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Kognitive Mechanismen der Blasenschwäche bei Morbus Parkinson

Dissertation

Eberhard Karls Universität Tübingen
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Kognitive Mechanismen der Blasenschwäche bei Morbus Parkinson

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Abbreviations / Abkürzungen

| | |
|-----------|---|
| AD | Alzheimer's Disease |
| ADL | Activities of Daily Living |
| ARS | Anticholinergic Risk Scale |
| HI | Healthy Individuals |
| HRQoL | Health Related Quality of Life |
| H&Y | Hoehn und Yahr |
| iADL | Instrumental Activity of Daily Living |
| MMSE | Mini-Mental State Examination |
| MoCA | Montreal Cognitive Assessment |
| PANDA | Parkinson Neuropsychometric Dementia Assessment |
| PD | Parkinson's Disease |
| PDD | Parkinson Dementia |
| PD-MCI | Mild Cognitive Impairment in PD |
| PD-NC | Parkinson's Disease, normal Cognition |
| PD-NUU | PD without urinary problems |
| PD-UU | PD with urinary problems |
| SD | Standard deviation |
| UPDRS-III | Unified Parkinson Disease Rating scale |

Introduction

The improvements in healthcare over the last century have resulted in increased demographic aging over time. Today's generation's average lifespan is approximately four years longer than that of their parents', a trend that is predicted to continue. Since the world population has a greater proportion of older individuals, the number of neurodegenerative diseases has also increased. To date, idiopathic Parkinson's Disease (PD) is the second most common neurodegenerative disease in Europe, with a prevalence of 1.8% at the age of 55 (de Rijk et al., 1997). The risk of PD is associated with age and the prevalence after the age of 65 doubles nearly every five years (de Rijk et al., 1995). Therefore, by the year 2030 PD will probably increase by 25% relative to 2005 (Winge, Friberg, Werdelin, Nielsen, & Stimpel, 2005), dramatically affecting health care costs and patients quality of life (Martinez-Martin, Rodriguez-Blazquez, Kurtis, Chaudhuri, & Group, 2011).

Parkinson's Disease is characterized by its motor symptoms: resting tremor, rigidity and bradykinesia, which are caused by loss of neurons in the substantia nigra and Lewy bodies in the surviving neurons (Halliday, Hely, Reid, & Morris, 2008). In addition to the cardinal symptoms, non-motor impairments, such as autonomic failure, cognitive worsening or psychiatric symptoms often occur during the course of disease, representing a significant burden of PD patients by lowering their health-related quality of life (HRQoL) (Martinez-Martin, Rodriguez-Blazquez, et al., 2011) and contributing to the disease progression (Antonini et al., 2012; Khoo et al., 2013).

One of the most bothersome non-motor symptoms, as well for patients as for their caregivers, are urinary symptoms. Studies show that bladder problems have a considerable negative impact on quality of life, lead to early institutionalization and higher health costs (Araki, Kitahara, Oida, & Kuno, 2000; Rahman, Griffin, Quinn, & Jahanshahi, 2008). The prevalence of bladder dysfunction is significantly higher among PD patients, when compared to the healthy individuals (HI) of the same age (Badri, Purohit, Skenazy, Weiss, & Blaivas, 2014). Even though, urinary symptoms might appear throughout the course of the disease, even preceding motor symptoms, the prevalence rises among patients who experience dementia and in late stages of the disease (Miyasaki, 2016; Winge & Nielsen, 2012).

There seems to be no agreement on the origin of the urinary problems in PD (PD-UU). The conservative view of urinary problems does not assign them to the degenerative processes of dopaminergic neurons in the substantia nigra (Sakakibara et al., 2014), however neuroimaging studies have revealed further insight concerning the regulation of micturition in both, healthy subjects and PD patients, showing the involvement of several cortical and subcortical structures, such as basal ganglia, thalamus, anterior cingulate cortex and prefrontal cortex (Fowler, Griffiths, & de Groat, 2008; Fowler & Griffiths, 2010;

Griffiths & Fowler, 2013). Interestingly, in PD, degenerative processes can be found in most of these cortical structures (Fowler, 1999; Fowler et al., 2008). Generally, bladder problems have been divided into storage and voiding symptoms, dependent on both, sacral autonomic reflex and brain regions, such as the pontine center, hypothalamus, basal ganglia, frontal cortex (de Groat, Griffiths, & Yoshimura, 2015; Fowler et al., 2008; Griffiths & Fowler, 2013; Yoshimura & de Groat, 1997). The difficulties of distinguishing between age-related changes of micturition and neurodegenerative symptoms originate from the age group of PD patients. Men over 60 years of age might experience bladder symptoms as a result of prostate hyperplasia, whereas women might experience stress urinary incontinence, or impairments connected to birth. The prevalence rates vary between studies, as some of them were published before the diagnosis of multiple system atrophy (Gilman et al., 1999). Furthermore, the influence of dopaminergic treatment on the bladder is not well understood and rather random (Uchiyama, Sakakibara, Hattori, & Yamanishi, 2003). In addition to the above-mentioned factors, prevalence of UD among PD patients has its onset mostly after the appearance of motor disorder. Additionally, the variation of prevalence and appearance might reflect the methodology used to assess the symptoms and reflects differences in patient population (McDonald, Winge, & Burn, 2017). Although bladder symptoms can appear throughout the course of the disease, PD-UU seems to be a late manifestation and correlates with incidence of other non-motor symptoms with its peak at the state of dementia (Khoo et al., 2013; McDonald et al., 2017). To date, the association between urinary and cognitive function has only been investigated sparsely, even though the role of prefrontal cortex in PD-UU has been accepted (Kitta, Chancellor, de Groat, Shinohara, & Yoshimura, 2016; Kitta et al., 2006; Kitta et al., 2015). Furthermore, the association between motor symptoms, disease severity, other non-motor symptoms and cognitive impairment have been documented (Kadastik-Eerme, Rosenthal, Paju, Muldmaa, & Taba, 2015; McDonald et al., 2017; Moriarty, Robinson, Bunting-Perry, & Bradway, 2016; Picillo et al., 2017; Sakakibara et al., 2014; Skorvanek et al., 2015). The close connection of cognitive worsening and urinary dysfunction has magnified the need to characterize those PD patients, with cognitive-driven urinary dysfunction, which was the main focus of this doctoral thesis.

The second research motivation for this thesis was to improve early detection of cognitive deterioration in PD. A screening tool, often used in a clinical daily routine is Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). Developed for Alzheimer's Disease (AD) patients, the MoCA has also become the go-to screening tool for PD patients, as it focuses on the executive functions, the main drive of cognitive deterioration in PD (Dirnberger & Jahanshahi, 2013). However, studies show that the course of cognitive impairment is different for PD than AD patients (Fengler et al., 2016). Therefore, our primary objective was the validation of a scoring algorithm, which would improve the MoCA's psychometric accuracy in PD. An early diagnosis of cognitive impairment in PD is considered to be of high importance, since therapeutic measures are effective, especially in the early stages of neurodegeneration (Olanow & Obeso, 2012). Possible neuroprotective approaches can be indicated only when the subgroup of patients is correctly diagnosed. Therefore, it is important to identify reliable, objectively measurable tool that detects early symptoms of PD Mild cognitive impairment (PD-MCI) that narrow a risk group of PD Dementia (PDD).

The aim of this thesis was to evaluate the link between cognition and PD-UU. We broadly investigated cognitive functions and other non-motor aspects, which allowed us to identify a subgroup of PD patients whose urinary problems may have been caused and/or worsened by accompanied cognitive impairment. In the final step, we validated a new scoring algorithm for a sensitive, economic cognitive test battery, which has been only sparsely investigated in a non-demented PD population, in order to improve diagnostic tools used in a clinical every day routine.

Parkinson's Disease

PD is a progressive neurodegenerative movement disorder, which is characterized by its motor symptoms: resting tremor, rigidity and bradykinesia. PD is the second most common neurodegenerative disorder, with a prevalence of 1.8% in the general population for subjects of 55 years of age, or older (de Rijk et al., 2000). The prevalence of PD increases with an individual's age and is more common for people of European decent as opposed to Asian (Pringsheim, Jette, Frolkis, & Steeves, 2014).

