderly group and the PD-ND group were assessed using MANCOVA, with each neuropsychological test score constituting dependent variables, group (PD-ND vs NE) as a between-groups factor, and age and education as covariates. The group effect was significant ($t^2 = 1.0$, $p = 0.001$). Corresponding univariate F tests revealed the following tests to contribute to this effect: SRT ($p = 0.008$), Orientation ($p < 0.001$), COWAT ($p = 0.007$), Category naming ($p = 0.004$), Rosen Drawing ($p = 0.036$), and Cancellation time ($p < 0.001$). In all cases, the performance of PD-ND patients was worse than that of normal subjects. All these tests were shown to correspond to EPS in the above correlational and regression analyses. To assess possible confounding effects

Table 4. Summary Multiple Regression Statistics for the PD-ND Group

Cognitive Variable	Independent Variable	β	*p*
SRT total	Age	−0.37	<0.0001
	Factor 2	−0.36	<0.0001
	Language	−0.26	0.0016
SRT delay	Age	−0.35	0.0001
	Factor 2	−0.25	0.0049
BVRT delay	Factor 2	−0.36	<0.0001
	Education	0.33	0.0001
	Factor 3	0.20	0.0159
Orientation	Factor 2	−0.32	0.0004
	Language	−0.22	0.0148
	Age	−0.20	0.0243
Similarities	Education	0.49	<0.0001
	Language	−0.21	0.013
Identities/Oddities	Education	0.36	0.0002
Naming	Education	0.32	0.0005
	Age	−0.24	0.0087
COWAT	Education	0.30	0.0011
	Factor 2	−0.21	0.0237
Category	Factor 2	−0.34	0.0001
	Age	−0.31	0.0004
	Language	−0.30	0.0004
Repetition	Education	0.21	0.0268
Comprehension	Education	0.34	0.0002
	Factor 2	−0.25	0.0055
Rosen Drawing	Education	0.42	<0.0001
	Factor 2	−0.30	0.0005
BVRT matching	Education	0.44	<0.0001
	Duration	−0.22	0.0118
Cancellation time	Factor 2	0.46	<0.0001
	Age	0.25	0.0033
Cancellation errors	Education	−0.35	0.0002

PD-ND = nondemented patients with Parkinson's disease; SRT = Selective Reminding Test; BVRT = Benton Visual Retention Test; COWAT = Controlled Oral Word Association Test.

of anticholinergic medication, this analysis was repeated after excluding patients who were taking anticholinergics. With the single exception of a loss of significance for the Rosen Drawing Test, results were unchanged.

The MANCOVA was then repeated for all PD-ND patients, adding the brief EPS summary score as a covariate. When this covariate was added, the group effect became nonsignificant. In fact, inspection of the neuropsychological test score means, adjusted for the covariates, indicated *better* performance for the PD-ND patients in all neuropsychological tests. This analysis suggests that cognitive changes in nondemented patients with PD were specifically associated with motor signs of PD because they were abolished (and, to some extent, even reversed) when EPS activity was controlled for.

Relationships Between EPS and Neuropsychological Performance: PD-D Group

CORRELATIONS BETWEEN TOTAL EPS SEVERITY AND NEUROPSYCHOLOGICAL TEST SCORES. Age-adjusted correlation coefficients were calculated for the PD-D group and are shown in Table 3, alongside those for the PD-ND group. For tests of verbal and nonverbal memory, orientation, abstract reasoning, COWAT, repetition, and comprehension, coefficents were larger for demented patients with PD than nondemented patients with PD. However, the reverse was true for category naming, drawing-to-copy, visual matching, and cancellation time.

COMPARISON OF NEUROPSYCHOLOGICAL TEST PERFORMANCE BETWEEN PD-ND AND PD-D GROUPS. t tests revealed that the PD-ND patients were significantly younger than the PD-D patients ($p < 0.001$), but had an equal level of education. MANCOVA, with each neuropsychological test score as dependent variables, group (PD-ND vs PD-D) as a between-groups factor, and age and education as covariates revealed a highly significant group effect ($p < 0.001$). Corresponding F tests indicated poorer performance in PD-D patients at the ≤ 0.001 level for each neuropsychological test except Repetition and Cancellation error rate. Results were essentially unchanged when EPS was added as a covariate, suggesting that the cognitive deficit in PD-D cannot be accounted for by EPS activity.

