Published in final edited form as:

Parkinsonism Relat Disord. 2014 November ; 20(11): 1135–1139. doi:10.1016/j.parkreldis.2014.08.001.

Relationships among cognitive impairment, sleep, and fatigue in Parkinson's disease using the MDS-UPDRS

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Abstract

Background—Non-motor complications of Parkinson's disease (PD), specifically cognitive impairment, sleep disturbances, and fatigue, are recognized as important contributors to poor patient outcomes and quality of life. How sleep problems and fatigue interrelate and impact cognitive function, however, has not systematically been investigated across the stages of PD. The aim of our study was to investigate the relationships among cognitive impairment, night-time sleep problems, daytime sleepiness, and fatigue across all severities of PD.

Methods—We examined these non-motor problems using the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in a study of 1319 PD patients drawn from three large cohort studies: the Parkinson's Progressive Markers Initiative, the Rush University PD Cognitive-Behavioral-Imaging study, and the Movement Disorder Society-Unified Parkinson's Disease Rating Scale Clinimetric testing program study, which spanned the gamut of disease, from early to advanced PD. Generalized linear mixed models with logit linking functions and covariates including study cohort, age, PD duration, and presence/absence of PD medications were used to examine relationships between these three non-motor symptoms and cognitive impairment.

Results—Of these three frequent, and often inter-twined, non-motor complications, greater daytime sleepiness and fatigue were associated with worse cognitive impairment across the full spectrum of PD ($F[16,1158]=2.40$ and $F[16,1158]=3.45$ respectively, $p's < 0.0005$), but an association with night-time sleep was not detected ($p=0.83$).

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Conclusions—Given this association of daytime sleepiness and fatigue with cognitive impairment, clinical monitoring for these problems should be considered across all points in the PD spectrum, from early to more advanced disease.

Keywords

Cognitive impairment; Daytime sleepiness; Fatigue; Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS); Parkinson's disease

1. Introduction

Cognitive impairment and dementia in Parkinson's disease (PD) have attracted attention as common and disabling non-motor features.[1] Their detrimental impact is not only evidenced by worsened quality of life[2], but also by increased nursing home admissions and health-related costs.[3] Sleep abnormalities also occur frequently in PD and contribute to worsened quality of life and patient outcomes. Excessive daytime sleepiness has been associated with increased cognitive impairment in PD, and furthermore, may be distinct from night-time sleep dysfunction in its relationship with cognition in PD.[4, 5] Fatigue has become increasingly recognized as an important feature in PD, affecting over 50% of patients and strongly correlating with high distress levels and worse health-related quality of life.[6, 7] Although fatigue per se is a distinct symptom, it is often associated with the feeling of tiredness or exhaustion, either physically or mentally. In addition, fatigue has been linked conceptually to sleepiness in the general population and in other neurological disorders such as multiple sclerosis or PD, and thus, may potentially impact cognitive functioning.[8, 9] Little is known, however, regarding the interactions of night-time sleep problems, daytime sleepiness, and fatigue with cognitive impairment in PD.

Prior studies examining the relationships between cognitive impairment and other non-motor symptoms in PD have been limited by several elements. These include: inclusion of PD populations with narrow ranges of motor and cognitive impairments; emphasis either on only early, de novo PD or only moderate-advanced PD subjects; use of varied rating scales for specific non-motor features; a focus on single aspects of sleep disturbances (i.e., rapid eye movement behavior disorder [RBD], daytime problems, or nighttime dysfunction); emphasis on exploring the presence or frequency/severity of a broad array of non-motor symptoms with screening instruments; confounding effects of PD medications on cognition and sleep; and, in some studies, small samples sizes.[4, 7, 10-12] It is important to recognize that inter-relationships among non-motor symptoms and cognitive impairment may differ with disease severity. These connections need to be disentangled to fully understand their contributions to PD cognitive impairment and whether treatment strategies for these non-motor symptoms, individually or in combination, influence PD outcomes.

