Predictors of Mental and Physical Fatigue in Parkinson's Disease

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Master Thesis - Klinische Neuropsychologie

S3387267
August 27th 2022
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Abstract

Parkinson's Disease (PD) is a common neurodegenerative disease. Fatigue is one of the most debilitating non-motor symptoms of PD and is associated with other symptoms related to PD. Fatigue consists of different aspects, including mental fatigue and physical fatigue. Because fatigue has been assessed differentially in prior studies, there are conflicting findings concerning the association between fatigue and other PD-related symptoms. Therefore, the current study used the *Dutch Multifactor Fatigue Scale,* a fatigue scale which assesses different aspects of fatigue. Current research questions are: 'Which factors of fatigue are increased in *de novo* PD patients compared to the healthy control group?' and: 'What are predictive factors of mental and physical fatigue in the early phase of PD?' First, fatigue levels of 155 *de novo,* drug-naïve PD patients were compared with 106 healthy controls. Additionally, the predictive value of apathy, anxiety, depression, cognitive function, and motor function on mental and physical fatigue is examined through a multiple linear regression analysis. It was found that PD patients experience more mental and physical fatigue compared to the HC group. Additionally, it was found that anxiety is predictive for mental fatigue ($R^2 = 0.205$, $p < .001$), whereas anxiety, apathy, and depression are predictive for physical fatigue ($R^2 = 0.327$, $p < .001$). By dividing fatigue into different subscales, this study provided additional information on the role of fatigue in *de novo* PD patients. Future research could focus on treatment of anxiety, depression, and apathy to reduce fatigue among PD patients.

Key words: fatigue, Parkinson's Disease, cognitive function, motor function, apathy, depression, anxiety

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease, with slow progression and accumulating disability for affected individuals (Bloem, Okun, & Klein, 2021). In PD, dopaminergic neurons degenerate in the substantia nigra, resulting in functional changes throughout the basal ganglia. The basal ganglia network regulates voluntary movement, which explains the typical motor symptoms of PD (Blandini, Nappi, Tassorelli, & Martignoni, 2000). The motor components of the disease, such as tremor, bradykinesia, and rigidity, have long been the focus of research. However, during the last two decades, focus has shifted to the various nonmotor symptoms that are typical in PD, including fatigue (Kluger et al., 2016).

Fatigue is one of the most common and debilitating non-motor symptoms of PD with an estimated prevalence of 50% (Ongre et al., 2021; Siciliano et al., 2018). Fatigue can be described as "a lack of energy or a need for increased effort needed to attempt daily activities that is distinct from sleepiness, lack of motivation, and depression" (Kluger et al., 2016, pp. 626). The symptom might appear in the early (premotor) stages of PD and tends to be persistent and worsens over time. However, a few studies concerning fatigue in treatment-naïve, *de novo* patients are available and provide mixed results about the prevalence and the predictors of fatigue (Schifitto et al., 2008; M. Siciliano et al., 2017). Furthermore, fatigue has a severe negative impact on patients' quality of life (Mantri et al., 2022; Ou et al., 2021; Siciliano et al., 2017, 2018) and is associated with disease duration and severity. Taken together, fatigue is a symptom accompanied with a high burden, making it critical to investigate its predictors. The underlying pathophysiology of fatigue is still unknown, as well as effective therapies, implying the need to investigate which factors are predictive for fatigue (Kluger et al., 2016; Kluger, Krupp, & Enoka, 2013; Ou et al., 2021; Spirgi, Meyer, Calabrese, Gschwandtner, & Fuhr, 2019). However, Kluger et al. (2013) state that fatigue is

difficult to evaluate as a symptom since there is no unanimous terminology for fatigue. It is unclear if fatigue should be defined as a central, physical, cognitive, peripheral, or mixed/complex symptom because the symptom is poorly understood (Chong, Albor, Wakade, & Morgan, 2018).

