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Age of disease onset influences cognition in Parkinson's disease

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Abstract

It is controversial whether age of disease onset is related to cognitive decline in Parkinson's disease (PD). We administered 7 cognitive measures assessing visuospatial skills, memory, and executive functions to 222 patients with idiopathic PD and 108 normal control participants. Regression analyses demonstrated that older age of disease onset consistently predicted cognitive decline above and beyond normative aging and duration of illness. These findings suggest that older age of disease onset is a critical determinant of cognitive deterioration in PD. (*JINS*, 1998, *4*, 285–290.)

Keywords: Parkinson's disease, Cognition, Cognitive decline, Age of onset

INTRODUCTION

It is controversial whether the age at which an individual develops Parkinson's disease (PD) is related to cognitive decline. Some studies have found younger age of disease onset to be associated with increased impairments (Freidman, 1994; Lesser et al., 1979; Mjones, 1949), while others have shown that older age of disease onset results in a more rapid course of cognitive decline (Biggens et al., 1992; Caparros-Lefebvre et al., 1995; Celesia & Wanamaker, 1972; Dubois et al., 1990; Heitanen & Teravainen, 1988; Korczyn et al., 1986; Martilla & Rinne, 1976). Still others have argued that after controlling for chronological age, age of disease onset has little effect on cognitive performance (Huber et al., 1991).

To date, all studies examining age of disease onset and its effect on cognition have treated age as a categorical variable. Pedhazur and Schmelkin (1991) argue that this practice forces the researcher "to resort to an arbitrary categorization of continuous variables in order to fit them into the ANOVA straightjacket." As a result, information is lost and the relationship between variables in the design may be altered. Furthermore, comparison across studies is problematic because there is little agreement as to what constitutes "young" *versus* "old" age of disease onset. Dubois et al. (1990) defined young onset as less than age 45 years and "old" onset as greater than age 60 years. Others have split PD patients into groups using an arbitrary cutoff (<60 and >60; Heitanen & Teravainen, 1988), or categorized young and old onset, as 1 standard deviation below and above the mean age of onset, respectively (Freidman, 1994). No research has utilized age of PD onset as a continuous variable in the prediction of cognitive functioning.

In addition most studies do not consider how current age and duration of disease interact with the effects of age of disease onset. This may in part be due to the complex nature of the relations between these variables. Age, age of disease onset, and duration are frequently confounded, and their individual effects are difficult to disentangle. Therefore, they are often studied separately without taking into account the confounding influences of the other two variables.

In fact, studies have shown that advanced age and duration individually influence cognition in PD. Advanced age has been linked to cognitive decline (Cummings & Benson, 1992; Salthouse, 1989). Specifically, memory (Cummings & Benson, 1992; Dorfman et al., 1986; Moscovitch, 1982; Wechsler, 1961), language (Bayles & Kaszniak, 1987; Cummings & Benson, 1992; Goodglass et al., 1980; Obler & Albert, 1981) and visuospatial functions (Cummings & Benson, 1992; Eslinger & Benton, 1983; Read, 1988; Schaie, 1977) have been shown to decline with advancing age.

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The effect of disease duration on cognition in PD is less clear. Many studies have shown disease duration to be unrelated to cognitive deterioration (Elizan et al., 1986; Garron et al., 1972; Martilla & Rinne, 1976). Matthews and Haaland (1979) found an initial decline in cognition, followed by a plateau with few significant cognitive changes. Other researchers have demonstrated demented patients have a longer duration (Biggens et al., 1992), while Leiberman et al. (1979) found patients with a shorter duration to be more seriously affected.

The present study investigated the influence of age of disease onset on cognitive performance in PD. Specifically, this study examined whether age of PD onset exerts an effect on cognitive deterioration after controlling for an individual's current age and disease duration. In order to examine these variables in an ecologically valid context, we utilized a continuum model.

