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Health comorbidities and cognition in 1948 patients with idiopathic Parkinson's disease

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Abstract

Background: Health comorbidities, particularly cardiovascular factors, are well known to pose risks for cognitive decline in older adults. This study examined the prevalence and contribution of comorbidities on cognitive performance in a large cohort of Parkinson patients.

Methods: Data on 1948 PD patients were obtained from the National Parkinson Foundation Quality Improvement Initiative (NPF-QII) registry, a multi-site initiative from NPF Centers of Excellence. Available comorbidity data included six common conditions (heart/circulation problems, diabetes, arthritis, cancer, respiratory disease, and other neurologic disease) that were clinician-rated for presence and severity. Available cognitive measures included semantic fluency and a 5-word recall memory task. The unique effects of comorbidities on cognition were analyzed (multiple hierarchical regression) controlling for demographic, PD disease severity (duration, Hoehn-Yahr), and medication status.

Results: The two most reported comorbidities were arthritis (46.6%) and heart/circulation problems (36.3%), with diabetes affecting 9% of the sample. Severity of heart/circulation problems independently contributed to worse delayed recall performance ($p = 0.03$). A trend emerged for more severe diabetes as contributing to worse semantic fluency scores ($p = 0.06$).

Conclusions: This study with a large cohort of PD patients provides evidence for a small detrimental influence of specific health comorbidities, particularly heart/circulatory and diabetes, on general measures of cognition. This effect is present, above and beyond the influences of basic demographic information (age), duration and staging of PD, and medication status. Future studies involving more refined cognitive indices and direct assessment of comorbidities are warranted.

Keywords

Parkinson's disease/Parkinsonism; Neuropsychology; Cardiovascular; Comorbidities; Prevalence

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder of late life and involves progressive changes in a family of segregated motor and nonmotor circuits influencing multiple neurotransmitter systems [1]. Although commonly treated as a dopaminergic depletion disorder, PD is a multisystem disorder with classic motor symptoms (tremors, rigidity, bradykinesia), but also autonomic, mood, and cognitive changes. Typical cognitive changes include slowed thinking, increased forgetfulness, and problems with working memory and multi-tasking [2]. Cognitive changes can occur early in the disease course [3,4], and have been attributed to disruption of dopamine-dependent frontalstriatal circuitry [5]. Superimposed on this prototypical frontal profile, subsets of Parkinson patients develop additional memory and visuospatial deficits that may reflect broad based cholinergic disruption [4,6]. Over time, up to 75−80% of Parkinson patients eventually transition to dementia, particularly those surviving longer than 10 years after disease onset [7].

While PD-related neural degeneration is the primary contributor of cognitive decline, it is unclear whether additional factors, like co-occurring health comorbidities, might also be contributory. Indeed, a wealth of literature over the past decade has pointed to cardiovascular conditions, particularly hypertension and diabetes, as posing risks for cognitive decline in older adults [8,9]. These comorbidities have been associated with small vessel vascular disease observed on magnetic resonance imaging (MRI) scans as leukoaraiosis (LA) or white matter abnormalities [10]. Hypertension-related alterations in white matter, particularly those connecting frontal and subcortical regions, have been linked to changes in set-shifting, working memory, and processing speed [11]. A recent quantitative study using semi-automated volumetric techniques, found that LA affecting as little as 3−13% of white matter volume detrimentally influenced cognition [12].

The question arises as to whether cardiovascular comorbidities negatively influence cognition in Parkinson patients, similar to that observed in normal elderly. Previous studies have failed to show a detrimental affect of cardiovascular disease on dementia status [13–17]. The proposed reasons why cardiovascular risk factors may not relate to cognitive status were a possible protective factor from PD related to lower blood pressure from levodopa medication and reduced likelihood of smoking among individuals with PD [18]. However, while cardiovascular risk factors were not related to cognition, LA, a proposed mechanism mediating hypertension and cognition, did predict cognitive status [16,17]. A possible explanation for the non-significant findings includes being underpowered (no sample sizes were larger than 171 among the previously mentioned studies) to detect subtle differences which may precede dementia onset.