Fatigue can be described as a multifactorial symptom with both motor and non-motor components (Kluger et al., 2013). Therefore, it can be beneficial to divide fatigue into a mental and physical aspect by using the Dutch Multifactor Fatigue Scale (DMFS; Visser-Keizer, Hogenkamp, Westerhof-Evers, Egberink, & Spikman, 2015). Mental fatigue is described as "a sustained feeling of exhaustion, lack of energy, and reduced initiative, resulting from performing mentally demanding activities, and accompanied by other symptoms such as stress sensitivity and irritability" (Buunk et al., 2018, p. 1315). Physical fatigue is characterized as a "physically felt exhaustion, with coexisting symptoms such as bodily pain" (Buunk et al., 2018, p. 1315).

According to the literature, fatigue has been linked to various symptoms which are associated with PD, such as depression, anxiety, apathy, and sleep difficulties (Friedman et al., 2016; Ongre et al., 2021; Ou et al., 2021; Siciliano et al., 2018). Female gender, comorbidity of other somatic conditions at the time of diagnosis, as well as dependency in ADL activities were also associated with fatigue (Ongre et al., 2021). However, some factors associated with fatigue remain controversial in the literature, for example the association between fatigue and motor symptoms. Kataoka & Sugie (2021) and Solla et al. (2014) found that motor symptoms and fatigue are positively associated. In contrast, other authors found that motor function did not predict fatigue levels (Siciliano et al., 2017; Ongre, Larsen, Tysnes, & Herlofson, 2017). Concerning the association between fatigue and cognitive function, Siciliano et al. (2020) found no relationship, whereas Kluger et al. (2017) did found

an association between various aspects of cognition and fatigue, including processing speed and executive functions. Finally, the impact of demographic factors like age and gender on fatigue remain controversial (Mantri et al., 2022; Siciliano et al., 2018). Because of the inconsistent results in existing literature, this study will focus on anxiety, apathy, depression, and cognitive function as symptoms to characterize mental fatigue, since these symptoms are mental constructs and were considered to be associated with (mental) fatigue (Carney, Moss, Lachowski, & Atwood, 2014; Lou, Kearns, Oken, Sexton, & Nutt, 2001). Motor function is included as a predictor of physical fatigue because on the basis of existing literature, physical fatigue is associated with, for example, a lack of energy or less muscle power (Lou et al., 2001).

The inconsistent results on the relationship between PD symptoms and fatigue could be due to two reasons. First, a variety of scales are available to assess fatigue. For example, the Fatigue Severity Scale (FSS) and the Parkinson Fatigue Scale (PFS) are widely used to assess fatigue in PD. However, these two questionnaires are expected to examine slightly distinct components of fatigue and are linked to motor and non-motor symptoms in various ways (Siciliano et al., 2017). For example, the PFS appears to mainly focus on the physical aspects of fatigue in PD (Friedman et al., 2010). Second, the contradictory findings in the literature are likely the consequence of evaluating fatigue levels as a single entity rather than dividing fatigue into different components. Since there is no unanimous terminology for fatigue and it has never been separated into a mental and physical aspect in order to investigate its predictors, the role of fatigue in *de novo* PD patients can be better understood by dividing fatigue into a mental and a physical component.

Given the negative effects on quality of life, understanding the risk factors for fatigue in PD is critical in this patient population and could lead to effective treatments (Mantri et al.,

2022). Additionally, it is crucial to investigate the role of fatigue in *de novo* PD patients to obtain more knowledge about the symptom in the early phase of PD. Therefore, our aim is to investigate if fatigue is more prevalent among *de novo* patients with PD compared to healthy controls and which factors predict mental and physical fatigue in the early phase of PD. The research question is threefold: (1) 'Are mental and physical fatigue increased in *de novo* PD patients compared to the HC group?' and: (2) 'What are predictive factors of mental fatigue in the early phase of PD?', and: (3): 'What are predictive factors of physical fatigue in the early phase of PD?'.