Because of the above limitations of prior studies, the complex relationship between night-time and daytime sleep problems, and the conceptual link between fatigue and sleepiness, the aim of our study was to specifically examine the relationships among cognitive impairment, night-time sleep, daytime sleepiness, and fatigue in PD across the full motor and cognitive spectrum of the disease, using a single measurement tool. We hypothesized

that problems with sleep and fatigue would be associated with worse cognitive function across the PD spectrum, but that while these non-motor symptoms are frequently intertwined, distinct relationships with PD cognitive impairment would emerge. Therefore, we investigated these *a priori*-selected non-motor symptoms in three PD cohorts that represented a broad range of PD patients who were administered the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which has been designated by the National Institutes of Health (NIH) Common Data Elements as a recommended scale for the overall assessment of PD motor and non-motor features.[13, 14]

2. Methods

2.1. Participants

PD subjects included in our study were drawn from three well-characterized, large PD studies that spanned the disease severity spectrum from de novo patients to more advanced patients. These cohorts included: i) the Parkinson's Progression Markers Initiative (PPMI), ii) the Rush University PD Cognitive-behavioral-imaging study (Rush PD-CBI), and iii) the MDS-UPDRS Clinimetric testing program study (CTPS).[4, 13, 15] Briefly, PPMI is a 5-year, multi-center, international, observational, clinical study that aims to identify potential biomarkers of PD progression using clinical, imaging, and biospecimen data from newly diagnosed PD patients and healthy controls. The Rush PD-CBI study is a NIH-funded prospective study (K23NS060949) of clinical and imaging markers associated with cognitive and behavioral complications of PD. The CTPS was designed to validate MDS-UPDRS by comparing the original UPDRS to the new MDS-UPDRS in a large cohort of PD patients representing all Hoehn and Yahr (H&Y) stages.

2.2. Inclusion/Exclusion criteria

Specific criteria and recruitment details for each of the cohorts have been previously described.[4, 13, 15] All subjects met clinical diagnostic criteria for PD and were examined by movement disorder specialists or experienced study coordinators, in accordance with the individual study protocols.[16] The present study included only English-speaking subjects; non-English speaking subjects from PPMI were excluded, and the Rush PD-CBI and CTPS studies enrolled only English-speaking subjects. Cross-sectional data were examined and included: i) baseline data from the fully enrolled PPMI PD cohort as of April 2013 (www.ppmi-info.org), ii) baseline Rush PD-CBI data accessed with the consent of the study's Principal Investigator (JGG), and iii) a single assessment from the CTPS, also accessed with the consent of the Principal Investigator (CGG). The present study included newly diagnosed and untreated PD subjects (PPMI and CTPS studies) and those with disease duration > 3 years and treated with dopaminergic medications (Rush PD-CBI and CTPS studies). Exclusionary criteria in general included atypical and secondary parkinsonian symptoms. Of the 402 PD subjects with baseline PPMI data, 60 were excluded due to being non-English speaking or having incomplete data, leaving 342 subjects available for our analyses. All subjects from the Rush PD-CBI study (n=101) and the CTPS study (n=876) were included in our study. The combined datasets yielded data for a total of 1319 PD subjects.

2.3. Evaluations

Clinical data obtained from the three studies included demographic and disease-related features (e.g., age, sex, PD duration, and PD medication use [defined based on the CTPS study with presence=levodopa and/or other symptomatic treatment, absence=no PD medications]). The MDS-UPDRS was administered to subjects and/or caregivers as part of each study.[13] The MDS-UPDRS has four parts: Part I – Non-motor experiences of daily living; Part II – Motor experiences of daily living; Part III – Motor examination; Part IV – Motor Complications. Part I includes two parts: Part IA, an assessment by a trained investigator based on information reflecting the past week and reported by the subjects and/or caregivers, and Part IB, which similarly reflects the past week but completed by the subject with or without the aid of a caregiver.