In the present study, we aimed to determine the unique relationship that common comorbidities may exert on simple measures of cognition in a large sample of almost 2000 Parkinson patients who were part of the National Parkinson Foundation Quality Improvement Initiative (NPF-QII). This initiative was a multi-center effort that has resulted in a large standardized clinical practice and longitudinal registry for the purpose of comparative effectiveness research and quality improvement studies [19]. Variables collected in this database were chosen for their ability to quickly capture a broad range of symptoms

with minimal interruption to routine clinical care. Of relevance to the current study, this database included information about the occurrence of six common comorbidities: heart-circulatory, diabetes, arthritis, cancer, respiratory diseases, and other neurologic conditions. Based on findings with normal elderly, we hypothesized that co-occurring "vascular" comorbidities (i.e., heart/circulation problems, diabetes) would be associated with worsened cognitive status in patients with PD even when controlling for disease severity and duration.

2. Methods

2.1. Design and standard protocol approvals, registrations, and patient consents

A cross-sectional study design was used, whereby data were obtained from the NPF-QII registry [19]. The data in this registry were drawn from 17 participating NPF Centers of Excellence. A diagnosis of idiopathic PD was made by a movement disorders specialist using the UK Brain Bank criteria [20]. The study was approved by the Institutional Review Board of each of the following participating centers: University of Pennsylvania, Oregon Health and Science University, Northwestern University (Illinois), Struthers Parkinson's Center (Minnesota), Markham-Stouffville Hospital (Ontario, Canada), the Parkinson's Institute and Clinical Center (California), Muhammad Ali Parkinson Center (Arizona), University of Kansas, Baylor College of Medicine (Texas), Georgia Health and Sciences University, University of South Florida, John Hopkins University (Maryland), Vanderbilt University (Tennessee), Beth Israel Deaconess Medical Center (New York), Nijmegen Medical Center (Nijmegen, Netherlands), Tel Aviv Sourasky Medical Center (Tel Aviv, Israel) and the University of Florida. Informed consent was obtained prior to administration of any study procedure.

2.2. Participants

Participants included all patients registered in the NPF-QII registry between 2009 and 2010 with a diagnosis of idiopathic PD but no history of undergoing deep brain stimulation (DBS) surgery. The database query from NPF-QII yielded 2646 PD patients without DBS. Individuals were further excluded if one or more of the following coded variables were unavailable: comorbidity ratings (described below), disease duration, Hoehn and Yahr stage [21], PD type (tremor predominant vs other), cognitive data (see below), gender, age, living conditions (living at home independently, with skilled care, or other), and information about medication category. Medication category consisted of whether the patient was receiving the following treatments: levodopa, dopamine agonists, antidepressants, cognitive enhancers, or stimulants. Within these treatment categories, there was no further breakdown in terms of specific dosage or specific type of medication. Additionally, height and weight were obtained in order to compute a body mass index (BMI). After meeting all inclusion/exclusion criteria, the final *N* was 1948 participants.

2.3. Cognitive measures and health comorbidities from NPF-QII

Scores from two cognitive measures were available from the NPF registry: semantic verbal fluency and verbal memory. The "semantic" verbal fluency task involved naming as many animal exemplars as possible during a 1 min period (i.e., *Animal* fl*uency*; dependent variable = total number of correct animal names) [22]. The verbal memory task involved oral

presentation of the five-word list from the *Montreal Cognitive Assessment* [23], with an immediate recall and a 90-s delayed recall by the patients. For the present study, we focused on delayed recall, a more sensitive memory index, with total number of words correctly recalled as the final variable.

Six categories of *health comorbidities* were available and rated by the NPF clinician for presence and severity of impact using a 5-point scale: 0 = absent; 1 = asymptomatic/minimal; 2 = moderate; 3 = severe; 4 = very severe. These comorbidities included: *heart/circulation problems*, *diabetes*, *arthritis*, *cancer, respiratory disease* and "*other neurological disorders*." Note that hypertension was subsumed under the heart/circulation category, which also included past heart attack, heart failure, irregular heartbeat and peripheral artery disease. It was not possible to isolate independent effects of hypertension vs. cardiac disease in this dataset. The "o*ther neurologic*" category included conditions such as stroke, neuropathy, etc. The "*arthritis*" category included pain in joints hips, knees, shoulder and spine, and did not distinguish between osteoarthritis and rheumatoid arthritis.

2.4. Statistical analyses

To assess the independent contribution of health comorbidities on cognitive status, we conducted separate multiple hierarchical regression analyses on each of the two cognitive measures (Animal fluency, 90" delayed recall of the 5-item word list). Scores from each cognitive measure were normally distributed. Each hierarchical regression analysis included four blocks of "predictor" variables consisting of 1) available demographic information (age, sex, living condition); 2) disease-related variables (duration of PD, Hoehn and Yahr (H&Y) stage, PD subtype); 3) medication types; and 4) health comorbidities including a computed measure of BMI. Health comorbidities were entered as the last block into the hierarchical regression, so that "variance" associated with other variables (disease, demographic, etc.) could be extracted prior to considering the influence of comorbidities. Statistical significance was evaluated at the a = 0.05 level. Variation Inflation Factor (VIF) revealed low multicollinearity (VIF < 5) among predictors for all analyses.