Method

Participants

The current study is part of the Dutch Parkinson Cohort (Boertien et al., 2020). In total, 155 patients with PD and 106 age-matched healthy controls (HC) were included in the study. Inclusion criteria of the PD group were: (1) *de novo,* treatment-naive PD patients (2) Dutch citizens. Exclusion criteria of the PD group were: (1) insufficient knowledge of the Dutch language and (2) dopaminergic medication use. Inclusion criteria of the HC group were: (1) no PD diagnosis and (2) Dutch citizens. HC were excluded when the knowledge of the Dutch language was insufficient. PD patients were recruited via the Parkinson Platform Noord Nederland. HC were recruited by the purposive sampling method. The age of the participants in the Parkinson group variates between 36 and 85 years (M = 65.35; SD = 9.39, including 111 (71.6%) males with an average education level (M = 5.03; SD = 1.28), based on the Verhage scale (Verhage, 1964;). The age of the HC variates between 41 and 84 years (M = 64.6; SD = 8.84), including 57 (53.8%) males with an average education level, based on the Verhage scale (M = 5.45; SD = 1.01).

Materials

Motor examination. The *Movement Disorders Society Unified Parkinson's Disease Rating Scale part* III (MDS-UPDRSIII; Goetz, Fahn, & Martinez-Martin, 2008) is used as a measure of disease severity and motor functioning. Higher scores indicate more severe impairments. The MDS-UPDRSIII is a part of the MDS UPDRS and consists of 33 items, with a minimum score of 0 and a maximum score of 199 points**.** The internal consistency is considered as high. The *Hoehn and Yahr scale* (Hoehn & Yahr, 1967) is used to describe PD progression different stages of motoric disability related to PD ranging from 1 (minimal/no functional disability) to 5 (confinement to bed or wheelchair unless aided).

Questionnaires. The *Dutch Multifactor Fatigue Scale* (DMFS; Visser-Keizer et al., 2015) is used to assess fatigue levels. This self-report scale measures four aspects of fatigue levels: Mental fatigue (Cronbach's alpha = 0.86), Signs and direct consequences of fatigue (Cronbach's alpha = 0.83), Physical fatigue (Cronbach's alpha = 0.77), Impact of fatigue (Cronbach's alpha = 0.91), and Coping with fatigue (Cronbach's alpha = 0.69). The self-report scale consists of 38 items, with a 5-point Likert scale ranging from 0 (no, totally disagree) to 5 (yes, totally agree). Higher scores indicate more subjective feelings of fatigue. Current study focuses on the scales 'Mental fatigue' and 'Physical fatigue'. The subscale 'Mental fatigue' measures fatigue experienced after performing mentally demanding activities. An example item is: 'I can follow conversations without getting tired'. The minimum and maximum scores on this subscale are 7 and 35, respectively. The subscale 'Physical fatigue' measures physical fitness and consequences of physical fatigue, with a minimum score of 6 and a maximum score of 30 (Visser-Keizer et al., 2015). An example item is: 'After a good night sleep, I wake up rested'. The internal consistency of the subscales is high, except for the subscale Coping with fatigue.

The *Hospital Anxiety and Depression Scale* (HADS; Zigmond AS, 1983) assesses the levels of anxiety (7 items, Cronbach's alpha = 0.83) and depression (7 items, Cronbach's alpha = 0.82). The internal consistency of both subscales are considered as high (Bjelland, Dahl, Haug, & Neckelmann, 2002)**.** The self-report scale consists of 14 items in total, with a 4-point scale ranging from 0 to 3. Both scales have a minimum score of 0 and a maximum score of 21. A subscale score of 8 or above suggests the presence of anxiety or depressive symptoms. Higher scores indicate a greater likelihood of the presence of anxiety and/or depression.

The *Apathy Evaluation Scale* (AES; Marin, Biedrzycki, & Firinciogullari, 1991, Cronbach's alpha = 0.87) was conducted to measure apathy in patients with neurological

disorders. The self-report scale contains 18 items on a 4-point Likert-scale ranging from 1 (not at all) to 4 (very), with a minimum score of 18 and a maximum score of 72. Lower scores indicate higher levels of apathy. The internal consistency is considered as good.