For the present study, the MDS-UPDRS questions for Cognitive impairment (Part I, item 1.1), Sleep problems (Part I, item 1.7), Daytime sleepiness (Part I, item 1.8), Fatigue (Part I, item 1.13), total motor score (Part III), and H&Y stage (Part III) were the specific variables of interest (Table 1). The MDS-UPDRS items from Part I in general were scored as 0: normal, 1: slight, 2: mild, 3: moderate, 4: severe - with each item having tailored descriptive text to accompany each numeric designation for that item. The progression of disability or impairment, which ranged from 0-4, was based on a consistent infrastructure.[13]

All subjects gave written consent to participate in their respective studies, each of which received approval from ethical standards committees before study initiation. In accordance with PPMI policies, data used in the preparation of this article were obtained from the PPMI database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org.

2.4. Statistical Analysis

Statistical analyses were performed using SPSS (version 21.0) for Macintosh (Chicago, IL). Demographic variables and scores on MDS-UPDRS items were compared across the cohorts using one-way analysis of variance and Scheffe post-hoc comparisons, or non-parametric tests, as appropriate. The relationships among the MDS-UPDRS items for sleep problems, daytime sleepiness, fatigue and cognitive impairment were investigated in a generalized linear mixed model with a logit linking function, which is identical to an ordered categorical logistic function but allows a random effect in the modeling. The MDS-UPDRS item for “Cognitive impairment” was the outcome; the cohort data source (PPMI, Rush PD-CBI, CTPS) was entered as a random effect with unstructured covariance structure; and age, PD duration, sex, presence/absence of PD medication use, and MDS-UPDRS items for “Sleep problems,” “Daytime sleepiness,” and “Fatigue” as predictor variables. Generalized logit functions were used to compare different combinations of predictor variables, using a reduced model analysis and Bayesian Information Criteria (BIC). BIC were used for model selection because adding parameters can falsely increase the likelihood function; this model has utility in large datasets and avoids over-fitting the model by introducing a stringent penalty term for the number of parameters included.[17] These analyses were carried out in two steps: i) a full model of all variables of interest, and ii) entry of those variables corresponding to the minimum BIC value, thereby building a model based on the relative

importance of the factors and associated with the highest posterior probability. The significance of the overall model was tested with the F statistic. The contribution of individual variables to the presence or absence of cognitive impairment (defined by MDS-UPDRS = 1 versus MDS-UPDRS = 0, respectively) was assessed by odds ratio (OR) and 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Clinical features of the PD cohorts

The clinical characteristics of the 1319 subjects from the three studies are presented in Table 2. There were significant differences in the mean age of the subjects across the cohorts, with PPMI subjects being younger than the Rush PD-CBI and CTPS subjects, but with no significant difference between the Rush PD-CBI and CTPS cohorts. There were significantly more males in the Rush PD-CBI cohort compared to the PPMI and CTPS cohorts, though all groups had a male predominance. Disease duration differed significantly across the cohorts, as expected due to study design, with the shortest durations in the PPMI cohort (i.e., de novo subjects). There were significant differences across the studies regarding motor severity as measured by the MDS-UPDRS Part III and by the H&Y stage, with the lowest severity scores in the PPMI subjects and higher scores in the Rush PD-CBI and CTPS subjects. PD medication use also differed significantly across subject groups, consistent with the individual study protocols (i.e., untreated PPMI subjects at baseline). Comparisons of the scores on MDS-UPDRS items for cognitive impairment, sleep problems, daytime sleepiness, and fatigue revealed significant cohort differences with the lowest scores, or mildest symptoms, in the PPMI subjects and higher scores in the Rush PD-CBI and CTPS subjects.

