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Neuroimaging and clinical predictors of fatigue in Parkinson disease

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Abstract

Background—Fatigue is disabling in Parkinson disease. It is often associated with other non-motor symptoms, but little is known about its underlying pathophysiology.

Objective—To investigate neuroimaging (using dopaminergic and cholinergic PET) and clinical factors associated with fatigue severity in PD.

Methods—133 PD subjects (96M/37F) completed the Fatigue Severity Scale, Movement Disorders Society-Sponsored Revision of the Unified PD Rating Scale (MDS-UPDRS), Hoehn-Yahr staging, validated scales for depression, anxiety, apathy, sleep, and cognition, and underwent [^{11}C]methyl-4-piperidinyl propionate (PMP) acetylcholinesterase (AChE) and [^{11}C]dihydrotetrabenazine (DTBZ) monoaminergic PET imaging. We explored contributions to PD fatigue using separate regression models based either on neuroimaging parameters or clinicometric scales.

Results—In a neuroimaging regression model, neither striatal DTBZ uptake nor AChE PMP uptake were predictors of fatigue in PD. In a post-hoc neuroimaging regression model, stratifying

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the total cohort into mild vs. moderate-to-severe PD, striatal DTBZ uptake was a significant predictor of fatigue in mild but not moderate-to-severe PD. In a clinicometric regression model, higher Beck Depression Inventory-somatic subscore, higher levodopa dose equivalents and younger age were all significant predictors of fatigue in PD, but the MDS-UPDRS non-motor experiences of daily living score was the best predictor overall.

Conclusions—Cholinergic uptake was not a predictor of fatigue in PD, but nigrostriatal dopaminergic denervation predicted fatigue in mild disease. Total non-motor symptom burden, somatic affective symptoms, levodopa dose equivalents, and younger age were independent clinical predictors of fatigue.

Keywords

Parkinson disease; Fatigue; PET imaging

1. Introduction

Fatigue is a problem for up to 58% of Parkinson disease (PD) patients[1, 2], and over half consider fatigue to be one of their 3 most disabling symptoms[2]. It is even present in early PD[3, 4], and while most studies have found no significant association between fatigue and PD motor severity[1], some have reported significant correlations between increasing fatigue and increasing disease severity[5, 6]. Fatigue has a negative impact on activities of daily living and quality of life in PD[3, 6], and is commonly associated with other non-motor symptoms such as sleepiness, apathy, and depression[1], yet little is known about its underlying pathophysiologic mechanisms.

Levodopa treatment may partially improve fatigue[4, 7], suggesting involvement of the dopaminergic system, but previous imaging studies have suggested that the degree of nigrostriatal denervation is not different between fatigued and non-fatigued PD patients[4, 8]. Although dopaminergic denervation is a critical early step in PD pathophysiology, its presence does not fully explain the heterogeneity of PD clinical features, many of which develop or progress years after the onset of the disease. A sequential model of disease progression has been proposed where a predominant hypodopaminergic state marks the early clinical stage of PD with subsequent degeneration of extra-nigral non-dopaminergic systems as disease advances[9]. This emerging concept has great clinical implications as it is the non-dopaminergic symptoms that cause the greatest disability in the later stages of the disease[9, 10]. Early dopaminergic losses have a robust association with appendicular motor impairment in PD, but also contribute to non-motor symptoms, including mild cognitive impairment, especially in the domain of executive function[11, 12]. In later stages of PD, patients may develop levodopa unresponsive symptoms such as falls and dementia, which have been associated with cortical and subcortical cholinergic denervation and deposition of β-amyloid fibrillary plaques[11, 13–15].

We hypothesized that both nigrostriatal dopaminergic and cholinergic denervation might contribute to fatigue in PD, because of involvement of the dopaminergic system early on in the disease and cholinergic dysfunction as the disease progresses. Because fatigue in PD is

also associated with other non-motor symptoms, we also explored which clinical measures best predict fatigue.

2. Methods

2.1 Subjects

This cross-sectional study included 133 PD subjects (96 men/37 women) who were recruited from Movement Disorders Clinics at the University of Michigan and the Veteran Affairs Ann Arbor Health System (ClinicalTrials.gov Identifier: NCT01565473, NCT01106976). All subjects met UK PD Society Brain Bank Research Center clinical diagnostic criteria for PD[16] and completed [^{11}C]dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) as well as [^{11}C] methyl-4-piperidinyl propionate (PMP) acetylcholinesterase (AChE) PET imaging. Subjects with MMSE scores < 24 were not eligible, and subjects with diabetes mellitus were excluded from analysis because a history of diabetes represented a contraindication for an overlapping imaging study in the same cohort. Of the 133 subjects, 60 (45%) took carbidopa/levodopa only, 14 (11%) took a dopamine agonist, 48 (36%) took a combination of carbidopa/levodopa and a dopamine agonist, and 11 (8%) subjects did not take any PD medications. Twenty (15%) were on antidepressant drugs. No subjects were taking cholinesterase inhibitors or pure anticholinergic drugs.