Comparison of Neuropsychological Test Performance Between NE Subjects With and Without EPS

One hundred fourteen normal individuals (37% of the NE group) showed at least 1 EPS. Of these individuals, 10 showed speech abnormalities, 17 showed reduced facial mobility, 11 had tremor, 25 has rigidity, 85 showed postural abnormality, and 48 had bradykinesia. In fact, 8 of these individuals met study criteria for PD (i.e., they had at least 2 of the cardinal motor signs of PD listed in Methods), but were not judged to have PD by the physician.

Because of the relatively low frequency and severity of EPS in the NE group, the EPS score was not treated as a correlate in this group. Instead, NE subjects were dichotomized into those with EPS (EPS+) and those with no evidence of EPS (EPS−). t tests revealed that the EPS+ subjects were significantly older ($p < 0.001$) and more highly educated ($p = 0.009$) than the EPS− subjects. In addition, EPS+ subjects were more impaired in all three measures of functional capacity (BDRS, Barthel, and ADL; $p < 0.001$ in all cases). There was no difference between EPS+ and EPS− subjects in current use of antidepressant or anxiolytic medication and short Blessed mental status scores in these two groups were virtually identical.

Neuropsychological test scores were subjected to MANCOVA, with EPS (±) as a between-groups factor and age and education as covariates. The multivariate t^2 test for group was significant ($p = 0.001$). Corresponding univariate F tests revealed significantly poorer performance in EPS+ subjects than EPS− subjects for the following tests: SRT ($p = 0.001$), Orientation ($p = 0.001$), Similarities ($p = 0.003$), Naming ($p = 0.011$), COWAT ($p = 0.004$), Category Naming ($p < 0.001$), BVRT matching ($p = 0.01$), and Cancellation time ($p = 0.044$). To some extent, this pattern of impairment reflects that found for the PD-ND group, although the EPS+ subjects had more diffuse cognitive changes, including those of abstract reasoning, naming, and visual matching.

Discussion

The results of the present study provide clear evidence of an association between severity of EPS and degree of cognitive impairment in patients with PD and elderly individuals without PD.

For nondemented patients with PD, separate but convergent analyses revealed that this association was strongest with the neuropsychological tests that best differentiated patients with PD from normal subjects. These tests were those of verbal memory, orientation to time and place, verbal fluency (word generation), construction (drawing-to-copy), and psychomotor speed (cancellation time). With the exception of orientation (which has not been well investigated in patients with PD), selective impairments in all these domains have been demonstrated in PD patients with dementia [1–4]. However, a comprehensive model representing convergence between neuropsychological tests that distinguish patients with PD from normal subjects and neuropsychological tests that correlate with motor signs within the same patients has not been previously established. There are two possible reasons for this. One is that few large-scale studies have simultaneously carried out patient–control compari-

sons with a broadly based neuropsychological battery and within-patient correlations between the latter and motor function. Second, this convergent model may be associated with the population-based cohort. PD prevalence studies using door-to-door surveys have reported rates of up to 42% of cases that were newly diagnosed by the studies [37–39]. This raises the possibility that patients with PD, but who have never sought entrance into the health care system, may have characteristics that are not well represented in clinical series. Conversely, particular clinical and demographic features may be overrepresented in patients who *do* seek medical attention. By investigating PD patients identified by a community survey, the present results cut across these influences and uncover relationships that are highly generalizable. The simplicity of the above model may therefore be a consequence of this generalizability.