The motor symptoms of PD are caused by the neurodegenerative processes of substantia nigra and presence of Lewy Bodies in brain cells. The degenerative processes are linked to synuclein pathology with Lewy neurites and interneuronal Lewy bodies in sympathetic ganglia and the peripheral autonomic nervous system (Berg et al., 2014). Furthermore, changes in the central parts of autonomic system as well as the dorsal vagal nucleus, the hypothalamus and the spinal cord contribute to the pathology (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004; Hughes, Daniel, Blankson, & Lees, 1993; van der Heeden, Marinus, Martinez-Martin, & van Hilten, 2016), causing additional non-motor problems.

Motor symptoms are, however, insufficient to subtype PD patients. PD varies in its clinical manifestations, and therefore has been divided into subtypes. The classification is based on the heterogeneous symptoms of the disease: clinical- with motor Parkinsonism, prodromal-motor, or non-motor symptoms present and preclinical- when neurodegeneration is present, but asymptomatic (Postuma et al., 2015). Clinicopathological criteria, considering motor progression lead to the tremor-dominant and akinetic-rigid subtyping, taking motor, non-motor and cognitive symptoms into account (Berg et al., 2014; Jankovic & Kapadia, 2001). Recently, a new subtype of more diffuse progression has been proposed (Fereshtehnejad et al., 2015). However, even with this approach, classifying PD into subtypes is not yet fully expended.

The non-motor aspects include autonomic symptoms, such as orthostatic hypotension (Damon-Perriere et al., 2012), bladder dysfunction (Picillo et al., 2017), or sexual dysfunction (Pfeiffer, 2010); sleep disturbances (Grover, Somaiya, Kumar, & Avasthi, 2015); gastrointestinal symptoms (Barone et al., 2009); cognitive impairment (Aarsland, 2016), or neuropsychiatric disorders, such as depression,

anxiety or apathy (Grover et al., 2015; Sveinbjornsdottir, 2016). Even though, some autonomic symptoms, such as orthostatic hypotension, or aspects of gastrointestinal tract have been associated with dopaminergic peripheral degenerative processes, most symptoms result from the non-dopaminergic pathological mechanisms (Chaudhuri, 2006).

The motor as well as non-motor symptoms develop progredient, and their initial onset can precede the clinical diagnosis of PD. Almost 90% of all patients report to have experienced some unspecific symptoms, years before PD was diagnosed (Goldman & Postuma, 2014). Retrospectively, over 98% of all patients, report up to six symptoms, such as loss of smell, up to 20 years prior the initial diagnosis of PD (Gaenslen, Swid, Liepelt-Scarfone, Godau, & Berg, 2011). During the course of the disease, almost all patients (98.6%) report about at least one non-motor symptom (Barone et al., 2009). The non-motor symptoms are mostly being diagnosed by using validated questionnaires and scales (Chaudhuri, Healy, Schapira, & National Institute for Clinical, 2006; Chaudhuri, Martinez-Martin, et al., 2006). It is important to emphasize, that non-motor symptoms contribute to the disease progression (Fereshtehnejad et al., 2015) and have the biggest impact on the worsening of patients' quality of life, with PD-UU being one of the most frequent ones (Berganzo et al., 2016; Kadastik-Eerme et al., 2015; Prakash, Nadkarni, Lye, Yong, & Tan, 2016).

Bladder Symptoms in Parkinson's Disease

The prevalence of the urinary symptoms in PD ranges by about 27-39%, based on validated questionnaires (Araki & Kuno, 2000; Campos-Sousa et al., 2003) and is significantly higher than in HI, similar in age and gender. Bladder symptoms are classified in irritative, obstructive or mixed symptoms. Frequency, urgency and nocturia are irritative symptoms caused by hyperactivity of the bladder, mostly due to detrusor hyperreflexia (McDonald et al., 2017). Incomplete emptying, intermittence, weak urinary stream and hesitation are called obstructive symptoms and can appear as a result of bladder hypoactivity.

The most common urinary symptoms in PD are nocturia, frequency, urgency, and urge incontinence (McDonald et al., 2017; Zhang & Zhang, 2015). The prevalence of urinary symptoms is 27% to 39% (Araki & Kuno, 2000; Campos-Sousa et al., 2003) when based on a validated questionnaire, while it is over 40% (Yamamoto et al., 2009) or even up to 60% (Hattori, Yasuda, Kita, & Hirayama, 1992), when using a non-validated questionnaire. Urodynamic evaluation confirmed abnormalities in 36% to 90% of patients, which consist of detrusor hyperreflexia with or without complete relaxation of the pelvic floor musculature and sphincter during micturition (Andersen, 1985; Berger, Blaivas, DeLaRocha, & Salinas, 1987).

Even though, PD-UU might appear throughout the course of the disease, the prevalence rises especially in the late stages of PD (Uchiyama et al., 2011; Winge & Nielsen, 2012), with a median onset around 12 years after PD diagnosis (Wenning et al., 1999). The influence of PD-UU on daily life is very complex. Bladder questionnaires that examine “bother”, or influence on activities of daily living (ADL), show that symptoms that worry PD patients the most are overactive bladder and urinary incontinence (McDonald et al., 2017; Winge & Fowler, 2006). The association between ADL and PD-UU, however, changes as the PD progresses and advances with the disease duration (Berganzo et al., 2016; Kadastik-Eerme et al., 2015; Moriarty et al., 2016; Ogawa et al., 2017). The connection between PD-UU and motor- as well as other non-motor functions, has been studied in the last years. However, it is difficult to distinguish to what extent PD-UU is influenced by neurodegenerative processes, motor symptoms, or deteriorating cognitive functions.

Functional neuroimaging studies in HI have increased the understanding of the micturition reflex, which seems to be under the control of several cortical and subcortical areas, including the basal ganglia, thalamus, insular cortex, anterior cingulate cortex and prefrontal cortex (Fowler et al., 2008; Sakakibara, Haruta, et al., 2012; Sakakibara, Tateno, et al., 2012). It is important to mention, that in PD, most of these cortical structures undergo the neurodegenerative process throughout the course of the disease (Braak et al., 2004; Hawkes, Del Tredici, & Braak, 2010). As basal ganglia seem to suppress the micturition reflex (Sakakibara, Uchiyama, Yamanishi, & Kishi, 2010), logically, the deep brain stimulation of the subthalamic nucleus has been associated with improved PD-UU symptoms (Winge et al., 2007), through the modulation of the afferent bladder information processing (Herzog et al., 2008). Moreover, frontal lesions following stroke, or trauma have been long recognized to be associated with urinary symptoms, as the prefrontal cortex has been shown to be activated during bladder filling (Kitta et al., 2006; Kitta et al., 2015).

Taking into account the age of most PD patients, bladder emptying and/or continence may be influenced by other prior conditions, such as prostatic enlargement in men, or stress incontinence in women (Winge et al., 2007). It may also appear as a consequence either of neurodegenerative processes, or the given treatment (Kitta et al., 2015; Uchiyama et al., 2003). Patients themselves often conceal urinary symptoms, since they link it to the negative side effect of aging, rather than to the neurological disorder (Zhang, Gu, An, Wang, & Chan, 2014; Zhang & Zhang, 2015). Taking these facts into consideration and the high prevalence of PD-UU, it is of a great importance to improve diagnosis and the treatment of PD-UU.

Parkinson's Disease and Cognition

Cognitive impairment is one of the most frequent non-motor symptoms in PD and has been qualified by patients as a syndrome of a high distress (Herman et al., 2015; Litvan et al., 2012). Moreover, the point-prevalence of PDD is between 24% to 31% among PD patients and usually develops after 10 years after

PD onset (Aarsland, 2016; Aarsland, Hutchinson, & Larsen, 2003). Dementia has severe consequences for PD patients, which includes higher mortality, nursing home placement, high distress and more rapid motor and functional decline (Kawada, Anang, & Postuma, 2015).

About 27% of PD patients experience PD-MCI, which is characterized by clinical, cognitive and functional decline (Litvan et al., 2012). PD-MCI has been associated with higher risk of developing PDD (Dubois et al., 2007), diagnosed in up to 80% of PD patients during the longstanding disease course.

In 2012, the Movement Disorder Society published criteria that enable a partially standardized diagnosis of the PD-MCI. However, no recommendation of the assessment cut-off has been released, with regard to cognitive assessments. In the literature, PD-MCI prevalence rates are based on a cut-off below 1, 1.5 or 2 SD from the mean of a reference group of mostly HI. It means, that cognitive disorder can be diagnosed when 84%, 93% or 98% of the normal population has a better test performance (Foltynie, Brayne, Robbins, & Barker, 2004; Janvin, Larsen, Aarsland, & Hugdahl, 2006). According to the MDS Task Force recommendations severe impairment of ADL is a cardinal symptom differentiating PD-MCI and PDD patients (Dubois et al., 2007; Litvan et al., 2012).