Table 1. Participant characteristics

	Patients ($N = 222$)*		Controls ($N = 108$)**		
Characteristic	*M*	(*SD*)	*M*	(*SD*)	*p* value
Age	66.41	(10.13)	67.63	(11.81)	NS
Education	14.06	(2.91)	13.64	(2.28)	NS
MMSE	25.18	(7.61)	26.20	(1.53)	NS
BDI	10.39	(7.75)	5.30	(4.52)	.001
Age of onset	59.79	(11.17)			
Duration	6.59	(5.30)			
PD stage	2.30	(0.95)			
PD disability	18.55	(11.14)			

*Patients *N* varies (201–222) across variables due to missing data.
**Controls *N* varies (96–108) across variables due to missing data.

METHODS

Research Participants

Our study sample consisted of 222 patients (133 men and 89 women) with idiopathic Parkinson's disease referred from the Movement Disorders Clinic at the University of Miami. A sample of 108 control participants (41 men and 67 women), consisting of either the patients' spouses or senior citizens recruited from an adult retirement community were also included. Written informed consent was obtained, and each participant underwent a comprehensive neuropsychological assessment. Patients and controls with a history of drug or alcohol abuse, a major psychiatric disorder, cardiovascular disease, insulin-dependent diabetes, head injury, or other neurological problems, as well as patients who underwent neurosurgical operation, were excluded. Patients were also excluded if the neurological evaluation revealed signs or symptoms not consistent with a diagnosis of idiopathic PD, including lack of responsivity to Sinemet, a rapidly progressing dementia, or evidence suggestive of another movement disorder.

Procedures

Each participant underwent a 3-hr comprehensive interview and neuropsychological evaluation at the Division of Neuropsychology, at the University of Miami. The Mini-Mental State Examination (Folstein et al., 1975) and the Beck Depression Inventory (BDI) (Beck et al., 1961) were administered to all participants. All PD patients were evaluated by a neurologist and rated for degree of disability (modified Columbia Disabilities Scale, 1970), and stage of illness (Hoehn & Yahr, 1967). Demographic and clinical data of the samples are shown in Table 1.

Measures

The neuropsychological battery consisted of tests that were chosen on the basis of their clinical and empirical sensitivity to the spectrum of cognitive functions known to be compromised in PD. Cognitive functioning was assessed in the following domains: (1) *memory* [California Verbal Learning Test (CVLT) and Benton Visual Retention Test (BVRT)]; (2) *visuospatial* [Hooper Visual Organization Test (HVOT) and Ghent Embedded Figures Test]; (3) *executive functioning* [Wisconsin Card Sorting Test (WCST)]; and (4) *verbal fluency* (animals and FAS). These instruments are described in Lezak (1995).

Statistics

A four-step statistical procedure was utilized to isolate the contribution of age of disease onset from current age and disease duration. First, in order to measure the amount of change in cognition associated with normal aging, we calculated regression equations with age as the predictor of cognition in the control group. Given the discrepancy between the proportions of men and women within the patient and control groups, sex was also entered as a control variable in this analysis. Second, we applied these regression equations to the PD group and obtained a predicted value for each patient on each measure. Third, by subtracting the patient's observed value from their predicted value we obtained residualized cognitive functioning scores. These residualized values represent the change in cognitive functioning in PD that is not accounted for by normative aging or gender. Fourth, in order to control for duration, we simultaneously entered both age of onset and duration as predictors of the residualized cognitive functioning scores in a regression equation.

RESULTS

Individual *t* tests between the PD and control participants indicated no differences between groups on current age, education, and Mini Mental Status Exam (MMSE) scores (see Table 1). The level of depression differed between the two groups, with PD participants reporting more depressive

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symptomatology on the BDI relative to controls. Table 1 shows means and standard deviations for the PD groups' age of onset, duration of illness, PD stage, and level of disability. Means and standard deviation of the cognitive variables for the two groups are presented in Table 2.

Given that the level of depression differed between the control and PD group, the association between age and level of depression in both groups was calculated using Pearson product–moment correlations. This was done to assess whether prediction equations that were to be derived from the control group could be applied to the PD group. No association was found between age and level of depression for either group ($r = .06$ and $r = .04$, for control and PD groups, respectively). The correlation between age of onset and level of depression in the PD group was $r = -.02$.