3. Results

Table 1 shows the characteristics of the final sample of 1948 PD patients. The cohort was approximately 60% male with an average age of 66.6 years and average symptom duration of approximately 9 years (range 1−45 years). Disease severity as indexed by Hoehn and Yahr staging ranged from 1 to 5 with an overall mean of 2.49. Almost half the sample were taking an antidepressant and nearly one third were on a cognitive enhancer.

3.1. Prevalence of comorbidities

As shown in Table 2, arthritis and heart/circulation problems were the most common comorbidities (i.e., 47% and 36%, respectively), whereas diabetes was least frequently reported (i.e., 9%). The occurrence of comorbidities was also examined as a function of age, by dividing the sample into three groups: 59 years ($N = 451$), 60−69 yrs ($N = 726$) and *70* yrs ($N = 771$). As shown in Fig. 1, comorbidity prevalence significantly increased with age for four of the six recorded conditions: heart/circulation ($p < 0.001$), diabetes ($p < 0.001$),

cancer ($p < 0.001$) and arthritis ($p < 0.001$). There was a trend for neurologic conditions to increase with age ($p < 0.06$) (Table 3).

3.2. Cognitive outcomes

Table 3 shows the results of the hierarchical regression analyses. For *delayed recall*, the overall regression model was significant (F (19,1927) = 11.534, $p < 0.001$, R Squared =. 103). Specifically, being older, being female, having more severe PD (i.e. higher HY stage), having longer PD duration, and being on levodopa or cognitive enhancers were all related to lower delayed memory scores. Comorbidities *as a whole* failed to produce a unique effect on memory performance (F change (8,1927) 1.503, $p = 0.151$). However, when looking at individual comorbidities, we found that heart/circulation problems significantly contributed to memory performance ($p = 0.03$). Namely, PD patients with greater heart/ circulation problems had lower performance on the delayed memory task. None of the remaining comorbidities (i.e., diabetes, arthritis, cancer, other neurologic) significantly contributed to memory performance.

For *semantic fluency*, the overall regression model was also significant (F (19,1927) 19.49, $p < 0.001$, R Squared .162). Age, presence of tremor at rest, PD severity, and medication status (levodopa and cognitive enhancers) significantly influenced semantic fluency scores. Thus, being older, having a non-tremor presentation, being in more advanced stages of PD, and being on cognitive enhancers or levodopa were associated with worse fluency scores. The addition of comorbidities as a whole into the regression model *tended* to account for a significant amount of unique variance in our model (F change (8,1927) 1.869, $p = 0.061$). When looking at individual comorbidities, we also found trend relationships, with the presence of diabetes ($p = 0.06$) and "other neurologic" ($p = 0.098$) each tending to be associated with lower semantic fluency scores.

Post hoc analyses were conducted with 1802 PD individuals who were *not on cognitive enhancers* (i.e. Donepezil, Rivastigmine, etc.) in order to minimize inclusion of possible individuals for whom dementia or cognitive difficulties were of concern. Repeat analyses on this participant subset revealed findings consistent with our total sample. Heart/circulation problems were found to be a unique significant predictor of delayed memory recall ($p = 0.029$) and diabetes showed a trend pattern with semantic fluency scores ($p = 0.084$).

4. Discussion

The present study provides evidence that co-occurring health conditions, cardio/circulatory and diabetes, negatively influence the cognitive status of Parkinson patients. While demographic and clinical PD variables accounted for a majority of variance in cognitive domains, heart/circulation problems were associated with worse delayed verbal memory recall, whereas the presence of diabetes tended to be associated with worse semantic fluency scores. Importantly, this association was independent of disease severity, age, gender, and medication status (i.e., dopaminergic, psychotropic, cognitive enhancers). Although the model for *overall comorbidities* failed to reach significance, individual comorbidities contributed to cognitive scores. This implies that some of the variance in cognitive deficits in

PD is explained by specific disease states rather than reflecting a nonspecific global burden of increased comorbidities.