Not every PD patient will develop PDD. Regarding cognitive impairment, recent studies have revealed a substantial heterogeneity with different severity, ranging from minor cognitive deteriorations up to fully developed PDD. One of the earliest cognitive domains that suffer functional impairment is the executive function (Williams-Gray et al., 2009), which has been reported to be predictive for later PDD (Janvin et al., 2006). Frontal deficits are common in PD. Almost 70% of PD patients without dementia experience deteriorating deficits in cognitive functions (Janvin, Aarsland, Larsen, & Hugdahl, 2003). Executive dysfunction includes deficits in controlling mental processes, cognitive flexibility and problems solving, planning, or regulating complex behaviors and emotions (Emre, 2003). Executive dysfunction of PD patients is characterized by the loss of inhibitory control (Dirnberger & Jahanshahi, 2013), especially, within executive control tasks, that require inhibition of habitual or prepotent responses for selection of appropriate responses.

Executive functions are the main drive of cognitive deterioration in PD (Aarsland, 2016; Dirnberger & Jahanshahi, 2013), and an early diagnosis of PD-MCI is crucial, for its association to progression into PDD. The cognitive screening tools, often used in a clinical routine, are short and can be easily applied, contrary to more advanced neuropsychological assessments. For study purposes the Mini-Mental State Examination is often a go-to screening tool, even though its sensitivity has been proven to be lower than that of the MoCA, especially for detecting early mild cognitive impairments (Nazem et al., 2009). Research supports the assumption that choosing MoCA as a global screening tool is preferable to MMSE (Dalrymple-Alford et al., 2010; Hoops et al., 2009). As the MoCA has been designed for AD patients, a new scoring algorithm, which should improve the diagnostic accuracy of PD-MCI was developed (Fengler et al., 2016). The results showed, that through the transformed scoring algorithm, the sensitivity of MoCA increases, without losing the specificity or jeopardizing sensitivity for type I and II

errors. As PDD patients were included into the study, the results might be biased by these cases and the cut-off may be more applicable to the later stages of PD-MCI. Excluding PDD patients would allow one to evaluate if the novel scoring algorithm would also discriminate between early PD-MCI and PD-NC patients.

Cognitive Aspects of Urinary Dysfunction in Parkinson's Disease

The prevalence of urinary symptoms is common in PD and other neurodegenerative diseases and has been associated with dementia, as incidence of urinary problems is highest among demented patients (Chiang et al., 2015; Kessler, 2008; Ransmayr et al., 2008).

The prefrontal cortex, which also has projections to anterior cingulate cortex (ACC) or insula, plays a role in the sensation of bladder fullness (Kitta et al., 2016) and has been observed during bladder filling (Kitta et al., 2015). The basal-ganglia circuit suppresses micturition reflex in healthy adults (Sakakibara et al., 2010; Hattori et al., 1992). In PD, this circuit seems to be impaired causing range of bladder problems (Bonnet et al., 1997; Seki et al., 2001).

The activity and structural connectivity in the frontal lobe, ACC, anterior cingulate gyrus (Yuan & Raz, 2014) as well as the cortico-basal ganglia loops (Graybiel, 2000) has been attributed to both the executive functions and urinary control. Moreover, the direct and the indirect pathways between the basal ganglia and the frontal cortex have been attributed to the response selection, as well as initiation of action under competition or conflict (MacDonald & Byblow, 2015). The indirect pathway through the subthalamic nucleus inhibit the inappropriate, or no longer required responses, which allows one to execute (select and initiate) an appropriate response through the direct pathway (Middleton & Strick, 2000; Redgrave, Prescott, & Gurney, 1999). In PD, as a consequence of neurodegenerative processes, the pre-supplementary motor area becomes underactivated, with simultaneous over activity of subthalamic nucleus, which causes deficits in inhibitory control (Beste, Willemsen, Saft, & Falkenstein, 2010; Gauggel, Rieger, & Feghoff, 2004).

During the course of the disease, the neurodegenerative processes influence autonomic, limbic and somatomotor systems (Braak et al., 2004), impairing pathways involved not only in micturition reflex, but also in cognitive functions.

Due to the fact that both urinary symptoms and cognitive impairment are of a high prevalence, more likely to appear in late stages of the disease and have a common neurophysiological pathway (Fowler, 1999; Fowler et al., 2008; Fowler & Griffiths, 2010), it is important to investigate the connection between these two phenomena in order to evaluate if there is a causal link between cognition and

urinary symptoms. This connection, or even causal relationship, has only been sparsely investigated in PD and, therefore, is the main research focus of this doctoral thesis.

Publications and Scientific Research Question

The main goal of this PhD thesis was to establish a detailed clinical characterization of PD-UU (with or without incontinence) and to identify cognitive mechanisms associated with UU in a subgroup of PD patients. The thesis aimed to evaluate the question whether it is possible to characterize a subpopulation of PD patients whose UU is primarily influenced by cognitive control mechanisms. This subgroup might benefit from more cognitive-driven intervention of UU, as it would be helpful if a certain clinical profile associated to potential cognitive-driven UU could be identified. In the second part, we validated a sensitive, economic test battery- MoCA, which is often used in a clinical interview, even though the commonly used cut-offs were validated among Alzheimer's Disease patients. We aimed to establish better diagnostic accuracy for PD-MCI, in order to improve the diagnostic value of this commonly used screening test.

Research Question 1 / Publication 1:

In this explorative study, the possible link between cognition, especially in frontal lobe functions, PD-UU and other non-motor aspects was investigated. For this purpose, the analysis was carried out within a more heterogenous group of PD patients. The data was collected within the frame of the "Verlaufsstudie zur Charakterisierung kognitiver Störungen bei Parkinson Patienten" study, designed to identify the association between PD-UU, cognition, activity of daily living function and other non-motor symptoms. The aim of this study was to examine if there is a correlation between incidence/severity of urinary symptoms and cognition in a heterogenic PD group (all stages of the disease) in order to address the following research gaps:

- a) What is the prevalence of PD-UU in a heterogenic PD sample?
- b) Does the incidence of urinary symptoms in PD associate with other motor or non-motor symptoms of PD?
- c) Does the incidence and/or severity of PD-UU have any association with cognition in PD?

Research Question 2 / Publication 2:

The aim of the investigation was to examine which aspects of cognition associate with PD-UU more deeply in order to identify a subgroup of patients whose UU was triggered or worsened by cognitive impairment. Therefore, PD patients with and without UU were compared, while controlling for physical

conditions and medication interfering with bladder function or cognition in a large, more homogenous non-demented PD sample with the aim of further investigating the following gaps in the current research.

- a) What is the prevalence of PD-UU in the ambulatory treatment setting?
- b) Is it possible to identify a prototypical PD patient whose urinary urgency is associated, or even caused by cognitive impairment?
- c) Does PD-UU relate to the instrumental activity of daily living function (iADL), or health related quality of life (HRQoL)?

Research Question 3 / Publication 3:

In this study, we validated a weighted MoCA scoring algorithm in a large, non-demented PD population. Our aim was to investigate if the weighted algorithm would have better diagnostic accuracy for PD-MCI and would show a stronger correlation to results of more specific neuropsychological assessments.

- a) Does the incidence of PD-MCI change when using weighted MoCA scoring?
- b) Does the association with each cognitive domain (especially executive function) change in weighted MoCA scoring?
- c) What is the optimal cut-off value for weighted MoCA in order to reduce type II errors?

Results und Discussion

The main objective of this PhD thesis was to investigate the link between urinary urgency (with or without incontinence) and cognitive function in PD. The first step taken was to explore the theoretical and methodological background of this association in an unselected cohort, which included PDD cases and concomitant diseases. Based on the limitations detected in this step, the study design was specified and the investigation was conducted on a non-demented PD sample, excluding patients who receive medication and/or suffer from concomitant diseases could potentially influence either cognition or urinary symptoms.

An additional focus of this doctoral thesis was to find a way to improve early diagnosis of cognitive deterioration, which increases the risk for PDD. Thus, a new scoring algorithm developed to improve diagnostic accuracy when using the MoCA, a commonly used cognitive test battery, to detect PD-MCI was evaluated in a non-demented PD population.