3.2. Relationships of the MDS-UPDRS items: Cognitive impairment, Sleep problems, Daytime sleepiness, and Fatigue

When the MDS-UPDRS scores for items on sleep problems, daytime sleepiness, and fatigue were entered into the model as predictors of cognitive impairment, covarying for age, sex, PD duration, and presence/absence of PD medication use, the overall model was significant ($F[64,1158]=4.54$, $p<0.0005$). Nighttime sleep problems, however, did not contribute significantly to the model ($F[16,1158]=0.74$, $p=0.83$), whereas daytime sleepiness and fatigue did ($F[16,1158]=2.40$, $p=0.001$ and $F[16,1158]=3.45$, $p<0.0005$, respectively). Using BIC testing, the model improved with the removal of the MDS-UPDRS item for nighttime sleep, "Sleep problems," (reduced from 27,478 to 27,020 with lower scores being more favorable). With the MDS-UPDRS item "Sleep problems" omitted, daytime sleepiness, fatigue, age, sex, PD duration, and presence/absence of PD medication use were entered into a new model with cognitive impairment as the predictor outcome. This overall model remained significant ($F[48,1175]=5.88$, $p<0.0005$), with contributions from both daytime sleepiness and fatigue ($F[16,1175]=2.68$, $p<0.0005$ and $F[16,1175]=3.74$, $p<0.0005$, respectively).

3.3. Relationship of the MDS-UPDRS items for daytime sleepiness and fatigue and severity of cognitive impairment

Daytime sleepiness and fatigue severity demonstrated significant associations with the severity of cognitive impairment. The best differentiators between any cognitive impairment versus no cognitive impairment (e.g., MDS-UPDRS score for “Cognitive impairment” of 1 versus 0) were a score of 3 on the “Daytime sleepiness” item (“sometimes falling asleep while eating or talking with other people”) (OR 6.07; 95th CI 2.80,13.19) and a score of 4 on the “Fatigue” item (“fatigue stops me from doing things or being with people,”) (OR 4.52; 95th CI 2.07,9.87), followed by a score of 3 (“fatigue causes a lot of problems doing things or being with people”) (OR 3.50; 95th CI 1.98,6.15). Milder degrees of fatigue also were associated with the presence of cognitive impairment with a score of 2 on the “Fatigue” item (“fatigue causes me some troubles doing things or being with people,”) (OR 2.08; 95th CI 1.42,3.05) and a score of 1 (“fatigue occurs. However, it does not cause me troubles doing things or being with people”) (OR 1.53; 95th CI 1.12,2.09) (Table 3).

4. Discussion

Our study reveals several findings regarding the relationships among cognition, sleep, and fatigue in PD as measured by the MDS-UPDRS. Of these three frequent, and often inter-related, non-motor complications, greater daytime sleepiness and fatigue were strongly associated with worse cognitive function across the full spectrum of PD, whereas night-time sleep was not. These findings indicate a dissociation between day and night sleep problems in their relationships to cognitive impairment and highlight the association of fatigue with impaired cognition. To our knowledge, this is the first study to examine specific contributions of sleep dysfunction and fatigue to PD cognitive impairment using a single validated scale (the MDS-UPDRS) across a wide range of disease severity and duration. The MDS-UPDRS provides a uniform measure applicable across the breadth of PD consistent with the NIH Common Data Elements program goals. Documenting these non-motor symptom relationships with the MDS-UPDRS items in our study further supports the instrument’s utility in other PD-related clinical and research settings.

The association of increased daytime sleepiness and worse cognition detected by the MDS-UPDRS in our study corroborates findings in previous studies of PD and other dementias that used subjective sleep scales (e.g., Epworth Sleepiness Scale [ESS], Pittsburgh Sleep Quality Index [PSQI], Scales for Outcomes in PD [SCOPA]-Sleep)[4, 18, 19] or objective sleep measures (e.g., actigraphy, polysomnography, multiple sleep latency tests).[20, 21] Our results support differing relationships in PD between daytime sleepiness and PD cognitive impairment versus night-time sleep disturbances and cognitive impairment, thereby extending our prior report[4] to a larger, broader PD population. This dichotomy indicates that greater daytime sleepiness in PD cannot be solely a consequence of poor nighttime sleep. Excessive daytime sleepiness may be intrinsic to PD-related neuronal loss and Lewy body accumulation in brainstem, basal forebrain, hypothalamus, and thalamus. [22, 23] These regions are associated with sleep-wake regulation and with cognitive processes such as attention, executive function, and memory. Shared neurobiological substrates may underlie the association between daytime sleepiness and cognitive deficits.