In order to predict the amount of change in cognition associated with the normative aging process, simple regressions were calculated for control participants using age as a predictor of the cognitive performance scores. Sex was also entered as a control variable. Age significantly predicted performance on the HVOT [$t(1,97) = -4.01$, $p = .001$] , Ghent Embedded Figures Test [$t(1,88) = -3.66$, $p = .001$], animal fluency [$t(1,102) = -4.62$, $p \leq .001$], CVLT–immediate [$t(1,90) = -3.29$, $p = .001$] and delayed recall [$t(1,89) = -2.34$, $p = .022$], and the BVRT [$t(1,90) = -3.54$, $p = .001$]. A trend toward significance was observed on the WCST [$t(1,86) = -1.81$, $p = .074$]. Age did not predict performance on the FAS verbal fluency measure. Sex significantly predicted performance on the CVLT–immediate [$t(1,90) = 3.66$, $p = .001$] and delayed recall [$t(1,89) = 3.34$, $p = .001$]. Sex did not predict performance on the HVOT, Ghent Embedded Figures Test, WCST, FAS verbal fluency, animal fluency, or the BVRT.

Pearson product–moment correlations between the residualized cognitive functioning values and both duration and age of disease onset are presented in Table 3. These values reflect the simple correlations between both age of onset and duration and cognitive functioning within the PD group, after changes associated with normal aging and sex were removed.

Table 2. Mean cognitive scores in the PD and control groups

	Patients ($N = 222$)*		Controls ($N = 108$)**	
Measure	*M*	(*SD*)	*M*	(*SD*)
HVOT	6.12	(2.48)	7.23	(2.05)
Ghent Embedded Figures Test	31.00	(4.99)	33.13	(2.49)
WCST–categories	3.75	(1.91)	4.89	(1.40)
FAS	35.94	(14.38)	39.21	(11.36)
Animals	14.32	(5.15)	16.00	(4.34)
CVLT–immediate recall	6.35	(3.45)	8.77	(2.91)
CVLT–delayed recall	6.79	(3.58)	9.33	(3.10)
BVRT	8.50	(3.16)	10.08	(2.94)

*Patients *N* varies (201–222) across variables due to missing data.
**Controls *N* varies (96–108) across variables due to missing data.
HVOT = Hooper Visual Orientation Test; WCST = Wisconsin Card Sorting Test; FAS = FAS Controlled Word Association Test; Animals = categorical verbal fluency test; CVLT = California Verbal Learning Test; BVRT = Benton's Visual Retention Test.

Table 3. Simple correlations between residualized cognitive scores and age of onset and duration in the PD group

Variable	Age of onset	Duration
HVOT	−.03	−.19**
Ghent Embedded Figures Test	−.06	−.14*
WCST–categories	−.20**	−.20**
FAS	−.26**	−.07
Animals	−.13*	−.14*
CVLT–immediate recall	−.15*	.03
CVLT–delayed recall	−.22**	.01
BVRT	.01	−.13*
BDI	−.02	.12
Duration	−.42**	

*$p \leq .05$, **$p \leq .01$.
HVOT = Hooper Visual Orientation Test; WCST = Wisconsin Card Sorting Test; FAS = FAS Controlled Word Association Test; Animals = categorical verbal fluency test; CVLT = California Verbal Learning Test; BVRT = Benton's Visual Retention Test; BDI = Beck Depression Inventory.

Regression equations were utilized to examine the role of age of disease onset and duration of disease in the prediction of the residualized cognitive functioning scores. When both age of onset and duration were entered together, residualized scores of the HVOT, Ghent Embedded Figures Test, WCST, FAS, Animals, and CVLT–delayed recall were predicted significantly by the model. The BVRT and the immediate recall of the CVLT showed a trend toward significance.

When disease duration was controlled, age of onset significantly predicted residualized cognitive functioning on the Ghent Embedded Figures Test, WCST, FAS, Animals, CVLT–immediate recall and CVLT–delayed recall. A trend toward significance was found on the HVOT. Age of onset did not significantly predict residualized scores on the BVRT. Table 4 shows the results of the regression analyses.

The inclusion of duration of disease in the model improved the prediction of age of onset on all measures except for the CVLT–immediate recall. Semipartial correlations are presented in Table 5.