Idiopathic PD has been long considered a movement disorder, caused by degenerative processes of substantia nigra. The high prevalence of non-motor symptoms has recently been recognized and become a focus of scientific research (Berganzo et al., 2016; Marras & Chaudhuri, 2016; Pfeiffer, 2016;

Sauerbier, Jenner, Todorova, & Chaudhuri, 2016). Non-motor symptoms create a great challenge, for clinicians as well as for patients and their caregivers, appearing even before motor symptoms do, and in some cases dominating the clinical phenotype (Chaudhuri, Odin, Antonini, & Martinez-Martin, 2011). The scientific importance of investigating the relationship between PD-UU and cognitive function arises from the high prevalence among PD patients, strong negative impact on everyday life and predictive value for a faster disease progression (Bartoli, Aguzzi, & Tarricone, 2010; Fereshtehnejad et al., 2015). Bladder symptoms can be found in 28%-71% of PD patients, and are, therefore, significantly higher than in healthy elderly. Moreover, urinary symptoms are highly prevalent in other forms of dementia, suggesting an association with the severity of cognitive impairment (Chiang et al., 2015; Ransmayr et al., 2008; Tateno et al., 2015).

Association of Cognition and PD-UU

The association between urinary dysfunction and neuropsychological test performance in PD was initially investigated in a broad, unselected PD cohort, which included patients of all cognitive states: PD with normal cognition (PD-NC), PD-MCI and PDD. All concomitant diseases, except for depression, as it is known to worsen cognitive performance (Bhardwaj, Wilkinson, Srivastava, & Sharma, 2010) were taken into consideration. The association of cognition was analysed between PD-UU and PD-NUU patients, followed by a comparison within: PD-UU patients without urological treatment vs PD-UU patients who had received urological treatment. Patients who had received urological treatment were considered to experience more severe bladder symptoms than patients who had not received such treatment.

This explorative study showed that PD-UU patients suffered from a greater level of cognitive impairment than PD-NUU, measured by the PANDA (Parkinson Neuropsychometric Dementia Assessment-Test). This effect remained significant in a PD-UU within comparison. Additionally, we assessed a comprehensive neuropsychological test battery (see Publication 1) to the PANDA in order to evaluate cognitive domains, important for diagnosing PD-MCI, or PDD: executive functions, working memory, attention, memory, language and visuo-construction (Litvan et al., 2012; Martinez-Martin, Falup-Pecurariu, et al., 2011). Among these domains, PD-UU patients performed worse on visuo-construction tests than PD-NUU patients. Here as well, the results were able to be replicated in the subgroup comparison.

Hence, not only presence, but also severity of PD-UU was associated to cognitive impairment, especially visuo-construction, in the sample of PD patients. The findings of this study confirm previous studies that reported high prevalence of PD-UU in late stages of PD (Winge & Nielsen, 2012). Moreover, more advanced cognitive decline, represented by visuo-constructive deteriorations (Williams-Gray et al., 2009), was found to be associated with PD-UU. Visual perception deficits are a frequent manifestation

in PD (Aarsland, 2016). Neuroimaging studies taking into account activation of cortical areas and networks involved in visual perception processes showed reduced activation of basal ganglia networks and a greater- compensatory activation in prefrontal cortex (Caproni et al., 2014). The neurodegeneration of the part of the basal ganglia network that is involved in executive processes in PD, has a direct influence on visuo-constructive processes (Umarova et al., 2010).

Urgency, with or without incontinence can result from many origins, such as detrusor overactivity, cognitive and behavioural problems, urological causes or aging processes (Panicker, Fowler, & Kessler, 2015). The high prevalence of bladder dysfunction in other forms of dementia and a close link between other autonomic problems and cognitive impairment strengthens the hypothesis that these two neurodegenerative processes can influence each other during the course of the disease (Idiaquez & Roman, 2011). Autonomic functions, in general, have been investigated in the context of previous neuroimaging or neuropsychological studies in order to improve the understanding of the co-existence of autonomic failure and cognitive deterioration (Heims et al., 2006). Subtle cognitive impairment is almost universally distributed among PD patients and can even appear in early stages of the disease (Broeders et al., 2013; Muslimovic, Post, Speelman, & Schmand, 2005). The impairment relates to the front-striatal loop, with projections to the frontal cortex, related to executive dysfunction, which involves planning, goal oriented behaviour or inhibition of unwanted, or unneeded behaviour (Dirnberger & Jahanshahi, 2013; Dubois & Pillon, 1997; Yuan & Raz, 2014). Yet, the link between cognition and bladder symptoms has been sparsely investigated among PD patients (Heims et al., 2006; Pilleri, Koutsikos, & Antonini, 2013). Urinary problems are highly prevalent in dementia; however, the timing of its occurrence varies between neurological disorders (Aubin et al., 2015; Birder et al., 2010; de Groat et al., 2015; Ogawa et al., 2017). Neuroimaging studies suggest at least a neurophysiological relationship between PD-UU and cognition (Fowler, 1999; Fowler et al., 2008; Griffiths & Fowler, 2013), proposing that the integrated cortical neurodegenerative process might influence, or be dependent on bladder dysfunction, and the prevalence of urinary symptoms. The inhibitory effect of basal ganglia on micturition is disrupted in PD patients (Kitta et al., 2016; Kitta et al., 2006; Kitta et al., 2015). Furthermore, it has been shown that the frontal cortex plays an important role in regulating micturition (Griffiths & Fowler, 2013; Panicker et al., 2015), being a region with many direct and indirect connections with areas associated with autonomic control, and playing an inhibitory role (Fowler & Griffiths, 2010; Yamamoto et al., 2010).

During the course of the disease, impairment of executive functions occurs in approximately 30% of PD patients (Bronnick et al., 2006; C. C. Janvin et al., 2006; Puente, Cohen, Aita, & Brandt, 2016). Visuo-constructive impairment, which was found to be associated to presence and severity of PD-UU, appears later in the disease course and has been connected to accelerated cognitive decline and PDD (Williams-Gray et al., 2009). However, visuo-construction is a very complex cognitive function. To solve a visuo-construction task, subjects often use top-down and bottom-up systems that also refer to executive aspects, such as inhibiting irrelevant information, planning and unifying ambiguous stimuli (Kastner & Ungerleider, 2000; Miller & Cohen, 2001). It is possible, that executive impairment influenced visuo-

constructive performance, however, this finding needed to be reevaluated in a selected group of PD patients. To investigate the association of cognition and PD-UU more deeply, we took the limitations of the first study into account and designed our second study, excluding patients with either PDD, or whose medication/concomitant disease could influence either cognition or urinary function. To assess a global cognitive state, the MoCA, which is known to be a sensitive tool for early cognitive changes in PD (Hoops et al., 2009) was chosen. Additionally, an extended neuropsychological assessment was performed along with the creation of test clusters for every cognitive domain, making the measurement of each domain more robust with regard to reliability bias. To reduce the psychometric quality bias, a mean z-value for every cognitive domain was calculated, utilizing the cognitive subtests assigned to each domain. Only the mean z-value of executive function distinguished significantly between PD-UU and PD-UUU. This finding confirmed our theoretical hypothesis of a prefrontal cognitive involvement, expressed by executive impairment in PD-UU. This finding is also in line with other studies, which have found a connection between inhibitory function and urinary problems in other neurological disorders such as vascular dementia, leukaraiosis, or Alzheimer's disease (Del-Ser, Munoz, & Hachinski, 1996; Drachman, O'Donnell, Lew, & Swearer, 1990; Haruta et al., 2013), however, contradictory to a longitudinal study (Picillo et al., 2017).

To answer the question of why the findings of this thesis differ from previous finding (Picillo et al., 2017), the chosen assessment needs to be taken in to consideration. In their study, Picillo et al. observed no differences in the cognitive assessment while using the Minimental-State Examination (MMSE) (Picillo et al., 2017). The MMSE was originally designed to assess cognitive impairment in AD, nevertheless has been used as a screening tool for PDD. Values below 26 points would indicate possible dementia in PD (Hoops et al., 2009). However, it has been shown that MMSE cannot be used as a reliable screening tool for PD cognitive deteriorations especially in early stages of cognitive deterioration (Burdick et al., 2014), as it has a poor sensitivity for detecting cognitive impairment, including PD-MCI (Nazem et al., 2009). Moreover, a variety of cognitive problems, including PDD could have been observed even in patients who performed above a proposed cut-off (Hoops et al., 2009; Zadikoff et al., 2008). In order to improve the diagnosis of cognitive deterioration that can contribute to PD-UU, a more sensitive screening tool should be applied in daily clinical routine. The MoCA screening assessment has been shown to be more reliable to differentiate between cognitive states in PD, and covers a broad range of cognitive domains (Dalrymple-Alford et al., 2010; Wood et al., 2016), which will be discussed in the last study included into this thesis.