These findings roughly parallel those with normal elderly [8,9]. However, they contrast with those of five prior studies in Parkinson patients. In these previous studies, cardiovascular risk factors have been examined in relation to categorical classification of PD patients as "demented" or not. One study evaluated 173 newly diagnosed PD patients at baseline, re-assessed them 4 years later for presence of dementia, and identified 43 incident cases of dementia [13]. The major finding was that subjective report of cardiovascular risk factors at baseline (i.e., hypertension, stroke, diabetes, coronary artery disease, etc.) did not predict transition to dementia over the 4 year period. Four other studies were crosssectional [14–17]; three studies categorized their PD cohort into three cognitive subgroups: demented, mild cognitive impairment, and unimpaired groups. None of these studies found a differential occurrence of vascular comorbidities across the different cognitive subgroupings.

Our study differs from prior PD comorbidity-cognition research in several important ways. First, rather than using presence/ absence of dementia or MCI as the final endpoint, we examined parametric variation in cognitive scores due to comorbidity status in our Parkinson cohort. Parametric approaches may be more sensitive in detecting differences than are those using categorical outcome classifications [24]. Second, our sample size of 1948 was a great deal larger than previous studies. Because our findings indicated that the variance uniquely explained by heart/circulation comorbidities (as defined by NPF guidelines) was small, it is possible that previous studies with Parkinson patients lacked sufficient power to find small relationships between cardiovascular risk factors and cognition. Finally, although we do not know the influence of lifestyle/cultural factors, our study was primarily based on a large multi-center sample, whereas previous studies involved PD cohorts from a Norwegian epidemiologic study [13,15,17], from Poland [14] and from Korea [16].

In the present study, the most prevalent comorbidity was arthritis, at approximately 46%, and followed by heart/circulation problems in approximately 36% of the PD patients. Due to the manner in which the data were originally obtained through the NPF cohort, we were unable to determine the relative occurrence of hypertension vs cardiac problems (or both) to the heart/circulation category due. Regardless, the occurrence of hypertension in our sample is clearly lower than the 60−65% typically reported in prevalence studies in normal elderly over the age of 65 years [25]. The lower prevalence of hypertension in PD has been attributed, in part, to iatrogenic effects of levodopa medications [18]. The remaining comorbidities appear to more closely approximate those observed in the normal elderly. We also observed significant agerelated increases for arthritis, cancer, heart-circulatory, and diabetes.

While our study did not investigate possible mechanisms underlying the comorbidity −cognition relationships in PD patients, we presume that they are similar to those hypothesized in the normal elderly, specifically small vessel vascular disease. A number of large scale studies in normal older adults have provided support for the relationship between vascular risk factors (hypertension, pulse pressure, diabetes), white matter changes as observed on MRI, and cognitive status [26,27]. There is some suggestion that hypertension

may interact with genetic factors to increase likelihood of vascular changes [28], that diabetes may influence specific hippocampal regions [29] and that hypertension and diabetes have different influences with respect to vessel pathophysiology [10]. By contrast, studies in PD have not *consistently* shown a relationship between white matter abnormalities on brain MRI and cognition. Some studies have found that white matter abnormalities are related to an increased risk of dementia and impairment on general measures of cognition [16,17,30], whereas others have not [14,15]. The bases for these differences are unclear, however, a variety of methodologic factors may be contributory. The latter include variability in the assessment of risk factors (subclinical risk factors vs. presence of stroke), use of newly diagnosed versus older cohorts, variability in techniques for quantifying white matter lesions, and a lack of power to detect the small differences as demonstrated in the current study. It has further been suggested that the cognitive effects of white matter lesions may be more detectable in advanced stages of PD [15,17].

This study is not without limitations. First, due to the nature of how data were collected as part of the NPF-QII, we were unable to isolate the influence of hypertension on cognition, independent of cardiac disease. The use of direct measures of hypertension (i.e., blood pressure, pulse pressure, etc.) may be beneficial in light of frequent co-occurrence of both hypertension and hypotension in PD. Second, implementation of a more detailed and comprehensive neurocognitive assessment battery could better differentiate which cognitive domains are most sensitive to the influence of comorbidities. Additionally, both measures used in the current study have a strong verbal component which could confound the interpretation. Third, we could not address the contribution of education or mood (i.e., depression, apathy) as these variables were not specifically obtained as part of the NPF-QII. Further investigation into the relationship between comorbidities and mood in PD could be of interest given the high percentage of individuals on antidepressants. The addition of age match controls could provide information as to whether or not health comorbidities have a differential impact on cognition in PD. Lastly independent information about the “dementia” status of the participants was not obtained as part of the NPF-QII. Regarding the latter, however, when we removed individuals taking cognitive enhancers from our dataset and reran the analyses, identical findings were obtained.