Cognition. The *Montreal Cognitive Assessment* (MoCA; Nasreddine et al., 2005) is a screening tool to assess global cognitive functioning. The test is a 30-points test (Cronbach's alpha = 0.64). The internal consistency is acceptable (Kalbe et al., 2020). Scores on the MoCA range from zero to 30 and a score below 26 indicates mild cognitive impairment.

Procedure

The patients with PD visited the UMCG for a neuropsychological assessment and a motor function assessment. The neuropsychological assessment examines different components of cognitive function. Moreover, the participants completed various self-report questionnaires which examine the constructs fatigue, anxiety, depression, and apathy. The healthy control group only underwent the same neuropsychological assessment and completed the same self-report questionnaires. The study is approved by the Medical Ethics Review Board of the University Medical Centre of Groningen. All participants gave written informed consent.

Statistical analysis

Data is analyzed by using IBM SPSS Statistics (Version 28, IBM Corp., 2021). All statistical tests were two-tailed, and P-values < 0.05 were considered statistically significant. A Bonferroni-Holm correction for multiple comparisons was applied with alpha set at 0.05 (Holm, 1979). Effect sizes were classified according to Cramer's V and Cohen's D (0.2 = small, 0.5 = moderate, 0.8 = large; Cramer, 1946; Cohen, 1988). First, the demographic characteristics of the PD group and HC group were compared using the Mann Whitney U (non-parametric) test. Subsequently, levels of mental- and physical fatigue were compared between PD patients and HC. A chi-square goodness of fit test was performed to determine

whether the proportion of males was equal between the PD and the HC group. Normality was checked using the Shapiro Wilk test. Because of the number of variables, an explorative correlational analysis was performed to reduce the potential predictors. Spearman's rank correlations were performed to investigate the correlations between the DMFS-mental and DMFS-physical and the HADS-A, HADS-D, AES, MoCA, UPDRSIII, and Hoehn and Yahr. Subsequently, a multiple regression of the significant correlating variables was performed to examine predictors of mental and physical fatigue. For all variables in each model, the tolerance values were > 0.10 and the variance inflation factor values were < 10.0, which excluded multicollinearity. The assumptions for regression analysis, including homoscedasticity, absence of multicollinearity, and normal distribution of the residuals, were met for all models.

Hypotheses

The following research questions were examined (Appendix A): (1) 'Are mental and physical fatigue increased in *de novo* PD patients compared to the healthy control group?'. It is expected that DMFS-mental and DMFS-physical scores are higher in the PD group compared to the HC group (hypothesis 1). The second research question (2) is: 'What are predictive factors of mental fatigue in de novo PD patients?'. It is expected that higher scores on the HADS-A, HADS-D, and lower scores on the MoCA and AES are predictive for mental fatigue, but not physical fatigue (hypothesis 2). The third research question (3) is: 'What are predictive factors of physical fatigue scores in the early phase of PD?' It is expected that higher scores on the MDSUPDRSIII and Hoehn and Yahr predict physical fatigue, but not mental fatigue (hypothesis 3).

Results

Demographic and clinical characteristics

The describing statistics of each study variable are displayed in table 1, including the Mann Whitney U-test statistics, chi-square statistics and effect sizes. The PD group consists of significantly more males and has a significant lower educational level compared to the HC group. Furthermore, the PD group displayed significantly more fatigue compared to the HC group (table 2).

Table 1.

Demographic and Clinical Characteristics

	PD (N = 155)	HC (N = 106)					
Demographics	*M/Mdn (SD)*	*M/Mdn (SD)*	*U*	χ^2 (*df*)	*p*	Cohen's *d*	Cramer's *V*
Male, *n* (%)	111 (71.6%)	57 (53.8%)		8.735 (*1*)	.003**		.183
Age in years, mean (*SD*)	65.35 (9.39)	64.6 (8.84)	7578.50		.288	.132	
Educational level, mean (*SD*)	5 (1.28)	6 (1.01)	6554.50		.004**	.348	
Clinical Characteristics							
MoCA	25 (3.22)						
HADS anxiety	4 (3.03)						
HADS depression	3 (3.32)						
AES	60 (9.16)						
UPDRSIII	31.50 (11.57)						
Hoehn and Yahr	1.87 (.66)						

Note. N = sample size, * $p < 0.05$, ** $p < 0.01$. PD = Parkinson's Disease; HC = Healthy Controls; *M* = Mean; *Mdn* = Median; *MoCA* = Montreal Cognitive Assessment; *HADS* = Hospital Anxiety and Depression Scale; *AES* = Apathy Evaluation Scale; *UPDRSIII* = Unified Parkinson's Disease Rating Scale

Table 2.

