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A Data-Driven Approach to the Study of Heterogeneity in Idiopathic Parkinson's Disease: Identification of Three Distinct Subtypes

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Summary: Idiopathic Parkinson's disease (IPD) has been subclassified on the basis of predominant motor symptomatology, age at disease onset, depressive affect, and cognitive performance. However, subgroups are usually arbitrarily defined and not reliably based on qualitatively distinct neuropathology. We explored heterogeneity in IPD in a data-driven manner using comprehensive demographic, motor, mood, and cognitive information collected from 176 patients with IPD. Cluster analysis revealed three subgroups of patients at a disease duration of 5.6 years and two subgroups at 13.4 years. The subgroups may represent the clinical progression of three distinct subtypes of IPD. The ''motor only'' subtype was characterized by motor symptom progression in the absence of intellectual impairment. Equivalent motor symptom progression was shown by the ''motor and cognitive'' subtype which was accompanied by executive function deficits progressing to global cognitive impairment. The ''rapid progression'' subtype was characterized by an older age at disease onset and rapidly progressive motor and cognitive disability. There was no relationship between the motor and cognitive symptoms in any subtype of IPD. We conclude that the clinical heterogeneity of IPD is governed by distinct neuropathologic processes with independent etiologic influences. **Key Words:** Parkinson's disease—Heterogeneity—Cluster analysis.

The variance in the clinical syndrome of idiopathic Parkinson's disease (IPD) suggests the existence of meaningful subclassifications of the disease. Subtypes of IPD have previously been defined according to the predominance of specific motor symptoms, the age at disease onset, the cognitive performance, and the depressive symptomatology of the patient.

The particular motor syndrome of IPD in each patient is dependent on the differential expression of the three cardinal symptoms of bradykinesia, rigidity, and tremor. Subtypes of IPD have been investigated according to the predominant cardinal symptom.[1–4]

The mean age at onset of IPD is 56 years[5,6] with increasing prevalence beyond this age. However, IPD can occur in patients much younger providing the basis for an early-onset subclassification of IPD.[7–11]

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Cognitive performance is often impaired in patients with IPD and the prevalence of clinical dementia is approximately 10–15% greater than in an age-matched population.[12] Frontal lobe executive function deficits have been identified in tasks such as set-shifting,[13,14] sequencing,[15] and planning.[16] Poor visuospatial perception and memory performance have also been reported.[17,18] Subclassifications of IPD have been made according to discrete patterns of cognitive deficit[19] but are generally defined by the presence or absence of clinical dementia.[20–23]

Depression is the most frequent mental alteration in IPD affecting approximately half of all patients.[24] IPD with depression has been regarded as a distinct subtype in some investigations.[25,26]

Other subclassifications of IPD have been based on the laterality of motor symptomatology[27–29] and on disease severity.[5,30]

There is a lack of agreement in the literature concerning the mode of interaction of these clinical variants. Some studies show the motor symptoms of IPD progress independently of cognitive performance and age at onset,

implying each clinical variant is governed by independent neuropathologic processes.[1,19,31,32] However, others show that specific motor symptoms are related to the presence of cognitive impairment implying the involvement of similar underlying neurologic systems or processes.[2,4,6,33–36] Similarly, the risk of developing global cognitive impairment is thought to increase with the age at onset of IPD.[21,37–40]

Methodologic issues are, at least partially, responsible for the dispute over the mode of interaction of the clinical variants of IPD. Many of the subclassifications have been defined prospectively based on intuition and in an essentially arbitrary manner. For example, the defining age of IPD of early onset is accepted as less than 40 years but this has varied up to 55 years of age.[41] Inconsistencies of inclusion criteria and assessment methods between investigations limit the comparability of studies. For example, dementia has inaccurately been regarded in many studies as an ''all or none'' phenomenon with widely variant defining criteria and hence varying prevalence estimates from 21%[42] to 81%.[43]

IPD clearly manifests a heterogeneous clinical syndrome; however, it is still not clear whether this results from a continuous spectrum of neuropathologies with a single common etiology or whether it results from independent neuropathologic processes with different etiologic influences.

We recognized that the clinical variants of IPD could not be studied independently and wanted to investigate their heterogeneity in a data-driven manner. The aim of cluster analysis is to identify naturally occurring subgroups, hence avoiding prospective definition. Motor, cognitive, affective, and demographic variables from a large sample of patients with IPD were used for the initial subclassification. The relationship of the clinical variants in each resultant subgroup was then investigated.

METHODS

Patients

One hundred seventy-six outpatients with IPD (83 women, 93 men; mean age 63.2 years, standard deviation 10.2 years; mean disease duration 7.5 years, standard deviation 6.4 years), according to the Parkinson's Disease Society Brain Research Centre clinical diagnostic criteria,[44] who attended the Royal Hallamshire Hospital's movement disorders clinic between 1994 and 1996 were included in the study. Fifteen patients had early IPD and were not yet medicated. Levodopa was taken by 114 patients either alone or in combination with a dopamine receptor agonist, an anticholinergic, or a monoamine oxidase inhibitor. Twenty-six patients were medicated with a dopamine receptor agonist alone, one with an anticholinergic alone, and 11 with a monoamine oxidase inhibitor alone. The remaining patients were participating in a double-blind drug study and were medicated with either levodopa or a dopamine receptor agonist.