2.2 Clinical Assessments

Fatigue was measured by the Fatigue Severity Scale (FSS)[17], a 9 item, self-administered, fatigue scale. The items are brief and rated on a Likert scale from 1 “completely disagree” to 7 “completely agree”, and the average score of all 9 items represents the total FSS score. The FSS has shown high reliability, validity and internal consistency in both PD and non-PD populations[18].

Subjects also underwent clinical evaluation with Movement Disorders Society-revised Unified PD Rating Scale (MDS-UPDRS)[19], modified Hoehn-Yahr (H-Y), Epworth Sleepiness Scale (ESS)[20], Insomnia Severity Index (ISI)[21], Beck Depression Inventory (BDI)[22], State-Trait Anxiety Inventory (STAI)[23], the Marin Apathy Evaluation Scale (AES)[24], and a comprehensive neuropsychological test battery, which has been previously reported[25]. We computed somatic and affective BDI subscores to better distinguish somatic and affective elements that may underlie fatigue in PD. Composite z-scores were calculated for the different cognitive domains (memory, executive, attention and visuospatial functions) tested with the neuropsychological battery, based on normative data. A global composite z-score was calculated as the average of the four domain z-scores. The MDS-UPDRS, as well as imaging with the (+)-[^{11}C]DTBZ VMAT2 ligand, were conducted after withholding dopaminergic medications overnight followed by [^{11}C]PMP AChE ligand PET and brain magnetic resonance imaging (MRI).

2.3 Standard protocol approvals, registrations, and patient consents

The study was approved by the Institutional Review Boards of the University of Michigan. Written consent was obtained from all subjects.

2.4 Imaging Techniques

Magnetic resonance imaging was performed using a 3 Tesla Philips Achieva system (Philips, Best, The Netherlands) with an 8-channel head coil and the "ISOVOX" exam card protocol primarily designed to yield isotropic spatial resolution. A standard T1-weighted series of a 3D inversion recovery-prepared turbo-field-echo was performed in the sagittal plane using TR/TE/TI=9.8/4.6/1041ms; turbo factor=200; single average; field of view=240×200×160mm; acquired matrix = 240×200. 160 slices were reconstructed to 1 mm isotropic resolution. This sequence maximizes contrast among gray matter, white matter, and cerebrospinal fluid and provides high-resolution delineation of cortical and subcortical structures.

[^{11}C]PMP and [^{11}C]DTBZ PET Imaging were performed in 3D imaging mode using an ECAT HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquires 63 transaxial slices (slice thickness: 2.4 mm; intrinsic in-plane resolution: 4.1 mm full-width at half maximum over a 15.2 cm axial field-of-view. A NeuroShield (Scanwell Systems, Montreal, Canada) head-holder/shielding unit was attached to the patient bed to reduce the contribution of detected photon events originating from the body outside the scanner field-of-view. Prior to the DTBZ and PMP injections, a 5-minute transmission scan was acquired using rotating ^{68}Ge rods for attenuation correction of emission data using the standard vendor-supplied segmentation and re-projection routines.

No-carrier-added (+)-[^{11}C]DTBZ (250 to 1000 Ci/mmol at the time of injection) was prepared as reported previously[26]. Dynamic PET scanning was performed for 60 minutes as previously reported[25]. [^{11}C]PMP was prepared in high radiochemical purity (>95%) by N-[^{11}C]methylation of piperidin-4-yl propionate using a previously described method[27]. Dynamic PET scanning was performed for 70 minutes as previously reported[25].

All image frames were spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session. Interactive Data Language image analysis software (Research systems, Inc., Boulder, CO) was used to manually trace volumes of interest on MRI images to include the thalamus, caudate nucleus, and putamen of each hemisphere. Total neocortical VOI were defined using semi-automated threshold delineation of the cortical gray matter signal on the magnetic resonance imaging scan.