DISCUSSION

This study demonstrated that age of disease onset exerts an important influence on cognition in PD. In general, the older the age of onset, the greater the degree of cognitive impairment. Specifically, age of disease onset significantly predicted performance on measures of visuospatial ability, immediate and delayed verbal memory, and executive functions. This pattern of cognitive impairments is consistent with other reported studies (Boller et al., 1984; Canavan et al., 1989; Cooper et al., 1991; Heitanen & Teravainen,

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Table 4. Two-predictor model with age of onset and duration predicting residualized cognitive functioning in the PD group

Dependent variable	*b*	*t*	semipartial^2	*p*
HVOT				
Duration	−.104	−3.40	.050	.001
Age of onset	−.026	−1.32	.014	.071
[R^2_{model} = .051; $F(2,219)$ = 5.88, p = .003]				
Ghent Embedded Figures Test				
Duration	−.138	−2.75	.033	.007
Age of onset	−.063	−2.02	.018	.044
[R^2_{model} = .037; $F(2,219)$ = 4.23, p = .016]				
WCST–categories				
Duration	−.113	−4.92	.096	.001
Age of onset	−.054	−4.95	.097	.001
[R^2_{model} = .135; $F(2,219)$ = 17.10, $p \leq .001$]				
FAS				
Duration	−.576	−3.04	.038	.027
Age of onset	−.446	−4.96	.100	.001
[R^2_{model} = .105; $F(2,219)$ = 12.82, $p \leq .001$]				
ANIMALS				
Duration	−.213	−3.41	.050	.001
Age of onset	−.098	−3.31	.048	.001
[R^2_{model} = .068; $F(2,219)$ = 7.95, p = .001]				
CVLT–immediate recall				
Duration	−.025	−0.57	.001	.569
Age of onset	−.046	−2.24	.022	.026
[R^2_{model} = .023; $F(2,219)$ = 2.60, p = .077]				
CVLT–delayed recall				
Duration	−.077	−1.77	.013	.079
Age of onset	−.077	−3.73	.060	.001
[R^2_{model} = .060; $F(2,219)$ = 6.97, p = .001]				
BVRT				
Duration	−.093	−2.30	.024	.022
Age of onset	−.021	−1.12	.006	.263
[R^2_{model} = .024; $F(2,219)$ = 2.66, p = .072]				

HVOT = Hooper Visual Orientation Test; WCST = Wisconsin Card Sorting Test; FAS = FAS Controlled Word Association Test; Animals = categorical verbal fluency test; CVLT = California Verbal Learning Test; BVRT = Benton's Visual Retention Test.

Table 5. Partial correlations for age of onset from the two-predictor model with age of onset and duration predicting residualized cognitive functioning in the PD group

Measure	Age of onset Semipartial correlations
HVOT	−.119
Ghent Embedded Figures Test	−.134
WCST–categories	−.311
FAS	−.317
Animals	−.216
CVLT–immediate recall	−.150
CVLT–delayed recall	−.244
BVRT	−.075

HVOT = Hooper Visual Orientation Test; WCST = Wisconsin Card Sorting Test; FAS = FAS Controlled Word Association Test; Animals = categorical verbal fluency test; CVLT = California Verbal Learning Test; BVRT = Benton's Visual Retention Test.

1988; Huber et al., 1986; Lees & Smith, 1983; Levin, 1990; Levin et al., 1989, 1991; Levin & Katzen, 1995; Massman et al., 1990; Pillon et al., 1986; Pirozzolo et al., 1982; Riklan et al., 1989; Taylor et al., 1986; Warburton, 1967; Weingartener et al., 1984). Although our findings support other studies showing older age of disease onset is associated with a more severe profile of cognitive impairment in PD (Biggens et al., 1992; Caparros-Lefebvre et al., 1995; Celesia and Wanamaker, 1972; Diamond et al., 1989; Dubois et al., 1990; Elizan et al., 1986; Heitanen & Teravainen, 1988; Leiberman et al., 1979; Martilla & Rinne, 1976; Scott & Brody, 1971; Wolters et al., 1992), our study extends previous work by demonstrating that these effects are still present even after controlling for age-related cognitive changes, disease duration, and sex. Therefore, patients who develop the disease later in life may be at greater risk for a wide constellation of cognitive impairments.