Prevalence and Demographics of PD-UU

This thesis confirmed previous findings that urinary symptoms are highly prevalent in the PD population, as over 50% of the study participants reported at least mild urinary symptoms (Araki et al., 2000; Ogawa et al., 2017). For the first, exploratory study 94 PD patients were included, out of which

55.3% reported urinary problems. PD-UU patients were more frequently men, of higher education. When comparing PD-UU patients who received urological treatment with PD-UU patients without treatment, we found that higher educated men were more probable to receive medical treatment for PD-UU. However, this could be a potential inclusion bias, as no correlation between PD-UU and age of onset, age of diagnosis was evident in the second study. A possible explanation for this could be that within this age range men tend to be more highly educated than women. Consequently, men may seek medical attention more often or be keener on supporting scientific research. Misconceptions about urinary problems should also be taken into account, as patients often assume it to be related to the aging process, rather than PD itself (Moriarty et al., 2016).

In the PD-UU subgroup, 19.2% were diagnosed with PDD, contrary to PD-NUD patients, where PDD was only detected in 7.1% of patients. This finding was in line with previous findings, showing that urinary problems are more prevalent in dementia, based on community-dwelling and institutional studies (Ouslander, Palmer, Rovner, & German, 1993; Palmer, German, & Ouslander, 1991). Previous research has revealed, that incontinence episode were present in over 75% of demented patients, compared to only 5% of the general population of elderly individuals (A. R. Herzog & Fultz, 1990). This important finding strengthened the hypothesis of an association between PD-UU and cognitive impairment.

The link between dementia and urinary urgency, as well as the comorbidity of degenerative and vascular pathologies has been reported previously (Campbell, Reinken, & McCosh, 1985; Nakanishi et al., 1997; Skelly & Flint, 1995). However, even though the general correlation of cognitive worsening and prevalence of bladder symptoms was assumed (Marras & Chaudhuri, 2016; Postuma, Gagnon, Pelletier, & Montplaisir, 2013), it was important to investigate to what extent this correlation is valid. Furthermore, a causative relationship of these symptoms was not clear. Of particular importance is that urinary urgency must not be accompanied by cognitive impairment or dementia (Sakakibara et al., 2005), which implies that the association between these two non-motor symptoms is valid for a subtype of PD patients and cannot be generalized to the whole PD population.

Further Symptoms of a Prototypical PD-UU Patient

Motor Symptoms

It is still up to debate whether there is an association between motor progression and PD-UU. Some studies have concluded that urinary dysfunction can be associated to disease severity (Araki et al., 2000; Winge & Fowler, 2006) or motor symptoms, other studies have failed to prove this association (Campos-Sousa et al., 2003; Hobson, Islam, Roberts, Adhiyman, & Meara, 2003). In the research of this thesis, no correlation was found between motor impairment, measured by the Unified Parkinson Disease Rating scale (UPDRS III), or disease severity, measured by the Hoehn und Yahr (H&Y) and PD-UU. This finding

supports the hypothesis that motor symptoms and PD-UU might develop independently. However, some disproportion of the distribution of the H&Y stages was observed. In the second study, stage 2 was overrepresented as well among PD-NUU as PD-UU. As patients in more advanced stages of the disease generally might be less willing to participate in scientific studies, whereas patients in earlier stages may simply not have time for study participation because they are still well integrated in social and professional life, we cannot exclude the possible bias of the results. Considering these issues, the possibility of type 1 error is higher than anticipated. It is possible, that motor impairment contributes indirectly to PD-UU, however, our data cannot support this evidence.

The second study revealed, that PD-UU had in average a longer disease duration than PD-NUU patients. This effect was not supported by the discriminative analysis, which did not assign disease duration to the PD-UU group. It confirmed our previous finding that disease duration per se does not contribute independently to subtyping the PD-UU subgroup. In the literature, reports considering disease duration and PD-UU are heterogeneous. Some studies show that PD-UU can be detected at median 12 years after PD diagnosis (Wenning et al., 1999), whereas others report an early onset (Uchiyama et al., 2011). These conflicting outcomes emphasize the importance of differentiating between age-related and PD-related bladder problems as an important confounding variable (Zhang & Zhang, 2015). So far, two prospective studies have investigated, whether the frequency of PD-UU increases during the course of PD (Ou et al., 2016; Picillo et al., 2017). Both studies confirm an increasing tendency of a prevalence of bladder symptoms, over time. Additionally, another study determined that in advanced PD, prevalence and severity of PD-UU is significantly higher than in moderate PD (Winge & Nielsen, 2012) and that disease severity seems to influence bladder symptoms significantly (Campos-Sousa et al., 2003). These results support the hypothesis that urinary dysfunction caused by PD is a specific symptom that can be detected in a specific subtype of heterogeneity of the disease, rather than a consequence of dopaminergic degeneration or simply aging processes.

Other Non-Motor and Autonomic Symptoms

James Parkinson did not describe PD as a motor disorder exclusively (Horowski, Horowski, Vogel, Poewe, & Kielhorn, 1995). He also noted the prevalence of non-motor symptoms such as sleep disturbance, constipation or urinary incontinence. However, non-motor symptoms have not been focused on for many years, even though almost 100% of all PD patients report at least one non-motor symptom (Pfeiffer, 2016). The clinical spectrum of non-motor symptoms in PD is a consequence of a widespread neuronal pathology of this disorder. Patients with PD experience a combination of dysautonomic symptoms, cognitive impairment and fluctuations in non-motor symptoms, such as pain, sweating or fatigue (Witjas et al., 2002). Even though the neurological pathway of motor-; and non-motor symptoms seems to be of common origin, the neuropathology of PD-UU has not been fully explained yet. It has been shown, that PD-UU patients suffer from more frequent and severe non-motor symptoms than PD patients with no bladder dysfunction (Picillo et al., 2017), which we were able to

confirm in the second study of this thesis. Furthermore, evidence shows, that non-motor symptoms tend to aggregate, and bi-influence each other, resulting in a considerable negative impact on patients and their caregivers (Jain, 2011; Sauerbier et al., 2016).

Another important factor influencing PD-UU is the affective disorder, which is common in PD and may occur in every stage of the disease (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). Even though depression is attributed to the serotonin deficiency, levodopa medication has been shown to reduce depressive symptoms (Chaudhuri, Healy, et al., 2006), which indicates neuropathological connection. Bladder dysfunction is common in both, depression and in PD, but is more prevalent in PD patients than those suffering from depression (Sakakibara et al., 2013). The affective disorder contributes to the cognitive worsening, influencing performance in executive tasks (Marvel & Paradiso, 2004), which was also impaired in PD-UU patients in the second study of this thesis. Moreover, findings of neuroimaging studies confirm that cognitive impairment in depression is linked to disturbances in the activity of the prefrontal cortex, ACC and hippocampus (Degl'Innocenti, Agren, Sjogren, Zachrisson, & Backman, 1999), cortical structures also impaired in PD-UU patients (Griffiths & Fowler, 2013). Therefore, depression was assumed as a possible confounder and has been examined in all of our studies. No differences were detected for the PD-UU and PD-NUU groups, which strengthens the findings of the connection between cognitive impairment and PD-UU.

PD-UU and Quality of Life

The influence of urinary dysfunction on the daily life of PD patients is very complex. As introduced earlier, bladder dysfunction can occur throughout the course of the disease, but is more prevalent in late stages among PDD patients and can impair patients' quality of life to a greater extent than motor deteriorations do (Pfeiffer, 2016). Studies suggest that bladder dysfunction is perceived by patients as more bothersome than other non-motor symptoms, which results in a greater negative impact on quality of life (Yeo, Singh, Gundeti, Barua, & Masood, 2012).

In the first study, iADL was found to be more impaired in PD-UU, however this effect disappeared when different severity levels of PD-UU were compared. This finding indicates that in PD-UU, prevalence but not the severity of urinary symptoms contributes to the impairment of iADL. To investigate this issue, a post-hoc analysis was performed. It was shown, that the worsening of iADL function correlated to the cognitive worsening, which was observed in the PD-UU subgroup. Previous studies have shown that PD-MCI, which often precedes PDD, is accompanied by the worsening in iADL (Leroi, McDonald, Pantula, & Harbishettar, 2012).