AChE [^{11}C]PMP hydrolysis rates (k_3) in the thalamic and neocortical regions of interest were estimated using the striatal volume of interest (defined by manual tracing on the MRI scan of the putamen and caudate nucleus) as the tissue reference for the integral of the precursor delivery[28]. [^{11}C]DTBZ distribution volume ratio (DVR) was estimated using the Logan plot graphical analysis method with the striatal time activity curves as the input function and the total neocortex as reference tissue, a reference region overall low in VMAT2 binding sites, with the assumption that the non-displaceable distribution is uniform across the brain at equilibrium[29]

2.5 Data Analysis

Stepwise multivariable linear regression analysis with FSS score as the outcome parameter was used to identify predictors of fatigue in the entire cohort. The first model evaluated neuroimaging (PET) regressors of fatigue (striatal DTBZ, cortical and thalamic PMP) while accounting for age and disease duration. Clinical measures that predicted fatigue were evaluated in a second model including MDS-UPDRS non-motor experiences of daily living, motor experiences of daily living, and motor subscores, global cognitive composite z-score, ESS, STAI, BDI affective and somatic subscores, AES, ISI, levodopa equivalent dose (LED) as defined by Tomlinson et al.[30], age and disease duration. Because of a possible 'floor' effect from severe striatal denervation seen more uniformly in late-stage disease, a post-hoc stepwise regression of the neuroimaging predictors of fatigue was performed, stratified based on H-Y Stage 2 or less vs. 2.5 or greater. All analyses were performed using SAS version 9.2, SAS Institute, Cary, NC.

3. Results

Table 1 lists the mean demographics and clinical characteristics for the total cohort (n=133), and for subjects in the H-Y≤2 (n=42) vs. H-Y>2 (n=91) subgroups.

For the entire cohort in the neuroimaging stepwise regression model, only younger age (p=0.004) and greater disease duration (p=0.04) significantly predicted FSS scores (see table 2). Dopaminergic and cholinergic PET measures were not significant predictors of fatigue in this model. Because the absence of a relationship between dopaminergic PET measures might be due to a "floor effect", we performed a post-hoc regression analysis, stratifying the group into milder (H-Y≤2) and more severe disease (H-Y>2). In subjects with H-Y≤2 (n=42), younger age (p=0.001) and decreased striatal DTBZ (p=0.01) significantly predicted FSS scores. In subjects with H-Y>2 (n=91), younger age (p=0.05) was a marginally significant predictor. Disease duration and pedunculopontine nucleus (PPN)-thalamic or cortical cholinergic PET measures were not significant predictors of fatigue in either the mild or moderate-to-severe groups.

In the clinical stepwise regression model (n=133), a worse MDS-UPDRS non-motor experiences of daily living score (p<0.0001) was the most significant predictor of FSS (see Table 3). Higher BDI somatic score (p<0.0001), higher LED (p=0.002), and younger age (p=0.02) were also significant predictors of FSS. The MDS-UPDRS motor experiences of daily living and motor subscores, global cognitive composite z-score, ESS, STAI, BDI affective subscore, AES, ISI, and disease duration were not significant predictors in this model.

There were differences in FSS scores among subjects taking certain classes of medications in our cohort. Subjects on antidepressants (n=20; mean FSS = 4.22 ± 1.55) had higher FSS scores (t = 3.50, p =0.0006) than those who were not (n =113, mean FSS = 3.00 ± 1.42). Subjects taking dopamine agonists (n=62; 3.47 ± 1.51) showed higher fatigue scores than those not taking agonists (n=71; 2.93 ± 1.46; t= 2.12, p =0.036). To explore whether this dopamine agonist association persisted after controlling for possible confounders including younger age and LED, we conducted a post-hoc linear regression with FSS score as the

outcome variable and age, LED, and dopamine agonist use as covariates. The overall model ($F= 7.80$, $p <0.0001$) showed statistical significance with age ($t = -2.50$, $p = 0.0135$) and LED ($t = 3.31$, $p =0.001$), but not dopamine agonist use ($t = 0.63$, $p =0.32$).

4. Discussion

In this study, we explored the association between fatigue severity in PD with A) dopaminergic and cholinergic PET imaging parameters and B) clinical measures of motor and non-motor impairment in PD. In a pooled analysis, neither nigrostriatal dopaminergic nor PPN-thalamic or cortical cholinergic denervation were significant predictors of fatigue. In patients with lower H-Y staging, however, striatal DTBZ uptake associated significantly with fatigue. These results are in contrast to those of Schifitto et al., who found no difference in striatal dopamine transporter uptake (using [^{123}I]-β-CIT) between PD patients with and without fatigue as part of the ELLDOPA study[4]. However, subjects taking levodopa in the ELLDOPA study had better fatigue scores than those on placebo, suggesting some involvement of the dopamine system. There were also differences in baseline cohort characteristics between our study and the ELLDOPA study that may account for our findings. All of the patients in the ELLDOPA study were dopamine medication naive and less than 2 years from their initial diagnosis of PD, while most of our 43 subjects with H-Y≤2 were on dopaminergic treatment with a longer mean disease duration 4.5 ± 3.5 years. Pavese et al. compared ^{18}F-dopa uptake in the caudate and putamen in 10 fatigued PD subjects and 10 non-fatigued PD subjects and did not find significant differences[8]. While the mean disease duration of their cohort was similar to ours, theirs was a smaller study, and nigrostriatal innervation status was assessed using a different tracer. We postulate that the lack of association between fatigue and nigrostriatal loss in the more severe disease subgroup seen in our cohort may reflect a denervation 'floor' effect.