Measures

Motor Function

The Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale[45] rates the severity of IPD motor symptoms overall and for each side of the body separately, including measures of tremor, rigidity, and bradykinesia. Finger dexterity was assessed by the Alternate Finger Tapping Test in which the number of alternate taps on two keys, each assigned to a different finger of one hand, was counted for a 30-second period. The mobility measures were determined in the ''on'' state.

Mood and Affect

Severity of depressive symptomatology was determined from the Beck Depression Inventory.[46]

Global Cognitive Function

Premorbid intelligence was estimated from the full-scale IQ score of the National Adult Reading Test.[47] The Blessed Dementia Scale Information–Memory–Concentration Test[48] provided a global measure of cognitive function.

Visuospatial Function

The Pattern and Spatial Recognition Memory subtests[49] from the Cambridge Neuropsychological Test Automated Battery (CANTAB) evaluated the ability to discriminate familiar from unfamiliar patterns and spatial positions.

Executive Function

Working memory assessments included the CANTAB Spatial Working Memory subtest (SWM)[50] and the Digit Ordering paradigm.[32] SWM requires the retention and manipulation of spatial information during a visual search task. In the digit-ordering task, subjects hear seven random single digits and are required to put the digits into numerical order. Executive function was also determined using the CANTAB Attentional Set Shifting subtest.[14] There were nine shifts in total and scoring depended on the number of shifts completed. The Letter Fluency assessment[51] required the production of words beginning with a designated letter (F, A, and S) within a 60-second period. Proper nouns and derivatives were not permitted.

Demographics

Details of age at disease onset, disease duration, dopaminergic medications, and the presence of disease complications including response fluctuations, dyskinesias, falls, postural instability, and hallucinosis were recorded. The UPDRS Activities of Daily Living section was modified into a self-report format and was included at the end of the demographic questionnaire to provide an indication of the degree to which IPD interfered with daily functioning.

Procedure

The assessment battery was completed in a single private session lasting 2–3 hours at either the Royal Hallamshire Hospital or at the patient's own home. The assessments were administered in a uniform order and rests were provided, as required, throughout.

Statistical Analysis

All continuous variables were normalized and then subjected to a non-hierarchical cluster analysis (k-means method). Post-hoc comparisons of scores were conducted using either one-way analyses of covariance or independent samples *t* tests with strict application of the Bonferroni correction. The chi-square technique, or Fisher's Exact when expected values were small, with Yate's correction where relevant, was used for the comparison of categorical data. Relationships between variables were investigated with Pearson's product-moment correlation corrected for multiple comparisons with the Larzelere and Mulaik test.

RESULTS

Cluster Analysis

The non-hierarchical cluster analysis converged with a 0.01 criterion in nine iterations resulting in five distinct clusters. Table 1 illustrates the mean values of each continuous variable for the five identified clusters. The groups differed significantly ($p < 0.01$) on all demographic, motor, affective, and cognitive measures except one measure of spatial working memory (level 8 within errors) ($F = 1.93$, $p < 0.11$).

TABLE 1. *The mean (standard deviation) demographic, motor, and cognitive characteristics of the five groups of patients with IPD identified through cluster analysis (*p < 0.01)*