Concerning the relationship between cognitive function and particular EPS, we found that factor analysis identified three EPS factors, i.e., one reflecting posture, stability, gait, and bradykinesia, one reflecting rigidity and speeded, repetitive movements, and a third consisting of tremor. Although there were almost no associations between the first and third of these factors and neuropsychological performance, the rigidity/motor speed factor showed a strong correspondence with neuropsychological test scores. Once again, the associations were strong with tests that differentiated patients from normal subjects. It should be noted that the association between factor 2 and neuropsychological impairment is in conflict with the findings of Zetusky and colleagues [35] and Pillon and co-workers [40]. The former investigators reported a high correlation between performance on a brief mental status examination and their PIGD factor and (to a lesser extent) bradykinesia, but only a small correlation with rigidity. Consistent with this study, Pillon and co-workers [40] found that gait disorder, but not rigidity, showed significant correlations with tests of memory, executive function, and verbal fluency. On the other hand, studies that have used the classic tremor/rigidity/bradykinesia triad to summarize EPS in patients with PD have tended to show an association between cognitive function and both rigidity and bradykinesia [6, 8, 41]. An exception is the study by Mortimer and associates [7], who showed the association with bradykinesia only.

Turning to the relationship between EPS and cognitive function in demented patients with PD, the present results demonstrated significant correlations between EPS and neuropsychological performance. For many of these tests, coefficients were higher than those for the nondemented patients with PD. Because severity of EPS was shown to be greater in demented patients than in nondemented patients, it might be concluded that cognitive impairment in PD dementia is associated with increased motor involvement resulting from basal ganglia disease. Indeed, severity of motor impairment has been shown to be an important predictor of PD dementia [42]. However, these higher correlations were not uniformly observed in the PD-D group. Indeed, correlations were actually *lower* than those in the PD-ND group for three tests (Category Naming, Rosen Drawing, and Cancellation time) that discriminated the PD-ND group from the NE group. Furthermore, when neuropsychological performance in demented patients with PD was compared with that of nondemented patients with PD, nearly all test scores were markedly lower in the demented group, *even when these two groups were equated for EPS severity.* These findings suggest that there are important contributions to dementia in PD over and above those associated with motor impairment. Possibilities include Alzheimer's disease pathology, destruction of the cholinergic basal forebrain region, cortical cell loss, and the presence of cortical Lewy bodies. Accurate clinical–pathological correlation in this cohort will help to clarify the multifactorial nature of dementia in patients with PD.

A striking aspect of the present study was the finding of cognitive impairment in normal individuals with EPS, but without overt PD. There is evidence that bradykinesia (though not rigidity) increases with age in normal aging [12]. Indeed, normal subjects with EPS were older than those without EPS in the present study. However, it is unlikely that decreased cognitive ability and increased motor impairment in these individuals were merely secondary to aging, because age effects were controlled in our analyses. This finding has at least three implications.

First, the relationship between EPS and cognitive impairment may be general, with a common mechanism distributed within the population, regardless of neurological status. This hypothesis might predict similarities in the pattern of neuropsychological impairment across different neurological diseases that present with EPS, such as Shy–Drager syndrome, progressive supranuclear palsy (PSP), cortical Lewy-body disease, and Alzheimer's disease with EPS. On this basis, it is interesting that there are reports of similar disturbances in tests of frontal lobe function in patients with PSP and PD [43, 44].

Second, many of the neuropsychological tests that discriminated PD patients from normal subjects also showed the greatest impairment in normal subjects with EPS. It may be, therefore, that subtle EPS in normal subjects are a preclinical marker for PD and that some of these normal individuals will develop a full PD syndrome over time (whether idiopathically or by interaction with an environmental insult). Recent evidence suggests that changes in handwriting and speech may be sensitive indicators of PD development [45].

The present results suggest that other motor signs, particularly bradykinesia, postural change, and rigidity, in combination with subtle and/or self-reported changes in memory, orientation, and productive language, may be important in the early detection of this disease.

Third, broader cognitive changes were demonstrated in normal subjects with EPS (including impaired naming, abstract reasoning, and visual matching) than those observed in nondemented patients with PD. This raises the possibility that some of these individuals may develop PD dementia or may have an early manifestation of another dementia such as Alzheimer's disease (AD). In fact, studies in progress at our center have demonstrated that EPS frequency is significantly greater in patients with mild AD than in normal controls [46]. If prospective follow-up confirms a significant number of incident cases of PD, PD dementia, or AD among these individuals, then there are compelling reasons to incorporate assessment of EPS into the routine medical examination of the elderly.

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