As PD-UU patients in the first study experienced lower iADL, it can be assumed that PD-UU contributes to the progression of the disease and conversion to PDD. This finding could not be replicated in the

second study, however, changes in the HRQoL related to Stigma were assigned as a symptom of the PD-UU group. The surprising part of the result was, that Stigma related to HRQoL was lower among PD-UU patients than PD-NUU. Evidence shows, that stigma, arising from health-related symptoms is higher among PD patients than HI, as it can lead to social withdrawal (Hermanns, 2013; Ma, Saint-Hilaire, Thomas, & Tickle-Degnen, 2016). It is also known that PD patients have a reduced interoceptive sensitivity, leading to the reduced acknowledging of physiological abnormalities, when compared to the healthy population of the same age (Ricciardi et al., 2016). The reversed Stigma direction in our study can imply that PD-UU patients do not fully perceive the urinary urgency, or deny the symptoms. It is important to mention, that interoceptive perception is modulated by the ACC, which also modulates performance in executive tasks (Fowler & Griffiths, 2010). The results of this study may indicate that a lower stigma burden is a secondary outcome alongside with executive impairment among our PD-UU group. To gain further insight into this particular connection, further studies are required.

The Validation of a Weighted MoCA Scoring in Non-Demented PD Patients

Deficits in executive functions are common in PD (Dirnberger & Jahanshahi, 2013) and incorporate problems in planning, cognitive flexibility, inhibition, generating strategies, and abstract thinking (Stuss & Alexander, 2000). Even though, cognitive impairment has a vast impact on the daily life of PD patients, it frequently stays underdiagnosed in the early stages of the disease. Very often short screening tests are the only ones used to detect cognitive deteriorations, delivering many false positive and false negative results (Fengler et al., 2016). Prevalence studies report that during the course of the disease, up to 80% of PD patients are at risk for developing PDD (Aarsland, 2016), and up to 60% will develop bladder dysfunction (Araki et al., 2000). Based on these findings, there is clearly a great need for a valid diagnostic tool to identify those patients at risk for cognitive impairment early on. Therefore, it is important to focus on neuropsychological assessments that could be integrated into the everyday clinical routine and would be highly sensitive to initial cognitive deteriorations in PD.

In general, the PD-MCI concept has a relatively low specificity, as there is no consensus about which and how many cognitive tests are needed for cognitive profiling. For example, the diagnostic criteria of the Movement Disorder Task Force guidelines operate on dichotomous criteria of inclusion/ exclusion (Wood et al., 2016) and the cut-offs are often derived from the normative data (Aarsland et al., 2003; Foltynie et al., 2004). The cut-off for PD-MCI, is therefore defined as a SD < -1.5 of normative data (Hoops et al., 2009). A very commonly used test battery for detecting cognitive deteriorations is the MoCA (Nasreddine et al., 2005), originally designed for detecting cognitive changes in AD. The main critique concerning the MoCA is that the scoring system does not consider subtest discriminant power, which would represent the cognitive decline in PD more correctly, with a higher impact on executive decline (Fengler et al., 2016). As a result, a new a subtest-discriminant algorithm was proposed (Fengler et al., 2016). This algorithm has been reported to be more sensitive for cognitive deterioration in a PD.

However, this validation study included all the stages of cognitive impairment, which made it more difficult to determine whether or not this weighing method is an accurate way to distinguish between PD-NC and PD-MCI, or if the findings contribute to the cognitive impairment related to PDD. Therefore, an evaluation of a weighted MoCA scoring algorithm was conducted in a large, non-demented PD population in order to investigate the effect on the accuracy of PD-MCI diagnosis and the potential to minimize the risk of false-negative errors.

In the third study, the PD-MCI classification was defined as followed: The 1 SD cut-off 74 PD-NC (36.6%) and 128 (63.4%) PD-MCI patients, the 1.5 SD cut-off to 125 (61.9%) PD-NC and 77 (38.1%) PD-MCI patients, and the 2 SD cut-off to 162 (80.2%) PD-NC and 40 (19.2%) PD-MCI patients. According to the 1, 1.5, or 2 SD cut-off, 93.8%, 93.5%, and 95.0% respectively, of all PD-MCI patients were classified as multi-domain PD-MCI.

By applying a 2 SD cut-off, an interesting result was observed. The PD-NC patients scored significantly lower than in non-weighted MoCA, which let us assume that while using 2 SD cut-off few cases of an early PD-MCI can be observed. Whether or not this subgroup of patients was in risk of progressing to PD-MCI should be investigated in a longitudinal study, however, we assume that this cut-off is more sensitive to the subgroup of PD patients who will experience steeper cognitive decline.

As expected, the PD-MCI classification was highly dependent on the used cut-off as well, which in the study of this thesis was shown to be most accurate at 1.5 SD; 27 points (for the weighted MoCA). The cut-off in this study was higher than the cut-off proposed by the original work: 26 points (original MoCA) (Nasreddine et al., 2005). As the MoCA and the proposed cut-off were evaluated on AD patients, we assume that they are not appropriate for PD patients, and that our cut-off represents PD-MCI more accurate than the original MoCA does.

An interesting novelty was that only the 2 SD cut-off showed higher specificity and sensitivity, compared to original MoCA scoring. We found this result surprising, as the weighted MoCA prioritises subtests assigned to executive function, which are more present in early stages of PD. Our data, however, shows that the weighted MoCA is advantageous when detecting cognitive impairment in more advanced stages of PD, showing a higher sensitivity to visuo-cognitive deteriorations, which are known to be predictive for PDD (Williams-Gray et al., 2009). A possible explanation for this finding is that the weighted MoCA identifies PD patients at risk of developing PDD when applying a 2 SD cut-off. Nevertheless, longitudinal studies are needed to confirm this assumption.

Regarding the sensitivity and specificity of the cut-offs, significant higher values were observed than in the original MoCA (sensitivity 70.0% vs. 72.5%; and specificity 65.4% vs. 79.0%). The results of this study differ to Fengler's study, who tested the weighted algorithm, in a more heterogenic PD population, without excluding depression as a confounder (sensitivity: 68.8% vs 73.5%; specificity:66.7% vs 79%). Our findings show an improvement of the specificity, which reduces the likelihood of false negative

results. This is especially important in clinical practice, as screening tests are often the only tool used in a daily routine.

In general, as well the weighted as the original MoCA were able to differentiate between PD-NC and PD-MCI. However, PD-MCI patients scored lower in the weighted version compared to the original, implicating more advanced stage of PD-MCI. With regard to cognitive domains, both MoCA versions correlated moderately with every domain and did not differ significantly.

In conclusion, the results of this study showed that the newly weighted MoCA has a high sensitivity to detect a group of PD-MCI patients, who are likely to be in a later stage of the PD-MCI. At the 2 SD cut-off, the weighted MoCA seems to be more sensitive with regard to the detection of PD-NC patients, potentially at risk of PD-MCI. Screening tools such as the MoCA are indispensable for clinical daily routine as they are economic in time, easy to administer and, furthermore, can indicate whether it is necessary to evaluate patients' cognitive status more precisely.

Limitations and Considerations for Future Studies

This thesis research has limitations. First of all, the design of our first study allowed the inclusion of PDD patients. Even though, we found an association between cognitive impairment and presence as well as severity of PD-UU, we did not observe early changes in cognition or bladder symptoms, but rather put focus on late disease stages, where the neurodegenerative processes are highly developed. This was the reason why the visuo-construction was the cognitive function that associated to PD-UU in the first publication, rather than any other function. The impairment of visuo-constructive function appears late in the course of the disease and reflects a more advanced neurodegenerative state, indicating increased probability of progressing into PDD (Williams-Gray et al., 2009). However, even though PD-UU is overrepresented in dementia (Sakakibara, Uchiyama, Yamanishi, & Kishi, 2008), these symptoms may appear early in the disease, or even precede motor symptoms (Sakakibara, Uchiyama, Yamanishi, Shirai, & Hattori, 2008; Uchiyama et al., 2003). To investigate the nature of the relationship between cognition and PD-UU further studies, preferably of a longitudinal design, are needed. The second study in a non-demented PD population was designed with the limitations of the first study in mind. An association between executive functions and PD-UU was detected at this time and the discriminant analysis confirmed that executive functions contribute to the prediction of PD-UU. The results of the second study showed that in earlier stages of PD executive functions differentiate between PD-UU and PD-NUU. The chosen assessments, however, did not specify which aspects of executive functions specifically were deteriorated. Following theoretical background of neuroimaging studies, the basal ganglia and frontal cortex influence micturition in an inhibitory matter (Fowler et al., 2008; Fowler & Griffiths, 2010; Griffiths & Fowler, 2013). The ability to inhibit an ongoing reaction has been assigned to the executive domain (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron & Poldrack, 2006). Therefore, the

assumption can be made that PD-UU patients would perform worse on inhibitory tasks when compared to PD-NUU or healthy subjects. This aspect should be investigated in future studies. A link between urinary urgency and inhibition has been shown for patients with vascular dementia (Haruta et al., 2013), however, it has not yet been examined for PD-UU.