	Group 1 (n = 60, 34.1%)	Group 2 (n = 37, 21%)	Group 3 (n = 37, 21%)	Group 4 (n = 23, 13.1%)	Group 5 (n = 19, 10.8%)	F value
Demographics						
Disease duration	5.03 (4.17)	5.13 (4.15)	6.85 (5.76)	14.41 (7.94)	12.21 (6.31)	18.03*
Age at onset	53.2 (11.97)	58.17 (9.45)	61.04 (9.48)	46.93 (9.61)	55.16 (10.57)	7.67*
Motor function						
Alternate finger tapping right	74.36 (23.07)	102.00 (35.97)	61.09 (18.97)	53.10 (18.84)	35.40 (9.29)	21.76*
Alternate finger tapping left	72.58 (22.39)	88.05 (26.13)	56.03 (21.18)	51.38 (28.96)	31.30 (12.60)	16.76*
UPDRS motor right	6.42 (3.83)	5.54 (3.42)	8.76 (4.68)	9.68 (5.78)	12.47 (4.64)	11.16*
UPDRS motor left	5.35 (5.03)	6.32 (4.20)	9.51 (4.50)	11.33 (7.02)	13.21 (5.29)	13.21*
UPDRS motor total	19.22 (10.70)	20.32 (6.81)	31.38 (9.35)	35.36 (14.55)	44.21 (11.26)	30.54*
Duration IPD at dyskinesia	3.92 (3.12)	6.67 (3.35)	3.95 (4.25)	15.14 (6.62)	9.34 (8.38)	7.92*
Duration IPD at falls	3.04 (3.08)	6.28 (3.91)	1.65 (1.69)	10.77 (5.11)	9.14 (4.89)	13.86*
Duration IPD at fluctuation	2.34 (2.43)	3.00 (3.34)	4.98 (5.96)	9.09 (4.72)	6.65 (5.91)	4.92*
UPDRS daily activities best	8.07 (5.58)	8.49 (6.25)	12.78 (8.11)	15.74 (6.86)	23.05 (6.22)	23.41*
UPDRS daily activities worst	11.29 (7.88)	11.59 (7.35)	18.59 (8.43)	22.04 (7.16)	28.00 (6.67)	24.79*
Affect and cognition						
Beck depression inventory	10.12 (7.21)	8.61 (5.33)	12.16 (8.91)	14.57 (7.12)	17.39 (7.87)	5.89*
National adult reading test	112.32 (8.40)	113.67 (8.23)	106.62 (7.67)	111.65 (7.97)	104.00 (8.62)	6.82*
UPDRS mentation	2.32 (1.85)	3.08 (2.10)	4.07 (3.05)	3.36 (2.77)	8.00 (2.61)	7.44*
Blessed dementia scale	1.45 (1.93)	1.62 (1.86)	3.69 (3.09)	1.17 (2.06)	9.47 (5.33)	36.35*
Digit ordering	77.38 (16.42)	60.86 (16.62)	40.16 (16.73)	70.78 (10.92)	24.11 (18.41)	56.17*
Letter fluency	12.91 (4.62)	12.12 (3.99)	7.85 (3.16)	12.19 (4.05)	6.80 (3.87)	14.90*
CANTAB pattern recognition	20.82 (2.50)	19.58 (2.83)	17.33 (3.23)	19.57 (2.15)	15.59 (3.64)	16.07*
CANTAB spatial recognition	15.32 (2.15)	14.11 (2.41)	11.92 (3.01)	14.52 (2.31)	11.31 (2.85)	15.25*
CANTAB set shifting	8.68 (0.70)	6.47 (2.95)	8.14 (0.93)	8.65 (1.11)	1.75 (1.91)	64.68*
CANTAB SWM 4 between errors	0.63 (1.35)	3.80 (2.97)	4.50 (2.61)	1.95 (2.55)	7.47 (3.00)	35.70*
CANTAB SWM 6 between errors	5.53 (5.47)	18.17 (5.75)	20.94 (4.42)	14.86 (6.00)	23.47 (4.84)	69.92*
CANTAB SWM 8 between errors	21.05 (10.10)	35.80 (7.84)	38.09 (6.89)	29.14 (8.80)	43.54 (5.47)	36.23*
CANTAB SWM 4 within errors	0.03 (0.18)	0.37 (1.21)	0.39 (0.73)	0.09 (0.29)	2.59 (4.72)	8.79*
CANTAB SWM 6 within errors	0.27 (0.66)	0.74 (1.54)	0.44 (0.73)	0.68 (1.09)	2.40 (3.00)	8.37*
CANTAB SWM 8 within errors	0.75 (1.08)	1.60 (2.65)	0.91 (1.54)	1.00 (1.54)	2.00 (3.46)	1.93

IPD, idiopathic Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; CANTAB, Cambridge Neuropsychological Test Automated Battery; SWM, Spatial Working Memory subtest.

Expected Performance

Table 2 illustrates the comparison of mean group performance on each cognitive variable with expected performance of an age- and intelligence-matched normal population. Greater than one standard deviation below normal performance was defined as mild impairment and over two standard deviations as significant impairment. There was no evidence of impaired cognitive performance in groups 1 and 4. The performance of group 2 deviated from the norm on the digit-ordering and set-shifting assessments. Group 3 was mildly impaired on all cognitive measures except set-shifting and spatial working memory. Group 5 was either mildly or significantly impaired on every measure of cognition except spatial working memory.

Groups 4 and 5 reported mild depressive symptomatology.

Disease Duration

To control for the influence of disease duration on measures of movement, cognition, and affect, the significant F value for mean disease duration between the five groups was investigated with post-hoc procedures. Figure 1 shows that groups 4 and 5 had IPD of longer duration than groups 1, 2, and 3 (Tukey's HSD = 3.81, $p < 0.05$).

The heterogeneity of IPD was investigated separately for the shorter (groups 1, 2, and 3) and longer (groups 4 and 5) disease duration groups.

TABLE 2. *Abnormal neuropsychologic test performance according to normative values*

	Group 1	Group 2	Group 3	Group 4	Group 5
Beck depression inventory				*	*
Blessed dementia scale			*		†
Digit ordering		*	*		†
Letter fluency			*		*
CANTAB pattern recognition			*		†
CANTAB spatial recognition			*		†
CANTAB set shifting		*			†
CANTAB SWM total between errors					
CANTAB SWM total within errors					

CANTAB, Cambridge Neuropsychological Test Automated Battery; SWM, Spatial Working Memory subtest.

* ''Mild impairment,'' over one standard deviation below normal performance.

