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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 ($p = 0.83$).

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.

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

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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 interrelationships 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 inter-twined, 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 the 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

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.