Age of disease onset was not related to all memory measures. The finding that recognition visual memory was not related to age of onset may be explained by the fact that this task is less difficult and provides a multiple choice context from which to identify the correct answer. This supports the view that the memory deficits observed in PD may result from a retrieval deficit rather than impaired storage capacity. Further, a recognition format provides structure and does not rely on the patient's ability to organize the information. Therefore, it is possible that when the executive component of this visual memory task was minimized, the task demands changed, and performance was no longer compromised. This rationale is further supported by our finding that the other visuospatial tasks in our battery, which rely heavily on executive skills for successful completion, were more impaired in patients with an older age of disease onset.

Executive difficulties have been well documented in PD (Canavan et al., 1989; Cooper et al., 1991; Heitanen & Teravainen, 1988; Lees & Smith, 1983; Levin et al., 1989), and are believed to result from frontal lobe dysfunction *via* damage to the frontal subcortical pathways (Levin et al., 1989; Lezak, 1995). Complex cortical loops, known to connect the frontal lobes to the striatal structures are most effected by DA depletion (Hornykiewicz & Kish, 1987; Taylor et al., 1986). Visuospatial and memory impairments have also been well described in PD (Boller et al., 1984; Huber et al., 1986; Levin, 1990; Levin et al., 1989, 1991; Levin & Katzen, 1995; Massman et al., 1990; Pillon et al., 1986; Pirozzolo et al., 1982; Riklan et al., 1989; Taylor et al., 1986; Warburton, 1967; Weingartener et al., 1984), and are thought to result from a primary executive deficit (Flowers et al., 1984; Lees & Smith, 1983; Taylor et al., 1990).

The cognitive deficits found in our PD sample replicate other investigations, and show that individuals who acquire PD later on the aging continuum, are especially at risk for

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decline on measures that rely on the integrity of frontal lobe functions (Caparros-Lefebvre et al., 1995; Dubois et al., 1990). It is well known that a decrease in DA and other nondopaminergic neurotransmitters are associated with advanced age. However, it is controversial how much DA is lost as a result of normal aging. It would follow that an older individual is especially vulnerable to the loss of DA associated with PD. Dubois et al. (1990) proposed that while degeneration of nigrostriatal pathways may be the same within young and old onset PD groups, early age of onset may act as a protection against cognitive decline. Our data suggest that younger onset patients would show a decreased risk for developing cognitive impairments in the face of PD because these patients have not begun to experience the intrinsic vulnerabilities associated with aging.

While the focus of this study was on the role of age of disease onset in the prediction of cognitive impairments in PD, our findings also indicate that a longer disease duration is associated with greater cognitive decline in select areas. Specifically, decline in visuospatial skills, executive functions, and nonverbal memory were related to a longer disease duration after controlling for age-related decline and age of disease onset. However, disease duration did not predict performance scores on immediate and delayed verbal memory. Rather, these cognitive skills were related to the age at which a person develops the disease, indicating that age of disease onset is a stronger predictor of verbal memory impairment than disease duration.

Our results support studies such as Biggens et al. (1992) who found that dementia was related to a longer duration of disease, a finding supported by basic research showing that disease severity is positively correlated with the degree of cell loss in the striatum (Reiderer & Wuketich, 1976). In addition, changes in extrastriatal DA systems as well as non-DA neurotransmitter systems have been reported (Hornykiewicz & Kish, 1987). Starkstein and Leiguarda (1993) reported that severity of brain atrophy was related to PD disease duration and found longer duration to be associated with greater cognitive impairment.

This study investigated the influence of age of disease onset on cognitive impairments in PD, independent of changes associated with normative aging and disease duration. To our knowledge, the role of age of disease onset has never been investigated while both duration of disease and aging have been taken into consideration. Our results show that a variable such as age of disease onset should not be studied in isolation. In fact, age of disease onset is a better predictor of cognitive functioning when duration is added to the model. These findings emphasize the importance of examining the relative contribution of each variable and its relationship to other disease and subject parameters. Future studies investigating the role of these variables in the development of dementia in neurodegenerative disorders within an elderly population may wish to utilize a similar model in order to separate aging effects from those associated with the disease process. Future investigations should also recognize that aging is a process that gradually unfolds, and is best studied on a continuum.

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