† ''Moderate impairment,'' over two standard deviations below normal performance.

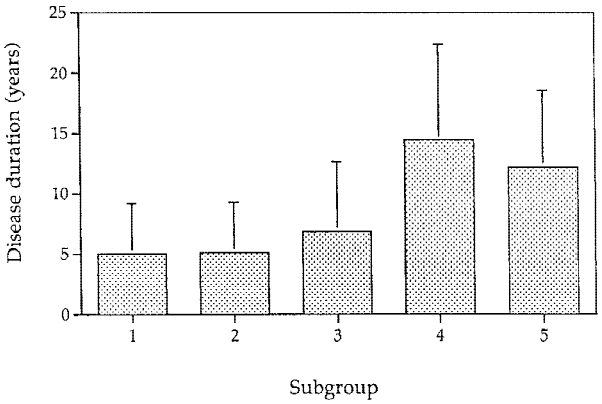

FIG. 1. Mean duration of IPD in the five naturally occurring subgroups.

Heterogeneity in IPD of Shorter Duration

The mean disease duration of groups 1–3 was 5.6 years (standard deviation = 4.7 years). Group 1 accounted for 44.8%, group 2 for 27.6%, and group 3 for 27.6% of the patients with IPD of short duration.

Patients in group 3 were significantly older than those of group 1 at the onset of IPD ($F = 6.64$, $p < 0.01$). Using the data summarized in Table 1, a series of one-way analyses of covariance controlling for the effect of age at IPD onset were carried out. These results are illustrated in Table 3. Cognitive variables were also controlled for the effect of premorbid intelligence. Significant F values were investigated with the conservative Tukey HSD post hoc comparison.

Medication

The three groups did not differ with respect to the nature of dopaminergic medication or the daily dosage of either levodopa or dopamine agonist therapy.

Affect

The three groups reported equivalent depressive symptomatology.

Motor Function

Group 3 was the most severely motor impaired differing from groups 1 and 2 on finger dexterity with the left hand (Tukey's HSD = 16.23, $p < 0.01$), UPDRS right motor score (Tukey's HSD = 2.05, $p < 0.05$), left motor score (Tukey's HSD = 3.02, $p < 0.01$), total motor score (Tukey's HSD = 6.02, $p < 0.01$), and activities of daily living (ADL; Tukey's HSD = 4.94, $p < 0.01$). In addition, group 3 also differed from group 2 in finger dexterity with the right hand (Tukey's HSD = 18.32, $p < 0.01$).

Group 2 appeared to have the best motor control

TABLE 3. *Motor, cognitive, and demographic comparisons of groups 1, 2, and 3*

	F value
Motor function	
Alternate finger tapping right	19.92†
Alternate finger tapping left	14.77†
UPDRS motor right	6.60†
UPDRS motor left	9.33†
UPDRS tremor factor	4.88†
UPDRS axial factor	13.03†
UPDRS speeded movement factor	10.84†
UPDRS motor total	21.05†
Duration IPD at dyskinesia	1.86
Duration IPD at falls	7.37†
Duration IPD at fluctuation	1.91
UPDRS daily activities best	6.50†
UPDRS daily activities worst	11.09†
Affect	
Beck depression inventory	2.19
UPDRS mentation	2.82
Cognition	
Blessed dementia scale	12.14†
Digit ordering	58.08†
Letter fluency	18.59†
CANTAB pattern recognition	17.35†
CANTAB spatial recognition	21.16†
CANTAB set shifting	19.85†
CANTAB SWM total between errors	92.94†
CANTAB SWM total within errors	3.25*
Demographics	
Maximum regular alcohol intake	0.19
Levodopa daily dose	1.27
Dopamine agonist daily dose	0.77

UPDRS, Unified Parkinson's Disease Rating Scale; IPD, idiopathic Parkinson's disease; CANTAB, Cambridge Neuropsychological Test Automated Battery; SWM, Spatial Working Memory subtest.
* $p < 0.05$.
† $p < 0.01$.

showing superior performance to group 1 in finger dexterity with both the right (Tukey's HSD = 18.32, $p < 0.01$) and left (Tukey's HSD = 16.23, $p < 0.05$) hands. This group also reported a longer duration of IPD before the onset of postural instability than either group 1 (Tukey's HSD = 2.81, $p < 0.05$) or group 3 (Tukey's HSD = 3.59, $p < 0.01$).

Motor disability was divided into three factors based on previous factor analyses of the UPDRS motor examination[34,52]: axial motor disability, speeded movements, and tremor. Each factor comprised the UPDRS items listed in Table 4. Group 3 was more disabled than groups 1 and 2 in both axial (Tukey's HSD = 2.33, $p < 0.01$) and speeded movements (Tukey's HSD = 4.17, $p < 0.01$). Group 3 was also more impaired than group 2 by tremor (Tukey's HSD = 1.73, $p < 0.01$).

Complications of IPD

Table 5 shows that in addition to the poorest motor control, group 3 also showed the greatest prevalence of postural instability (chi-square = 12.16, $p < 0.01$) and symptomatic orthostasis (chi-square = 17.41, $p < 0.01$).