A further limitation of the first study was that comorbid illnesses that could influence bladder symptoms, such as diabetes or prostate hyperplasia were not excluded. Previous studies have shown that men with mild to moderate PD report the same bladder symptoms as men with prostatic enlargement (Lemack, Dewey, Roehrborn, O'Suilleabhain, & Zimmern, 2000). Given this limitation, the results of the first study may not be specific enough to single out the bladder symptoms caused primarily by PD. Therefore, the second study included only a specifically selected sample of PD patients. PDD patients as well as any subject reporting bladder related disease, prior to PD were excluded. In addition, comorbidities such as diabetes, other age-related causes of urinary urgency or medication that would interfere either with urinary tract or cognition were excluded in order to identify a subgroup of PD patients that suffer from urinary problems caused intrinsic through PD itself. The results showed that PD-UU is highly prevalent among PD patients as the prevalence rate was of 60.8%, higher than in previous studies (Martinez-Martin et al., 2007). As mentioned earlier, the focus of this thesis was to investigate bladder symptoms that can be contributed to the neurogenic origin, therefore, through the high number of exclusions, a different prevalence rate was achieved. In none of our studies PD-UU was linked to age, which minimized the risk of including symptoms that are purely age-related.

An important fact was that groups in the post-hoc analysis of the first study were gender biased, as only highly educated men received urological treatment. The obstacles were bypassed by setting restrictions in the statistical analysis of the first study, using adjustments in a regression model while adding gender and education as confounders. However, the results may not mirror the aspects of PD-UU to the fullest extent.

Another noteworthy critique is that bladder symptoms might be influenced by the parkinsonian medication. Studies that have investigated this topic have revealed conflicting results. Some studies have reported that levodopa can improve the bladder symptoms (Aranda & Cramer, 1993), others studies have found the opposite results (Uchiyama et al., 2003). Furthermore, voiding difficulty is considered to be reduced during the "on" state (Araki et al., 2000; Hattori et al., 1992; Herzog et al., 2006). In the first exploratory study, no group effect according to LEDD intake was detected. The second study showed, that PD-UU was associated to a higher Levodopa intake, however, dopaminergic antagonist equivalent dosage did not statistically differ between study groups. In the second study, discriminant analysis showed that LEDD should not be interpreted as an independent predictor for PD-UU, but rather represents a group bias that was specific to the study sample.

Anticholinergic medication, that is often used as therapy against bladder dysfunction, has been shown to worsen cognitive performance (Ehrt, Broich, Larsen, Ballard, & Aarsland, 2010), which is why

patients who reported anticholinergic medication intake were excluded from further analysis and the adverse anticholinergic effect (ARS) caused by other medication, as suggested by Crispo and colleagues (2016) was examined. The computed ARS level was the same in our composed PD-NUU and PD-UU groups in both studies, which eliminated medication-induced bias and strengthened the results, as cognitive changes among PD-UU were disease-; and not therapy- driven.

A urodynamic examination was not a part of the study, however the assessment of urinary problems as based on validated self-reported questionnaires. When using self-reported data, one must assume that both, false negative and false positive cases can be assessed. The questionnaires however, were often used in studies investigating urodynamic and are validated for assessing urinary problems, which probably eliminated biasing cases of UU.

The next issue that should be addressed regards the quality of life. The results of the first study show that the presence and not the severity of PD-UU, reduces the iADL, which is characteristic for more advanced PD population. In the second study, HRQoL related stigma was significantly lower among PD-UU patients, rather than PD-NUU. Studies show that PD patients experience lower interoceptive sensitivity when compared to the age matched healthy population (Ricciardi et al., 2016), which could explain that PD-UU patients achieved lower score on Stigma related to HRQoL. Moreover, interoception has been shown to be modulated by the anterior cingulate cortex, a cortical structure which also modulates executive performance, that is impaired in PD-UU patients (Kitta et al., 2016). Future studies are required to gain the insight into to what extent PD-UU influences perceived quality of life.

An obvious limitation is the cross-sectional design of the studies. The collected data should be, therefore, interpreted as a snapshot and can be biased by the daily fluctuations of mood, tiredness etc. The classification of symptoms that characterize PD-UU patients should be addressed in a longitudinal study, in order to understand the possible co-development of cognitive functions and urinary symptoms.

Concerning the third study, the differences in the data between our study and study conducted by (Fengler et al., 2016; Hoops et al., 2009) could have resulted from the fact that the analysis for the purpose of this thesis was conducted among a non-demented PD sample. The higher cut-off value cannot be compared entirely, as our sample lacked PDD.

Moreover, for the purpose of the analysis a 1, 1.5 and 2 SD cut-offs were used. The original study by Fengler et al. used a cut-off of 1.28 SD for the CERAD subtests, as suggested in the manual. Due to these two design differences, our study is not completely comparable to the previous findings.

A further limitation that should be noted is, that the weighted MoCA was not associated to other non-motor symptoms. It is known that PD-MCI patients are likely to develop dementia in the course of the disease. Moreover, it is known that urological symptoms, as well as PD-MCI can attribute to the more prone disease progression and earlier conversion to PDD (Williams-Gray et al., 2009; Winge et al.,

2007). In the second study, MoCA did not contribute to the PD-UU independently. However, in this study we used the original scoring algorithm. Future studies should investigate the new scoring algorithm in association to other non-motor symptoms, especially PD-UU.

Conclusion

In conclusion, this thesis investigated the role of cognitive impairment in PD-UU, using a comprehensive neuropsychological test battery. We started in a broad unselected PD sample and shifted our focus into the selected sample, excluding PDD, concomitant diseases and medication influencing either bladder symptoms or cognition. In the second step, a new scoring algorithm for a cognitive test battery-MoCA, which is broadly used in clinical routine, was evaluated.

We were able to show that the global cognitive level and visuo-construction are associated to PD-UU in more advanced stages of the disease. The executive function was associated to PD-UU in early to moderate stages of PD. A discriminant analysis allowed to describe a prototypical PD-UU patient, who would suffer from a higher impairment of executive functions, a higher number of non-motor symptoms and experience changes in HRQoL related to stigma, when compared to the PD-UU patient.

Furthermore, findings of this thesis confirm a high prevalence of urinary dysfunction among the PD population. To our knowledge, these are the largest studies that investigated the role of cognitive impairment in PD-UU using a comprehensive neuropsychological test battery.

With regard to the weighted MoCA, this thesis showed that the new scoring algorithm can detect cognitive impairment in PD more effectively than the original MoCA, however, only if PD-MCI was classified with a 2 SD cut-off. Therefore, the weighted MoCA might have a greater discriminant power in detecting PD-MCI patients at risk of PDD. Our findings emphasize the need for further evaluation of MoCA in order to improve the diagnosis of PD patients at risk for future PDD.

Conclusion / Zusammenfassung

Parkinson ist die zweithäufigste neurodegenerative Erkrankung in Europa, mit einer Prävalenz von 1.8% ab dem 55 Lebensjahr. Zu den Kardinalsymptomen gehören Bradykinesie, Rigor, und Ruhetremor. Zusätzlich treten häufig nicht-motorische Symptome auf, die im Verlauf das Erkrankungsbild dominieren können, eine höhere Beeinträchtigung des Alltags verursachen und von Patienten als stärker aversiv wahrgenommen werden.

Zu den häufigsten nicht-motorischen Symptomen gehören, unter anderem, autonome Symptome – wie Harndrang mit oder ohne begleitender Harninkontinenz, Störungen der Sexualität, orthostatische Hypotension, oder kognitive Störung. Kognitive Störungen betreffen bis zu 30% aller Patienten (Aarsland, Bronnick, & Fladby, 2011; Aarsland et al., 2009) und nach acht Jahren Erkrankungsdauer beträgt die Wahrscheinlichkeit an einer Demenz zu erkranken etwa 78% (Aarsland et al., 2003).