DMFS scores

DMFS scale	PD (N = 155)	HC (N = 106)			
	Mdn (*SD*)	*Mdn* (*SD*)	*U*	*p*	Cohen's *d*
DMFS - Mental	18 (5.58)	16 (4.9)	6549.00	.005**	0.35
DMFS- Physical	16 (5.27)	12 (5.0)	5581.50	<.001**	0.56

Note. N = sample size, * $p < 0.05$, ** $p < 0.01$. PD = Parkinson's Disease; HC = Healthy Controls; *Mdn* = Median; *DMFS* = Dutch Multifactor Fatigue Scale

Mental and physical fatigue in PD and HC

Concerning the hypothesis that mental and physical fatigue are increased in the PD group compared to the HC group (hypothesis 1), the Mann-Whitney U test indicated that PD patients scored significantly higher on both mental (p = .005) and physical fatigue (p <.001) relative to the healthy control group (Table 2). Potential predictors were assessed using correlation to investigate their utility in being included in the multiple regression analysis. The Spearman's rank correlations of the study variables are displayed in Table 3.

Table 3.

Spearman Rank Correlation Coefficients

	MoCA	HADS-A	HADS-D	AES	UPDRSIII	Hoehn and Yahr
1. DMFS - Mental	-.03	.47**	.39**	- .24**	.09	.14
2. DMFS - Physical	-.09	.46**	.52**	-.42**	.16*	.22**

Note. N = 155, * $p < 0.05$, ** $p < 0.01$. *DMFS* = Dutch Multifactor Fatigue Scale; *MoCA* = Montreal Cognitive Assessment; *HADS* = Hospital Anxiety and Depression Scale; *AES* = Apathy Evaluation Scale; *UPDRSIII* = Unified Parkinson's Disease Rating Scale

HADS-A and HADS-D were positively significantly correlated to mental DMFS scores and physical DMFS scores, with weak to moderate strength. AES was negatively significantly correlated to mental and physical DMFS scores, with weak to moderate strength. Hoehn and Yahr and UPDRSIII scores were weakly positively related with physical DMFS scores. MoCA did not significantly correlate with either the mental or the physical DMFS scores.

Predictors of mental fatigue

To investigate the predictors of mental fatigue (hypothesis 2), a multiple linear regression analysis was carried out using the HADS-D, HADS-A, and AES as predictors. A significant regression equation was found ($F(6, 148) = 7.627$, $p < .001$) with an adjusted R^2 of 0.205, which indicates a small effect size (Table 4). Only HADS-A was a significant predictor for mental fatigue.

Table 4.

Regression Coefficients for Predicting Mental DMFS scores

	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	*t*	Sig.
(Constant)	10.535	5.433		1.939	.054
HADS - Anxiety	.753	.168	.409	4.488	<.001**
HADS - Depression	.109	.175	.065	.624	.534
AES - Apathy	-.021	.054	-.034	-.382	.703

Note. $N = 155$, * $p < 0.05$, ** $p < 0.01$. *HADS* = Hospital Anxiety and Depression Scale; *AES* = Apathy Evaluation Scale

Predictors of physical fatigue

Another multiple linear regression to evaluate the predictors of physical fatigue (hypothesis 3) was performed using the HADS-D, HADS-A, AES, UPDRSIII, and Hoehn and Yahr as predictors. A significant regression equation was found ($F(6, 148) = 13.476$, $p < .001$), with an adjusted R^2 of 0.327, which indicates a small effect size (Table 5). AES, HADS-A, and HADS-D were significant predictors for physical fatigue.