This current study adds to the literature on cognitive changes in Parkinson disease by providing evidence that comorbidities related to cardiovascular health are associated with reduced cognitive performance on simple measures of memory recall and verbal fluency. While these documented effects are small, they are present even when age, PD-related disease severity and medication use are “controlled for” (i.e., covaried). Given the high prevalence of cardiovascular risk factors that increase with age, both in Parkinson patients in the current study as well as normal elderly, further research may be important to better understand how these factors interact with and potentially exacerbate the phenotypic expression and rate of cognitive decline. Future studies should be performed using more direct measures of comorbidities, an assessment of multiple cognitive domains in a sample of non-demented PD patients, and coupled with investigation of possible mechanisms mediating this relationship. In sum, cardiovascular comorbidities may play a detrimental role on cognition in PD as they do among the normal elderly and further research is needed

to better understand the nature of this relationship in individuals who are already at risk for significant cognitive decline.

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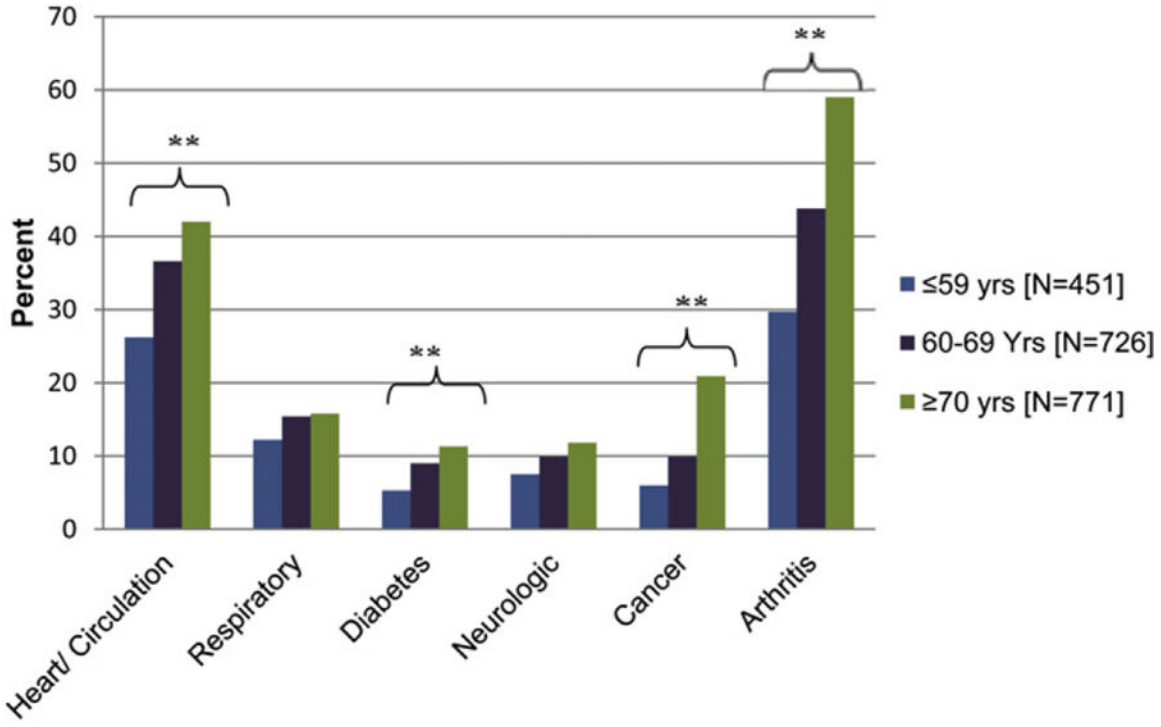

Fig. 1.

Comorbidity prevalence in Parkinson sample according to age, Percent of comorbidities present by age group. $^{**}p < 0.001$. *Heart/Circulation* by age group (young to old): 26.2%, 36.6%, 42.0%, (χ^2 (2) = 32.3, $p < 0.001$); *Respiratory* by age group: 12.2%, 15.4%, 15.8%, (χ^2 (2) = 3.6, $p < 0.163$), *Diabetes*: 5.3%, 9.0%, 11.3%, (χ^2 (2) = 12.3, $p < 0.001$), *Neurologic*: 7.5%, 9.9%, 11.8%, (χ^2 (2) = 5.6, $p < 0.061$), *Cancer:* 6.0%, 9.9%, 20.9%, (χ^2 (2) = 66.2, $p < 0.001$), *Arthritis*: 29.7%, 43.8%, 59.0%, (χ^2 (2) = 103.7, $p < 0.001$).