Group 1 reported less psychosis than groups 2 or 3 (chi-square = 6.67, $p < 0.05$).

Cognition

Group 3 was the most severely cognitively impaired, performing more poorly than groups 1 and 2 on the Blessed Dementia Scale (Tukey's HSD = 1.36, $p < 0.01$), letter fluency (Tukey's HSD = 2.34, $p < 0.01$), digit ordering (Tukey's HSD = 10.5, $p < 0.01$), pattern recognition (Tukey's HSD = 1.76, $p < 0.01$), and spatial recognition (Tukey's HSD = 1.58, $p < 0.01$). In addition, group 3 was also more impaired than group 1 on the spatial working memory assessment (Tukey's HSD = 14.18, $p < 0.01$). Group 3, however, had superior set-shifting performance compared with group 2 (Tukey's HSD = 1.04, $p < 0.01$).

Group 1 had the best cognitive performance showing superiority to group 2 on digit ordering (Tukey's HSD = 10.5, $p < 0.01$), set-shifting (Tukey's HSD = 1.04, $p < 0.01$), and spatial working memory (Tukey's HSD = 14.18, $p < 0.01$).

Table 6 summarizes the characteristics of the short disease duration subgroups of IPD.

Heterogeneity in IPD of Longer Duration

Groups 4 and 5 had a mean disease duration of 13.4 years (standard deviation = 7.3 years). Group 4 accounted for 54.8% and group 5 for 45.2% of the patients with IPD of longer duration.

Using the data summarized in Table 1, a series of independent sample *t* tests with application of the Bonferroni correction were carried out. These results are shown in Table 7.

Medication

Groups 4 and 5 did not differ with respect to the nature of dopaminergic medication or the daily dosage of levodopa or dopamine agonists.

TABLE 4. *Factorial division of the UPDRS motor subscale*

Axial motor disability	Speeded movements	Tremor
Speech	Rigidity	Tremor at rest
Facial expression	Finger taps	Action tremor
Arise from chair	Hand movement	
Posture	Hand prone-supination	
Gait	Leg agility	
Postural stability		
Body bradykinesia		

UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 5. *Demographic and treatment measures of groups 1–3 (categorical data)*

	Group 1 (n = 60)	Group 2 (n = 37)	Group 3 (n = 37)	Chi-square	Group differing
Demographics					
Sex	0.47 female	0.49 female	0.46 female	0.06	
Smoking history	0.49 (n = 59)	0.30	0.35	4.05	
Side of IPD symptom onset	0.60 right (n = 52)	0.48 right	0.52 right	1.12	
Medication					
Levodopa-medicated	0.57 (n = 54)	0.63 (n = 35)	0.76	3.23	
Dopamine agonist-medicated	0.36 (n = 56)	0.38	0.30	0.59	
Anticholinergic-medicated	0.05 (n = 56)	0.11	0	4.24	
MAO inhibitor-medicated	0.20 (n = 56)	0.22	0.24	0.29	
Unmedicated	0.09 (n = 57)	0.11	0.11	0.15	
Treatment complications					
Postural instability	0.42 (n = 59)	0.51	0.78	12.16†	Group 3
Symptomatic orthostasis	0.20 (n = 59)	0.24	0.60	17.41†	Group 3
Dyskinetic motor complications	0.22 (n = 59)	0.27	0.27	0.44	
Response fluctuation	0.36 (n = 59)	0.43	0.49	1.67	
Falling motor complications	0.31 (n = 59)	0.24	0.46	4.22	
Dopaminomimetic psychosis	0.06 (n = 53)	0.21 (n = 34)	0.24 (n = 33)	6.67*	Group 1

IPD, idiopathic Parkinson's disease.
* $p < 0.05$.
† $p < 0.01$.

Affect

Groups 4 and 5 reported equivalent depressive symptomatology.

Motor Function

Group 5 self-reported significantly more impairment on daily activities when they were ''at their best'' than group 4 ($t = 3.59$, $p < 0.05$) but the groups did not differ ''at their worst'' ($t = 2.77$, $p > 0.05$). There were no other differences between groups 4 and 5 in motor function.

Complications of IPD

Groups 4 and 5 reported equivalent complications of IPD as illustrated in Table 8.