Table 5.

Regression Coefficients for Predicting Physical DMFS Scores

	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	*t*	Sig.
(Constant)	15.470	4.722		3.276	.001
HADS - Anxiety	.459	.146	.264	3.143	.002*
HADS - Depression	.351	.152	.221	2.308	.022*
AES - Apathy	-.117	.047	-.203	-2.495	.014*
UPDRSIII - Motor function	-.019	.041	-.042	-.465	.643
Hoehn and Yahr - Motor function	1.308	.684	.164	1.913	.058

Note. $N = 155$, * $p < 0.05$, ** $p < 0.01$. *HADS* = Hospital Anxiety and Depression Scale; *AES* = Apathy Evaluation Scale; *UPDRSIII* = Unified Parkinson's Disease Rating Scale

Discussion

To our knowledge, the present study is the first to focus on various predictors of fatigue in *de novo* patients by dividing fatigue into subjective feelings of mental and physical fatigue. The key findings of this study are that *de novo* PD patients experience more subjective feelings of fatigue than healthy controls. Second, it is demonstrated that anxiety predicted both mental and physical fatigue. Additionally, it is found that apathy and depression predict physical fatigue, but not mental fatigue.

Various studies reported the choice of the scale assessing fatigue as a limitation and implicated the urge of using scales which assesses several specific fatigue domains, including mental and physical fatigue (Siciliano et al., 2017). Furthermore, fatigue is not clearly operationalized, which makes it a difficult symptom to evaluate. For example, Kluger et al. (2013) proposed a taxonomy of fatigue including objective fatigue and performance fatigue in order to bring consistency to clinical research on fatigue. Because of these two arguments, the current study assesses fatigue using the DMFS, a scale that considers different aspects of fatigue.

Fatigue in HC and in PD

The first question in this research was: 'Is fatigue increased in *de novo* PD patients compared to the healthy control group?'. It was expected that *de novo* PD patients experience more mental and physical compared to the healthy control group. In line with expectations, it was found that *de novo* PD patients experience more physical and mental fatigue than healthy controls. This finding is consistent with previous research (Ongre et al., 2021, 2017), who also investigated *de novo* PD patients, but evaluated fatigue as a single entity. According to this, current findings provide additional information regarding different aspects of fatigue in de novo PD patients.

Mental fatigue

The second research question was: 'What are predictive factors of mental fatigue in *de novo* PD patients?'. It was expected that anxiety, apathy, and depression predicted mental, but not physical fatigue. It was found that anxiety predicts both mental and physical fatigue. The expectation of mental fatigue being predicted by cognitive function, anxiety, apathy, and depression does not entirely match the reported results because only anxiety was predictive for mental fatigue. However, the reported relationship of anxiety and mental fatigue is consistent with earlier research (Ou et al., 2021; M. Siciliano et al., 2017; Mattia Siciliano et al., 2018; Solla et al., 2014).

Contrary to expectations, it was found that cognitive function was not associated with mental fatigue, therefore cognitive function was not included in the regression model. This finding is not entirely in line with previous literature. Siciliano et al. (2017, 2018, 2020) found an association between cognitive function and fatigue, but no predictive influence of cognitive function on fatigue. However, other studies did find predictive associations between fatigue and cognitive function (Goldman, Stebbins, Leung, Tilley, & Goetz, 2014; Kluger et al., 2017; Pauletti et al., 2017; Spirgi et al., 2019). These inconsistencies may be explained by the way cognitive performance is measured, since the MoCA assesses global cognitive functioning. This might suggest that the MoCA is not sensitive enough. Therefore, the relationship with fatigue might be better understood by dividing cognitive function into separate domains. For example, Kluger et al. (2017) found that only visuospatial dysfunction predicts fatigue in de novo PD patients. Another explanation for the inconsistent results could be the association between fatigue and sleep disturbances, since sleep disturbances are highly associated with fatigue and may have a negative impact on cognition (Carney et al., 2014).