We detected an association between fatigue and cognitive impairment in PD, a finding that, to our knowledge, has not been previously documented across the PD spectrum. The association of fatigue and presence of cognitive impairment was strongest when fatigue was rated as “moderate” to “severe” on the MDS-UPDRS, but this relationship was also significant with even milder reports of fatigue. Recent studies emphasize fatigue as a frequent and troublesome, but incompletely understood, non-motor symptom in PD.[6, 7, 24, 25] Although fatigue frequently co-exists with other non-motor features such as sleep and mood disorders, studies suggest that it is not explained by them alone. Moreover, there is conflicting evidence regarding whether fatigue correlates with PD duration, dopaminergic medications, motor severity, sleepiness, or depression.[6, 7, 25, 26] Prior studies have not focused specifically on the relationship between fatigue and cognitive impairment as a primary study aim. In the PRIAMO study, the frequency of fatigue, as measured by its presence/absence in a semi-structured interview, was significantly higher in PD patients with Mini-Mental State Examination Scores (MMSE) ≥ 23.8 . [7] However, a study of de novo, untreated PD patients did not find a correlation between MMSE scores and the Fatigue Severity Scale, though cognitive deficits were overall mild (mean [SD] MMSE 27.8 [2.3]). [27] Dysfunction in the basal ganglia and frontal lobes may provide a plausible neurobiological explanation that links fatigue and cognitive impairment. Neuroimaging studies reveal associations between fatigue in PD and decreased cerebral blood flow in the frontal lobe, [28] decreased serotonin transporter binding in the striatum, thalamus, cingulate gyrus, and amygdala, and decreased dopamine uptake in the caudate and insula. [29] Fatigue in PD may signify dysfunction in striatal and extra-striatal regions, including the limbic system, and involvement of non-dopaminergic systems. These regions overlap with those implicated in attentional, executive, memory, and visuospatial deficits in PD and may help explain the relationship of fatigue and cognitive dysfunction.

While some studies have examined the association of an individual sleep-related symptom (e.g., daytime sleepiness, RBD, night-time sleep quality) or fatigue with cognitive impairment in PD, our study focused on the interrelationships of a constellation of *a priori*, selected non-motor features, namely night-time sleep problems, daytime sleepiness, fatigue, and cognitive impairment, as they are frequently linked together clinically and may have shared substrates. Furthermore, within the MDS-UPDRS, the individual items correlate significantly with rating scales for night-time sleep problems, daytime sleepiness, and fatigue (i.e., 1.7 “Sleep problems” with the PSQI and SCOPA-night; 1.8 “Daytime sleepiness” with the ESS and SCOPA-day, and 1.13 “Fatigue” with the Fatigue Severity Scale). [30]

Strengths of our study include a very large cohort of well-characterized PD subjects, reflecting a broad spectrum of disease duration, motor and cognitive abilities, and early and advanced stages. In addition, our statistical design controlled for potential effects of PD medications on cognition and sleep variables of interest and differences in medication use among the cohorts. We used a single, well-validated scale, to assess relationships among PD features, with standardized metrics that examine the level of severity and impact on function across all topics of interest. [13] This feature of the MDS-UPDRS is rooted in its structural consistency and conceptual anchors of progressing disability from 0-4 scoring. This further

suggests that the severity/impact of scoring a 1 on one item is theoretically comparable to a 1 on another item.