Cognition

Group 5 showed severe global cognitive impairment, displaying inferior performance to group 4 on every measure of cognition (blessed dementia, $t = 6.41$, $p < 0.01$; digit ordering, $t = 10.11$, $p < 0.01$; letter fluency, $t = 4.32$, $p < 0.01$; pattern recognition, $t = 4.02$, $p < 0.05$; spatial recognition, $t = 3.88$, $p < 0.05$; set-shifting, $t =$

TABLE 6. *The characteristics of subgroups 1–3*

Group 1 (45%)	Group 2 (28%)	Group 3 (28%)
53 years at onset	58 years at onset	61 years at onset
Mild depressive affect	Mild depressive affect	Mild depressive affect
Good motor control	Good motor control	Poor motor control
Good cognition	Executive cognitive deficits	Poor global cognition

TABLE 7. *Demographic, motor, and cognitive comparisons of groups 4 and 5*

	t value
Motor function	
Alternate finger tapping right	2.79
Alternate finger tapping left	2.08
UPDRS motor right	1.69
UPDRS motor left	0.95
UPDRS tremor factor	0.70
UPDRS axial factor	2.08
UPDRS speeded movement factor	1.38
UPDRS motor total	2.15
Duration IPD at dyskinesia	1.64
Duration IPD at falls	0.81
Duration IPD at fluctuation	1.09
UPDRS daily activities best	3.59*
UPDRS daily activities worst	2.77
Affect	
Beck depression inventory	1.20
UPDRS mentation	3.37
Cognition	
Blessed dementia scale	6.41†
Digit ordering	10.11†
Letter fluency	4.32†
CANTAB pattern recognition	4.02*
CANTAB spatial recognition	3.88*
CANTAB set shifting	12.98†
CANTAB SWM total between errors	6.81†
CANTAB SWM total within errors	1.86
Demographics	
Age at onset	2.64
Maximum regular alcohol intake	0.33
Levodopa daily dose	1.12
Dopamine agonist daily dose	1.73

UPDRS, Unified Parkinson's Disease Rating Scale; IPD, idiopathic Parkinson's disease; CANTAB, Cambridge Neuropsychological Test Automated Battery; SWM, Spatial Working Memory subtest.
* $p < 0.05$.
† $p < 0.01$.

TABLE 8. *Demographic and treatment measures for groups 4 and 5 (categorical data)*

	Group 4 (n = 23)	Group 5 (n = 19)	Chi-square or Fisher's exact significance (FE)
Demographics			
Sex	0.48 female	0.47 female	0.00
Smoking history	0.48	0.67 (n = 18)	0.79
Side of IPD symptom onset	0.45 right	0.62 right (n = 18)	0.33
Medication			
Levodopa-medicated	0.78	0.74	1.00 (FE)
Dopamine agonist-medicated	0.61	0.53	0.29
Anticholinergic-medicated	0.23 (n = 22)	0.16	0.70 (FE)
MAO inhibitor-medicated	0.22	0.16	0.71 (FE)
Unmedicated	0.04	0.05	1.00 (FE)
Treatment complications			
Postural instability	0.83	0.89 (n = 18)	0.68 (FE)
Symptomatic orthostasis	0.39	0.67 (n = 18)	3.06
Dyskinetic motor complications	0.52	0.58	0.14
Response fluctuation	0.61	0.74	0.77
Falling motor complications	0.57	0.72 (n = 18)	1.07
Dopaminomimetic psychosis	0.22	0.40 (n = 15)	0.28 (FE)

IPD, idiopathic Parkinson's disease.

12.98, $p < 0.01$; and spatial working memory between errors, $t = 6.81$, $p < 0.01$).

Table 9 summarizes the characteristics of the long disease duration subtypes of IPD.

The Association of Motor and Cognitive Symptomatology

Table 10 shows that the UPDRS total and factor motor scores were not related to cognitive performance for any subgroup of IPD.

DISCUSSION

Traditionally there have been two methodologic approaches to the study of clinical heterogeneity in IPD: matched groups and unselected samples. The disadvantage of selecting matched groups of patients which differ with regard to the characteristic under study is that boundary conditions, often arbitrary, for the presence of that characteristic must be defined. The investigation of a particular characteristic in an unselected sample of patients is also problematic because it assumes that the characteristic influences the population in a homogeneous manner. We have overcome the constraints of these methods by approaching the study of clinical heterogeneity in IPD in a data-driven manner with a large sample of patients unselected for specific characteristics. Our results, however, may be specific to the movement disorders clinic outpatient sample used and therefore require validation in community-derived patient cohorts and in other countries.

TABLE 9. *The characteristics of subgroups 4 and 5*

Group 4 (55%)	Group 5 (45%)
47 years at onset	55 years at onset
Mild depressive affect	Mild depressive affect
Poor motor control and complications	Poor motor control and complications
Good cognition	Poor global cognition

Cluster analysis confirmed the clinical heterogeneity of IPD by identifying three naturally occurring subgroups at a mean disease duration of 5.6 years (groups 1, 2, and 3) and two at a mean disease duration of 13.4 years (groups 4 and 5). Group 1 was characterized by good motor control without cognitive impairment. Group 2 was characterized by good motor control with cognitive deficits of the ''executive'' type. Group 3 was characterized by an older age of disease onset, poor motor control with motor complications, and mild global cognitive impairment. Group 4 was characterized by poor motor control without cognitive impairment. Group 5 was characterized by poor motor control with moderately severe global cognitive impairment.