Physical fatigue

Present results show that depression only predicts physical fatigue. This finding is generally in line with previous research (Schifitto et al., 2008; Solla et al., 2014; Stocchi et al., 2014). It is known that the relationship between depression and physical activity is bidirectional (Roshanaei-Moghaddam, Katon, & Russo, 2009). Depression leads to decreased levels of exercise due to low motivation and energy, whereas decreased exercise could lead to more feelings of depression (Roshanaei-Moghaddam et al., 2009). This could be a possible explanation for the predictive value of depression on physical fatigue. It is interesting to note that the current study shows that depression predicts physical fatigue, but not mental fatigue, which is contrary to our expectations. This emphasizes the need to divide overall fatigue into different domains. It is important to note that some expectations were not met because the current study only included *de novo* PD patients. It is possible that fatigue is still not evident (in high levels) in *de novo* PD patients, making it difficult to identify clear predictors.

This study attempted to obtain a specific view of the relationship between apathy and fatigue, assuming that apathy predicted mental fatigue, but not physical fatigue. However, current findings show that apathy is only a significant predictor of physical fatigue. Our findings are generally in line with previous research (Siciliano et al., 2017, 2020). Fatigue has been attributed to a failure in integrating limbic input and motor function within the nonmotor areas of the basal ganglia and could be related to a loss of motivation, which is a feature of apathy. This might explain why patients with fatigue have a higher perceived effort completing a motor task (Siciliano et al., 2020). Taken together, the association discovered between apathy and physical fatigue may be caused by partially overlapping pathophysiological processes involving the limbic areas of the basal ganglia (Siciliano et al., 2020).

It was expected that anxiety predicted only mental fatigue, however, current findings show that anxiety predicts physical fatigue as well. This finding is consistent with previous research (Spirgi et al., 2019) and provides additional information about physical fatigue and anxiety in PD. The earlier described explanation for the association between depression and physical fatigue might also apply to the association between anxiety and physical fatigue since anxiety leads to decreased energy and motivation levels (Rabasa & Dickson, 2016).

Finally, contrary to our expectations, physical fatigue is not predicted by motor functioning. According to the meta-analysis of Siciliano et al. (2018), 50% of previous research reported associations between fatigue and motor function. Our results show that impaired motor function is associated with more physical fatigue. However, it cannot be stated that motor function is predictive of physical fatigue among de novo PD patients. These results are in line with previous research (Spirgi, Meyer, Calabrese, Gschwandtner, & Fuhr, 2019). The authors found that motor impairment predicted fatigue in terms of daily functioning rather than physical fatigue. Spirgi et al. (2019) assume that motor impairment significantly affects daily functioning, and therefore is a predictor of this aspect of fatigue. Consequently, Spirgi et al. (2019) did not find associations between physical fatigue and daily functioning, which may explain the lack of influence of motor function on physical fatigue (Spirgi et al., 2019). Furthermore, motor function is a broad concept and consists of multiple components which might explain why no predictive association was found because the current study examines overall motor function. For example, it is found that fatigue is associated with the specific UPDRSIII sub scores bradykinesia and postural instability (Shulman, Taback, Bean, & Weiner, 2001; Solla et al., 2014). This implies that there might exist different associations for each PD subtype: tremor dominant or postural instability gait disorder (Lee, Song, Kim, Ku, & Lee, 2019). Dividing motor function into different domains could thus be beneficial to get a clear view of the relationship with fatigue. According to

Siciliano et al. (2017), inconsistencies on the association between motor function and fatigue might be attributed to the different scales conducted for assessing fatigue. The *Parkinson's Fatigue Scale* (PFS) and *Fatigue Severity Scale* (FSS) are widely used to assess fatigue, however, Solla et al. (2014) show that the predictive value of non-motor symptoms on fatigue differs across these two scales**.**

It is worth mentioning that both regression models had a small explained variance. This means that anxiety explains a small part of the variance of mental fatigue, whereas anxiety, depression and apathy explain a small part of the variance of physical fatigue. This indicates that a part of the variance of both models can be explained through other variables. However, because of the novel components being explored among *de novo* PD patients, the small explained variance still contributes to the area of study, and the findings may still be useful.