We acknowledge limitations of our study. We cannot generalize our findings beyond PD patients in English-speaking North American and European countries; however, with the growing number of published translations of the MDS-UPDRS and validation studies in non-English speaking cohorts, future studies may examine these non-motor symptoms in PD cohorts of other nationalities. The MDS-UPDRS questions may not fully represent a patient's long-term functioning as they assess only symptoms experienced over the past week. Other scales such as the ESS, however, also focus on this timeframe. The MDS-UPDRS items are designed as single domain-based questions. While correlations between the MDS-UPDRS items are moderate to high for the majority of non-motor symptoms, the single item measure of cognitive impairment was modestly correlated with the Addenbrook's Cognitive Examination, the SCOPA-cog, and the Frontal Assessment Battery in one study.[30] Future studies using the MDS-UPDRS to examine cognition may incorporate additional neuropsychological tests to further characterize the severity and deficits of cognitive impairment. We recognize that each non-motor symptom also can have many aspects, as is the case of night-time sleep (e.g., insomnia, sleep fragmentation, RBD, recurrent PD symptoms). Nevertheless, the MDS-UPDRS provides an efficient, easy-to-use measure to capture the essence of the non-motor symptoms. Although we included the presence/absence of PD medication use in our analyses, details specifically regarding dopamine agonists or levodopa equivalent doses were not provided in the CTPS cohort and thereby limited our examination of medication type or dose influences on sleepiness or cognition. Further, as the aim of our study was to examine a specific constellation of non-motor symptoms in a large, combined dataset with a specific metric (MDS-UPDRS), we acknowledge that other non-motor symptoms may influence cognition and these items can be examined in future studies. Finally, we did not include formal, objective sleep and wakefulness tests. We cannot determine whether cognitive impairment causes the sleep problems or the sleep problems caused the cognitive impairment, though a clinical trial where sleep problems are treated and the subsequent effect on cognitive impairment is assessed could address this question.

Given that among the non-motor symptoms examined in our PD cohort, daytime sleepiness and fatigue were associated with cognitive impairment, further investigation of these two behaviors may unveil important discoveries related to cognitive deficits in PD. Objective, physiological, or neuroimaging markers of daytime sleepiness and fatigue may permit advances in our understanding of their neurobiological substrates and their relationships to PD cognitive impairment. Furthermore, clinical monitoring for these problems should be considered across all points in the PD spectrum.

Acknowledgments

PPMI is a public-private partnership funded by The Michael J. Fox Foundation for Parkinson's Research and funding partners including Abbott, Avid Pharmaceuticals, Biogen Idec, Bristol-Myers Squibb, Covance, Elan, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Merck, Meso Scale Discovery, Pfizer, Roche, and UCB (www.ppmi-info.org/fundingpartners). The Rush cohort was funded by the NIH K23NS060949 and Parkinson's Disease Foundation. The MDS-UPDRS Clinimetric study was funded by unrestricted grants to the MDS from Boehringer-Ingelheim (USA), GlaxoSmithKline, and Pfizer, Inc. The Rush University Medical Center Section of

Parkinson Disease and Movement Disorders receives funding and support from the Parkinson's Disease Foundation, New York, NY.

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Revised Highlights

- We studied how sleep problems and fatigue relate to cognitive function in Parkinson's disease.
- Increased daytime sleepiness and fatigue as reported on the MDS-UPDRS were associated with greater cognitive impairment.
- There was no relationship, however, between night-time sleep problems and cognitive impairment.
- Clinicians should monitor daytime sleepiness and fatigue throughout all stages of Parkinson's disease.