Because of the theory that PD transitions over time from a predominantly hypodopaminergic state to a multisystem degeneration involving extra-nigral mechanisms[9], we hypothesized that the cholinergic system would be more strongly associated with fatigue as the disease became more severe. In our cohort, however, fatigue was not associated with cholinergic dysfunction regardless of disease severity. Pavese et. al. found decreased serotonergic transporter uptake (using the PET ligand ^{11}C-DASB) in the caudate, putamen, ventral striatum and thalamus of fatigued PD subjects compared to non-fatigued subjects[8]. It may be that dopaminergic denervation contributes to PD fatigue initially, with serotonergic (and not cholinergic) denervation playing a larger role as disease progresses.

A novel finding in both regression models was that younger age predicted fatigue in PD. Previous studies of fatigue in PD have associated older age with fatigue or found no association[1, 3, 31]. It is possible that younger PD patients are more active and may feel the effects of their fatigue more noticeably. As they age, they may regulate their activities to the level of their fatigue, thus decreasing their perception of fatigue. An alternative explanation is that fatigue is a manifestation of a compensatory metabolic brain response to neurodegenerative changes that is more robust in younger subjects than older subjects. It is also possible that relative biological contributors to multifactorial fatigue shift with different stages of disease burden.

Our second aim was to investigate which clinical variables predicted fatigue severity in PD. The MDS-UPDRS non-motor experience of daily living scale was the best clinical predictor of fatigue in our cohort. The BDI-somatic but not the BDI-affective subscale was also a significant predictor of fatigue. Somatic and affective subscores of BDI were entered as separate variables in the clinical regression model to better characterize the specific depressive symptoms that relate to PD fatigue. The BDI-somatic subscale includes items such as loss of pleasure, agitation, loss of interest, indecisiveness, loss of energy, change in sleep patterns, irritability, change in appetite, concentration difficulties, tiredness, and loss of interest in sex. The MDS-UPDRS non-motor experience of daily living scale has items that overlap with the BDI-somatic subscale, but it also assesses other non-motor symptoms, including cognition, psychosis, pain, and autonomic dysfunction. Thus non-motor symptoms overall are related to fatigue in patients with PD. One of the main challenges of studying fatigue in PD is the frequent overlap of comorbid and confounding disorders, such as depression, apathy and sleep disorders. Clinical scales that assess these confounders were included in our model, but do not allow us to determine if fatigue was independent of depression in this cohort. Nevertheless, these symptoms are all typically associated with non-dopaminergic mechanisms and further support the theory of a multisystem degeneration as PD progresses.

In our clinical regression model, a higher LED was also a significant determinant of fatigue in mild and moderate-to-severe PD. This could be reverse causation, in that fatigued PD patients are prescribed higher doses of dopaminergic medications in an attempt to treat this disabling symptom. Alternatively, the association of fatigue with higher LED may reflect a medication side effect. These should be considerations in future studies of fatigue in PD. We found that subjects on antidepressants and dopamine agonists had higher FSS scores in our cohort. It is not clear if antidepressant use is specifically associated with fatigue in PD or just a marker for depression. Dopamine agonist use did not show a multivariable association with FSS score after controlling for relevant confounders including younger age and LED, thereby reducing the likelihood of a non-specific causal association with fatigue.

Limitations of this study include the predominantly male sample and its cross-sectional nature. Nevertheless, this is a relatively large, well-characterized PD cohort that has undergone PET imaging with both dopaminergic and cholinergic tracers using validated instruments for fatigue as well as other non-motor and motor problems. Though cholinergic denervation was not a significant predictor of fatigue, nigrostriatal dopaminergic denervation predicted fatigue in mild PD. Yonger age and non-motor symptoms in aggregate correlate with fatigue severity in PD. Future longitudinal studies will be needed to determine whether contributors to fatigue change with aging and advancing disease duration. Improving our understanding of the natural history of fatigue in PD is a critical step towards designing and implementing therapeutic strategies aimed specifically at reducing fatigue burden in PD.