The main strength of this study is the implementation of a new approach to assess fatigue by focusing on different aspects of fatigue. By using the DMFS, fatigue is more broadly investigated. Furthermore, the current study is the first focusing on these different aspects of fatigue among *de novo* PD patients, adding to the limited body of knowledge that exists regarding these patients (Schifitto et al., 2008). Another strength is the large sample size. However, this study has several limitations. First, the DMFS has originally been developed for patients with acquired brain injury, therefore it might be possible that the DMFS does not entirely correspond to the PD implications because there is growing evidence that the characteristics of fatigue after brain injury are different in other patient groups, such as patients with MS or cancer (Jones, Gray, & Newton, 2009; Kluger et al., 2013). For this reason, validating the DMFS for the PD patient group, involving multiple aspects of fatigue, would optimize the validity. Moreover, the underlying pathophysiology of the associations between fatigue, cognitive function, and motor function has to be studied more thoroughly,

for example, by dividing motor function and cognitive function into different domains. In addition, it has become quite evident that fatigue must be clearly operationalized. Because apathy, anxiety, and depression were found to be significant predictors of mental and physical fatigue in the current study, future research could focus on the treatment of these symptoms, which may result in less fatigue among de novo Parkinson patients.

Taken together, this study found that *de novo* PD patients experience more fatigue, including both physical and mental fatigue, than healthy controls. Despite the fact that not all of the study's predictions were fulfilled, current study established that anxiety, apathy, depression, cognitive function and motor function are all differentially associated with mental and physical fatigue. Furthermore, it was found that anxiety is predictive for mental fatigue, whereas anxiety, apathy and depression are predictive for physical fatigue. As a result, dividing fatigue into a mental and physical aspect provides a more accurate view of associated symptoms common in *de novo* PD patients. Current findings suggest that if fatigue is separated into different domains, different predictors emerge compared to investigating fatigue as a single entity, giving more implications for the future.

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Appendix A

Hypotheses

Hypothesis 1a. H_{01}: There is no significant difference in mean DMFS mental scores between patients with Parkinson's Disease and healthy controls.

H_{a1}: Mean DMFS mental scores are significantly higher in patients with Parkinson's Disease relative to healthy controls.

Hypothesis 1b. H_{01}: There is no significant difference in mean DMFS physical scores between patients with Parkinson's Disease and healthy controls.

H_{a1}: Mean DMFS physical scores are significantly higher in patients with Parkinson's Disease relative to healthy controls.

Hypothesis 2a. H_0: MoCA scores are not significantly predictive for mental DMFS scores.

H_{a1}: MoCA is a significant predictor of mental DMFS scores.

$H_{a2:}$ MoCA is a significant predictor of physical DMFS scores.

Hypothesis 2b. H_0: HADS-D scores are not significantly predictive for mental DMFS scores.

H_{a1}: HADS-D is a significant predictor of mental DMFS scores.

$H_{a2:}$ HADS-D is a significant predictor of physical DMFS scores.

Hypothesis 2c. H_0: HADS-A scores are not significantly predictive for mental DMFS scores.

H_{a1}: HADS-A is a significant predictor of mental DMFS scores.

$H_{a2:}$ HADS-A is a significant predictor of physical DMFS scores.

Hypothesis 2d. H_0: AES scores are not significantly predictive for mental DMFS scores.

H_{a1}: AES is a significant predictor of mental DMFS scores.

$H_{a2:}$ AES is a significant predictor of physical DMFS scores.

Hypothesis 3a. H_0: MDSUPDRSIII scores are not significantly predictive for physical DMFS scores.

H_a: MDSUPDRSIII is a significant predictor of physical DMFS scores.

$H_{a2:}$ MDSUPDRSIII is a significant predictor of mental DMFS scores.

Hypothesis 3b. H_0: Hoehn and Yahr scores are not significantly predictive for physical DMFS scores.

H_a: Hoehn and Yahr is a significant predictor of physical DMFS scores.

$H_{a2:}$ Hoehn and Yahr is a significant predictor of mental DMFS scores.