The identification of clinical subgroups with equivalent motor disability and different cognitive performance suggests that independent neuropathologic processes are responsible for the cognitive and motor symptoms of IPD. To further support this hypothesis, no aspect of cognitive performance was correlated with motor disability or any motor factor in the subgroups of IPD. Motor disability was recorded in the ''on'' state when dopaminergic therapy may have been masking motor dysfunction. The observed dissociation of intellectual

TABLE 10. *The association of motor and cognitive performance*

	Blessed	Digit order	Letter fluency	Pattern recognition	Set-shifting	Spatial recognition	SWM total between errors	SWM total within errors
Group 1								
Tremor factor	.16	.16	.01	.17	.16	.00	.01	.14
Speed factor	.05	.31	.08	.10	.18	.07	.06	.04
Axial factor	.17	.14	.02	.02	.26	.07	.10	.00
Total motor	.15	.27	.06	.11	.25	.01	.02	.05
Group 2								
Tremor factor	.21	.19	.13	.08	.09	.22	.05	.21
Speed factor	.06	.37	.02	.07	.27	.11	.18	.02
Axial factor	.08	.11	.34	.06	.06	.34	.13	.14
Total motor	.04	.28	.23	.02	.26	.17	.10	.02
Group 3								
Tremor factor	.10	.24	.04	.10	.05	.37	.11	.12
Speed factor	.21	.00	.16	.01	.18	.18	.15	.24
Axial factor	.01	.01	.11	.00	.29	.08	.03	.02
Total motor	.08	.01	.07	.02	.07	.11	.01	.10
Group 4								
Tremor factor	.51	.01	.34	.17	.03	.02	.18	.11
Speed factor	.53	.02	.02	.03	.39	.09	.32	.00
Axial factor	.43	.02	.19	.12	.08	.44	.02	.08
Total motor	.21	.04	.17	.08	.20	.22	.32	.07
Group 5								
Tremor factor	.14	.17	.06	.27	.04	.12	.20	.16
Speed factor	.02	.08	.19	.22	.18	.20	.12	.06
Axial factor	.20	.22	.17	.14	.29	.36	.35	.26
Total motor	.15	.22	.07	.01	.07	.05	.04	.05

SWM, Spatial Working Memory subtest.
* $p < 0.05$ with Larzelere and Mulaik correction.

and motor symptoms may be the result of the influence of dopaminergic medication, although it is unlikely because similar findings have been reported in untreated patients with IPD.[1,32]

The clinical subgroups at short and long disease durations are likely to represent early and later stages of progression of distinct subtypes of IPD. We propose that the five naturally occurring subgroups identified through cluster analysis actually represent three pathologically distinct subtypes of IPD. The progression from group 1 to group 4 represents a subtype of IPD characterized by motor symptom progression in the absence of intellectual impairment, a ''motor only'' subtype. The progression from group 2 to group 5 represents a subtype of IPD characterized by the progression of both motor and intellectual disability, a ''motor and cognitive'' subtype. Group 3 represents an aggressive form of IPD characterized by rapid progression of both motor and cognitive impairment, a ''rapid progression'' subtype.

The ''motor only'' subtype of IPD found in our study is supported by Mortimer et al.[19] who identified, in a data-driven investigation of IPD, two clusters of patients with comparable age at disease onset and motor disability, and either normal cognitive performance or both verbal memory and visuospatial reasoning deficits. In addition, a number of studies have selected matched patients with IPD with and without cognitive impairment for the purpose of clinical or pathologic comparison.[22,53,54]

The pathologic hallmarks of IPD are depletion of brain stem pigmented neurons and intraneuronal Lewy body inclusions.[55] Dopamine depletion in the nigrostriatal pathway results in the motor symptoms of IPD. Functional connections between the striatum and the frontal cortex involve at least five topographically distinct loops, in particular, the motor loop that is involved in motor control and the complex loop that serves cognitive functions.[56] Thus, the neuropathologic basis of the ''motor only'' subtype of IPD probably involves relatively selective nigroputaminal dopamine deficiency causing isolated disruption to the ''motor loop.''

The ''motor and cognitive'' subtype of IPD differs from the ''motor only'' subtype in early impairment on tasks of executive function which progresses to global cognitive disability later in the disease. Executive function involves skills required for anticipation, planning, initiation, and monitoring of goal-directed behaviors.[57] The ''motor and cognitive'' subtype of IPD showed early deficits in the digit-ordering, attentional set-shifting, and spatial working memory tasks, which all depend on intact executive function. Impairment on such tasks is thought to reflect frontal lobe dysfunction

and has frequently been reported in patients with IPD.[13,14,16,32,58] Longitudinal studies support our suggested progression from frontal lobe dysfunction to more widespread cognitive deficits. Jacobs et al.[59] observed that impaired verbal fluency performance independently predicted global cognitive disability later in the course of IPD. Tooth et al.[60] reported that poor digit ordering and recall performance in association with an abnormal computed tomography scan in early disease predicted later clinical dementia with a positive reliability of 78%.