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Highlights

- We investigated neuroimaging and clinical factors associated with PD fatigue.
- Cholinergic PET uptake was not a predictor of fatigue in PD.
- Nigrostriatal dopaminergic denervation predicted fatigue in mild PD.
- Non-motor symptom burden, levodopa dose equivalents and younger age also predicted fatigue in PD

Table 1

Clinical and PET Measures for PD subjects

	Total group (n=133)	H-Y≤2 (n=42)	H-Y>2 (n=91)
Age (years)	65.4 ± 7.5	62.6 ± 7.2	66.7 ± 7.3
Gender	96M/37F	33M/9F	63M/28F
Disease duration	6.1 ± 4.3	4.5 ± 3.5	6.8 ± 4.4
LED (mg)	673.6 ± 508.3	593.2 ± 389.5	710.8 ± 552.6
FSS	3.2 ± 1.5	2.9 ± 1.6	3.3 ± 1.4
MDS-UPDRS			
nM-EDL	6.5 ± 4.5	5.3 ± 4.1	7.0 ± 4.7
M-EDL	8.1 ± 5.8	4.9 ± 3.7	9.5 ± 6.0
Motor	31.8 ± 13.7	23.8 ± 10.1	35.4 ± 13.6
ESS	8.7 ± 4.5	7.2 ± 4.2	9.4 ± 4.5
ISI	7.2 ± 5.9	7.0 ± 5.4	7.4 ± 6.2
BDI			
Total score	7.9 ± 6.1	7.7 ± 6.7	8.0 ± 5.8
Affective subscale	1.7 ± 2.4	1.8 ± 2.9	1.7 ± 2.1
Somatic subscale	6.2 ± 4.3	5.9 ± 4.4	6.4 ± 4.2
Apathy Evaluation Scale	24.4 ± 6.0	23.1 ± 5.8	25.0 ± 6.0
STAI	37.1 ± 6.4	37.0 ± 7.2	37.2 ± 6.0
Global cognitive composite z-score[a]	−0.36 ± 0.91	−0.008 ± 0.72	−0.53 ± 0.94
PET measures			
Striatal DTBZ	1.92 ± 0.28	2.01 ± 0.27	1.88 ± 0.28
Thalamus PMP	0.054 ± 0.005	0.053 ± 0.005	0.055 ± 0.005
Neocortex PMP	0.024 ± 0.003	0.024 ± 0.002	0.023 ± 0.003

[a]Using our neuropsychological test battery, composite z-scores were calculated for four cognitive domains (memory, executive, attention and visuospatial functions) based on normative data. The global cognitive composite z-score was calculated as the average of the four domain z-scores

H-Y = Modified Hoehn and Yahr
LED = Levodopa equivalent dose
FSS = Fatigue Severity Scale
MDS-UPDRS nM-EDL = Non-motor experiences of daily living
MDS-UPDRS M-EDL = Motor experiences of daily living
ESS = Epworth Sleepiness Scale
ISI = Insomnia Severity Index
BDI = Beck Depression Inventory
STAI = State-Trait Anxiety Inventory
DTBZ = [^{11}C] dihydrotetrabenazine
PMP = [^{11}C] methyl-4-piperidinyl propionate

Table 2

Neuroimaging stepwise regression model listing all variables in the model that met the 0.05 significance level.

	Partial R^2	Model R^2	F value	Statistical Significance
Total group (n=133)				
Age	0.06	0.06	8.75	0.004
Disease duration	0.06	0.12	8.78	0.004
H-Y≤2 (n=42)				
Age	0.24	0.24	12.47	p=0.001
Striatal DTBZ	0.12	0.36	7.31	p=0.01
H-Y>2 (n=91)				
Age	0.04	0.04	3.81	p=0.05

H-Y = Modified Hoehn and Yahr

DTBZ = [^{11}C] dihydrotetrabenazine

Table 3

Clinical stepwise regression model of the total cohort (n=133) listing all variables in the model that met the 0.05 significance level.

	Partial R^2	Model R^2	F value	Statistical Significance
MDS-UPDRS nM-EDL	0.38	0.38	80.02	p<0.0001
BDI somatic subscale	0.10	0.47	24.32	p<0.0001
LED	0.04	0.51	9.95	p=0.002
Age	0.02	0.53	5.91	p=0.02

H-Y = Modified Hoehn and Yahr
BDI = Beck Depression Inventory
ESS = Epworth Sleepiness Scale
LED = Levodopa equivalent dose
MDS-UPDRS nM-EDL = Non-motor experiences of daily living