Table 1

Participant characteristics and cognitive data.

Age (yrs)	
Mean (±SD)	66.6 ± 10.2
Range (min-max)	25–95
Sex	
Male:female	1169:779
Disease duration (yrs)	
Mean (±SD)	9.25 ± 6.1
Range (min-max)	1–45
Tremor predominant, % sample	72%
Living situation (% sample)	
Living at home	98.1%
Skilled care	1.9%
Hoehn-Yahr staging	
Mean (±SD)	2.49 ± 0.8
Staging (% sample)	
Stage 1	13.9
Stage 2	59.0
Stage 3	21.1
Stage 4	3.6
Stage 5	.4
Medications (% sample taking)	
− Levodopa	82
− Dopamine agonists	41
− Antidepressants	46
− Cognitive enhancers	29
− Stimulant	2
Cognitive measures (mean ± SD)	
− Semantic fluency (animals)	19.1 ± 6.2
− 90″ Delayed recall (max = 5)	3.0 ± 1.3
Body mass index, mean ± SD	27.3 ± 5.4

Variables are reported as means ± standard deviations (SD's) with additional range data for certain variables.

Table 2

Prevalence of six common comorbidities among the Parkinson sample ($N = 1852$).

Comorbidity rating by physician										
Comorbidity	**Absent**		**Minimal**		**Moderate**		**Severe**		**Very severe**	
	N	***%***	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***
Heart/circulation	1240	63.7	496	25.5	175	9.0	33	1.7	4	0.2
Respiratory	1659	85.2	189	9.7	78	4.0	18	0.9	4	0.2
Diabetes	1772	91.0	108	5.5	55	2.8	12	0.6	1	0.1
Other neurologic	1751	89.9	118	6.1	58	3.0	15	0.8	6	0.3
Cancer	1688	86.7	187	9.6	43	2.2	28	1.4	2	0.1
Arthritis	1041	53.4	473	24.3	328	16.8	86	4.4	20	1.0

Heart/circulation category included: hypertension, past heart attack, heart failure, irregular heartbeat, peripheral artery disease; Respiratory include: asthma, COPD, etc. Other neurologic included stroke, neuropathy, head injury, etc. Arthritis category included pain in joints, hips, knees, shoulder, and spine, with no distinction between osteoarthritis and rheumatoid arthritis.

Table 3

Cognition.

Predictors		Outcomes							
	Variables	Animal fluency				Delayed 90″ recall			
		*F*Δ	R^2 Δ	Beta	Sig.	F Δ	R^2 Δ	Beta	Sig.
Final model		19.498	0.162		<0.001	11.534	0.103		<0.001
Demographics		85.575	0.117		<0.001	47.562	0.069		<0.001
	Age			−0.252	<0.001			−0.162	<0.001
	Sex			0.002	0.927			0.149	<0.001
	Living			−0.021	0.340			−0.009	0.690
PD severity		17.693	0.024		<0.001	12.180	0.017		<0.001
Model	Resting tremor			−0.05	0.018			0.024	0.266
	H&Y stage			−0.115	<0.001			−0.081	0.001
	Disease duration			−0.008	0.733			−0.057	0.017
Medication		6.631	0.015		<0.001	4.653	0.011		<0.001
Model	Levodopa			−0.067	0.004			−0.047	0.048
	Dopamine agonist			0.021	0.332			0.017	0.462
	Anti depressant			−0.017	0.434			−0.008	0.731
	Stimulant			0.012	0.562			0.025	0.245
	Cognitive enhancer			−0.093	<0.001			−0.092	<0.001
Comorbidity		1.869	0.007		0.061	1.503	0.006		0.151
Model	Heart/circulation			−0.002	0.918			−0.050	0.030
	Respiratory			−0.017	0.430			0.025	0.260
	Diabetes			−0.041	0.061			−0.018	0.417
	Neurological			−0.035	0.098			0.000	0.992
	Cancer			−0.035	0.100			0.001	0.979
	Arthritis			−0.032	0.150			0.036	0.120
	BMI squared			−0.009	0.677			−0.018	0.414
	BMI			0.006	0.802			−0.031	0.176

Results from separate hierarchical regression analyses examining the relationship between comorbidities and cognitive tasks (animal fluency and delayed memory recall). Variables pertaining to demographics, PD severity and medication status were statistically controlled for in preceding blocks of predictors.