Dopaminergic depletion in the frontal lobes may be responsible for the early cognitive deficits associated with the ''motor and cognitive'' subtype of IPD. The ''complex'' loop that connects the caudate nucleus to the prefrontal cortex suffers dopamine depletion as a direct result of loss of nigrostriatal projections.[56] Additional dopaminergic pathology in the ventral tegmental area causes deafferation of the frontal cortex through the nesocorticolimbic pathway.[61] In support of this, impaired frontal performance in IPD is improved by enhancement of dopaminergic activity[32]; however, correction of deficits even in early disease is incomplete and dopamine replacement sufficient to improve motor control may have deleterious effects on cognition.[62] Also, dopaminergic therapy does not generally improve the cognitive deficits of clinical dementia. These observations suggest that nondopaminergic pathology contributes to cognitive impairment in both early and late disease in the ''motor and cognitive'' subtype of IPD which is in accordance with recent suggestions.[63,64]

The nature of the nondopaminergic pathology that is relevant to the cognitive impairment remains speculative at this stage. However, it has previously been shown that innominato-cortical and septo-hippocampal cholinergic lesions, coeruleo-cortical noradrenergic lesions, and ascending serotonergic lesions can occur in patients with IPD[65] and have been directly linked to poor cognitive performance in these patients.[66,67] In addition to poor executive function, memory and attention are impaired producing the clinical presentation of global cognitive deficiency. There is also clinicopathologic evidence that dementia in patients with IPD can occur in the absence of structural cortical changes.[53,68–70]

Alternatively, the progressive cognitive impairment of the ''motor and cognitive'' subtype may reflect the spread of diffuse cortical pathology either alone or in combination with nondopaminergic subcortical changes. Earlier in IPD, the cortical changes may be mild and therefore only affect performance on the most demanding cognitive tasks which in our battery were those of executive function. With time, the cortical pathology spreads and impairment on the less demanding tasks, such as the Blessed Dementia Scale, becomes apparent.

The ''rapid progression'' subtype of IPD, characterized by an older age at disease onset, rapidly progressive motor and cognitive disability, and more orthostasis, has been described previously.[6,21,22] The risk of mortality in IPD increases with increasing age,[71] the development of dementia,[72] and the severity of motor disability.[71–73] We propose that the absence of the ''rapid progression'' subtype from the later stage of IPD reflects the high combined risk of mortality in this subtype. Alternatively, this subtype may be underrepresented in the sample because the most motor and cognitively disabled patients either refused to participate or failed to complete the entire assessment battery.

The neuropathologic basis of the ''rapid progression'' subtype of IPD is likely to be multifactorial, including cortical Alzheimer or Lewy body changes in addition to the dopaminergic and nondopaminergic subcortical pathology. Alzheimer-type pathology has been identified in patients with IPD and clinical dementia.[53] The cognitive impairment of IPD associated with cortical senile plaques and neurofibrillary tangles is thought to be more severe than when these changes are absent.[74] Other neuropathologic alterations that have been linked to global cognitive decline in IPD include the presence of Lewy bodies in the cerebral cortex.[75] However, cortical Lewy body disease alone may not be the pathology that characterizes the rapid cognitive decline of this subgroup because hallucinosis, which has been considered a core feature of dementia with Lewy bodies,[76] was not more common in this subgroup than the other subgroups with cognitive impairment.

Investigation of the clinical heterogeneity of IPD is complicated by the erroneous inclusion of patients with other neurodegenerative disorders which appear clinically indistinguishable from IPD, especially in the early stages. These include multiple system atrophy, progressive supranuclear palsy, striatonigral degeneration, corticobasal degeneration, Alzheimer's disease, and cortical Lewy body disease. When the clinical evaluation is conducted by a neurologist, the misdiagnosis of IPD using the Parkinson's Disease Society Brain Research Centre clinical diagnostic criteria is estimated at 18%.[55] It is possible one or more of the clinical subtypes identified through cluster analysis may disproportionately reflect the inclusion of false-positive cases. We think this is unlikely because previous studies have identified similar clinical subclassifications of IPD, but we do intend to seek confirmation through the neuropathologic investigation of our sample.

This study was not designed primarily to provide es-

timates of the presence of dementia in IPD. However, our results suggest that global cognitive impairment at 13 years' disease duration may affect a larger proportion of patients (up to 45%) than previously suspected. We are currently evaluating this with greater accuracy by longitudinal study of the early subgroups and by broader sampling of a large community-derived cohort of IPD patients.

In summary, we have identified through data-driven analysis three distinct subtypes of IPD. The ''motor only'' subtype characterized by motor disability in the absence of cognitive impairment probably reflects isolated nigroputaminal dopamine deficiency. The ''motor and cognitive'' subtype characterized by advancing motor and cognitive impairment may reflect nigrostriatal and mesocorticolimbic dopamine deficiency with involvement of nondopaminergic subcortical lesions or cortical pathologic alterations. The ''rapid progression'' subtype, characterized by rapidly progressive motor and cognitive disability, may reflect multifocal pathology, including lesions of several neurotransmitter systems and intrinsic cortical pathology. The identification from empiric study of both qualitative and quantitative heterogeneity within IPD suggests that a number of etiologic factors are involved in producing different neuropathologic processes within the clinical spectrum of IPD.

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