Table 1
MDS-UPDRS items and descriptions

Item	Question
1.1 "Cognitive impairment"	Have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding their way around the house or in town over the past week? Scored as 0: normal, no cognitive impairment; 1: slight, impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions; 2: mild, clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions; 3: moderate, cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions; 4: severe, cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.
1.7 "Sleep Problems"	Have you had trouble going to sleep at night or staying asleep through the night over the past week? Scored as 0: normal, no problems; 1: slight, sleep problems are present but usually do not cause trouble getting a full night of sleep; 2: mild, sleep problems usually cause some difficulties getting a full night of sleep; 3: moderate, sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night; 4: severe, I usually do not sleep for most of the night.
1.8 "Daytime Sleepiness"	Have you had trouble staying awake during the daytime over the past week? Scored as 0: normal, no daytime sleepiness; 1: slight, daytime sleepiness occurs but I can resist and I stay awake; 2: mild, sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV; 3: moderate, I sometimes fall asleep when I should not. For example, while eating or talking with other people; 4: severe, I often fall asleep when I should not. For example, while eating or talking with other people.
1.13 "Fatigue"	Have you usually felt fatigued over the past week, differentiating this from being sleep or sad? Scored as 0: Normal, no fatigue; 1: slight, fatigue occurs. However it does not cause me troubles doing things or being with people; 2: mild, fatigue causes me some troubles doing things or being with people; 3: moderate, fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything; 4: severe, fatigue stops me from doing things or being with people.

Table 2
Clinical characteristics of the PD cohorts

	Total	PPMI	Rush PD-CBI	CTPS	p value
Subjects, n	1319	342	101	876	
Age, years	68.9±11.1	61.5±9.6 [†]	73.4±6.3	71.2±10.8	<0.0005
Males, %	63.1	58.3	75.2 [#]	63.6	<0.0005
PD duration, years	6.7±6.7	0.54±0.56 [†]	10.5±4.6 ⁺	8.3±6.7	<0.0005
MDS-UPDRS total motor score	31.9±16.8	21.3±8.8 [†]	37.3±12.5	35.5±17.8	<0.0005
Hoehn & Yahr stage, median (range)	2 (1-5)	2 (1-3) [†]	2 (2-5)	2 (1-5)	<0.0005
Dopaminergic medications used, %	72.3	0 [†]	97.0	92.2	<0.0005
MDS-UPDRS item scores					
1.1 Cognitive impairment, median (range)	0 (0-4)	0 (0-2) [†]	1 (0-4) [*]	1 (0-4)	<0.0005
1.7 Sleep problems, median (range)	1 (0-4)	1 (0-4) [§]	1 (0-4)	1 (0-4)	<0.0005
1.8 Daytime sleepiness, median (range)	1 (0-4)	1 (0-3) [†]	2 (0-4) ^{**}	2 (0-4)	<0.0005
1.13 Fatigue, median (range)	1 (0-4)	1 (0-4) [†]	1 (0-4)	1 (0-4)	<0.0005

Results are expressed as mean ± SD, unless otherwise noted.

[†] p<0.0005, PPMI vs. Rush PD-CBI and PPMI vs. CTPS

[#] p=0.003, Rush PD-CBI vs. PPMI, p=0.02, Rush PD-CBI vs. CTPS

⁺ p=0.002, Rush PD-CBI vs. CTPS

^{*} p<0.0005, Rush PD-CBI vs. CTPS

^{**} p=0.001, Rush PD-CBI vs. CTPS

[§] p<0.0005, PPMI vs. CTPS

Table 3
Relationship of individual items and severity to the presence or absence of cognitive impairment

	Odds Ratio	95% CI
Age	1.01	1.0-1.03
PD duration	1.07	1.05-1.10
PD medication use	1.86	1.26-2.74
1.8 Daytime sleepiness score=4	4.22	0.89-19.94
1.8 Daytime sleepiness score=3	6.08	2.80-13.19
1.8 Daytime sleepiness score=2	1.32	0.95-1.83
1.8 Daytime sleepiness score=1	1.10	0.77-1.54
1.13 Fatigue score=4	4.52	2.07-9.87
1.13 Fatigue score=3	3.49	1.98-6.15
1.13 Fatigue score=2	2.08	1.42-3.05
1.13 Fatigue score=1	1.53	1.12-2.09

Reference range, MDS-UPDRS "Cognitive impairment" item 0 (normal)