Blasensymptome können bis zu 60% aller PD Patienten (PD-UU) betreffen (Araki, Kitahara, Oida, & Kuno, 2000) und treten signifikant häufiger als bei gesunden Kontrollpersonen auf. Das Vorkommen wird mit der motorischen Progression, als auch der kognitiven Beeinträchtigungen in Zusammenhang gebracht.

Die Ursache der Drangsymptomatik bei PD ist sehr komplex. Die zentrale Regelung des Miktionsreflexes setzt sich aus Bahnen zwischen Frontalhirn und Basalganglien zusammen, die die Kontrolle und interozeptiven Prozesse der Miktion modulieren (Kitta et al., 2015). Dieser Regelkreis, der an emotionalen und Verhaltensaspekten der Miktion beteiligt sei, steuert generell das menschliche Verhalten, insbesondere unsere exekutiven Fähigkeiten, wie Inhibition, Monitoring und Update der wahrgenommenen Signale (Fowler, Griffiths, & de Groat, 2008). Der Zusammenhang zwischen kognitiver Verschlechterung und den PD-UU lässt sich also auf Ebene der Architektur kortikaler Netzwerke ableiten.

Der Hauptfokus dieser Dissertation lag darin, die Rolle der Kognition in PD-UU zu überprüfen. Die erste Arbeit, die in einer unselektierten Kohorte von PD Patienten durchgeführt wurde, bestätigt hohe Prävalenzrate der PD-UU – etwa 57% der eingeschlossenen Patienten berichteten von unspezifischen Blasenproblemen. Weiterhin wurde das Auftreten von PD-UU mit Beeinträchtigung des globalen kognitiven Status, sowie Visuo-konstruktiven Fähigkeiten und Schwierigkeiten in der Alltagsbewältigung assoziiert.

Die zweite Arbeit baut auf den Ergebnissen der ersten Arbeit auf, wobei die Limitationen aus der explorativen Analyse weitgehend aufgehoben wurden. Die Forschungsfrage richtete ihren Fokus darauf, ob es möglich wäre, einen prototypischen PD-UU Patienten anhand seiner nicht-motorischen Merkmale zu identifizieren. Ein prototypischer PD-UU Patient wies Beeinträchtigungen der exekutiven Funktionen auf, hatte eine hohe Anzahl an anderen nicht-motorischen Symptomen und berichtete niedrige Stigma, bezogen auf die Lebensqualität (Health related Quality of Life, HRQoL). Die Zuordnung der aufgezeigten Gruppenmerkmale wurde mithilfe von der Diskriminanzanalyse überprüft, deren Kombination mit hoher diagnostischer Genauigkeit von 72.4% einen PD-UU Patienten charakterisierte.

Die zweite Hauptfrage dieser Promotion beschäftigt sich mit dem Thema der Validierung eines Algorithmus, der für ein Screening Tool-MoCA (Montreal Cognitive Assessment) entwickelt wurde (Fengler et al., 2016). Wir validierten den neuen Algorithmus und überprüften dessen Sensitivität und Spezifität, kognitive Veränderungen zu diagnostizieren, in einer nicht dementen PD Kohorte.

Identifikation der leichten kognitiven Beeinträchtigung in PD (PD-MCI) ist von hoher Bedeutung, weil die Konversionsrate zur Demenz dadurch erhöht wird (Williams-Gray et al., 2009). Der MoCA-Test wurde als ein sensitives Tool für das Entdecken von leichten kognitiven Beeinträchtigungen und Demenz bei Alzheimer Patienten konzipiert (Nasreddine et al., 2005). Durch Validierungsstudien ist es aber zu einem der wichtigsten Screening Tools im Bereich der PD geworden (Hoops et al., 2009). Ein neuartiger Gewichtungsalgorithmus zeigte einen diagnostischen Vorteil gegenüber der originalen MoCA. In einer nicht dementen PD Kohorte konnten wir zeigen, dass der Cut-Off von zwei Standardabweichung die größte Trennschärfe aufzeigte und mit hoher Sensitivität PD-MCI Patienten identifiziert, die Risiko für Konversion zu Demenz aufzeigen.

Attachment

Published Work:

1. "Association between cognitive impairment and urinary dysfunction in Parkinson's disease"
Published in Journal of Neural Transmission, January 2017
2. "Validation of a novel Montreal Cognitive Assessment scoring algorithm in non-demented Parkinson's disease patients"
Published in Journal of Neurology, January 2018

Submitted Manuscript:

1. "Executive function is related to urinary urgency in non-demented patients with Morbus Parkinson"
Submitted in Neurology, January 2019

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Association between cognitive impairment and urinary dysfunction in Parkinson's disease

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Abstract

Urinary dysfunction (UD) is a common non-motor feature of Parkinson's Disease (PD), and might be secondary to neurodegeneration involving cortical and subcortical brain areas. The possible link between UD and cognitive deficits has never been examined in frontal cortex impairment, and is still not completely understood in PD.

In the present study, 94 PD patients underwent a comprehensive motor, cognitive and non-motor assessment. It was shown that 55.3% of patients reported UD, of which 17% needed specific urological treatment. Patients who reported UD performed worse on global cognition (PANDA, $p=.05$), visuo-constructive functions (CERAD/praxis, $p=.03$; and Figure Test, $p=.03$), and instrumental-activities-of-daily-living functions (IADL, $p=.03$), than patients without UD. The group with UD medication performed worse on global cognition (PANDA, $p=.02$) and visuo-constructive functions (CERAD: praxis, $p=.05$; CERAD: praxis recall $p=.05$) than the UD group without medication, independent of anti-cholinergic treatment effect. Our findings suggest an association between cognitive impairment and UD in PD independent from symptomatic treatment.

Background

Non-motor symptoms are now recognised as part of the typical features of Parkinson's disease, increasing during stages of disease and influencing patients' and their caregivers' quality of life (Martinez-Martin et al. 2011).

Urinary dysfunction (UD) is a common non-motor feature and is typically characterized by urgency, frequency, or nocturia with little or no post-void residuals (Matthew Smith 2015). Several reports suggest that UD is twice as common in PD than in the general population, occurring in 27% to 64% of patients (Winge and Fowler 2006; Winge and Nielsen 2012), according to the different cohorts and diagnostic tools. A high prevalence of UD was reported for PD dementia (PDD) and dementia with Lewy Bodies (Sakakibara et al. 2014; Tateno et al. 2015), suggesting a possible association between this symptom, cognitive impairment and the spreading of cortical alpha-synuclein.

The presence of urinary dysfunction (UD) appears to be modulated by patient's age, disease duration, concomitant medication, and severity of motor symptoms (Sakakibara 2008). It is known that the frontal basal ganglia D1 dopaminergic circuit, which suppresses the micturition reflex in a healthy brain, is abnormal in PD (Winge and Nielsen 2012). Apart from peripheral and basal ganglia involvement, the influence of higher cortical areas has been discussed (Sakakibara et al. 2014), with neuroimaging studies showing that frontal cortical regions are involved in controlling the micturition (Fowler and Griffiths 2010). There is evidence that the neural circuits in frontal areas controlling human behaviour, such as those involved in decision making, attention processes, and integration of extrinsic input, also participate in urinary control (Blackett et al. 2009). Therefore, PD patients whose cognition, especially in frontal lobe functions, is affected, might be of higher risk for UD, since both bladder control and cognition originate from the same brain lesions. Investigating this possible link is the aim of this explorative pilot study.

Patients and Methods

Participants

We included 94 patients with idiopathic PD according to the United Kingdom Brain Bank criteria, who were recruited from the outpatient clinic of the University hospital of Tübingen (Liepelt-Scarfone et al. 2012). The study included patients who: i) were older than 50 years, ii) had optimized medication, iii) had adequate or corrected hearing/visual abilities, and iv) with German as mother tongue. Exclusion criteria were: a) other neurological diseases affecting the central nervous system, b) prior surgery for PD, and c)

MMSE < 18 (the above limit suggested by the local committee to sign an informed consent). The local ethics committee approved the study. Informed consent was obtained from all individual participants.

Assessments

We obtained demographics and a full drug history, which included the total daily dose of all dopaminergics [expressed by the levodopa equivalent daily dose (LEDD) (Tomlinson et al. 2010)], monoamine oxidase, and dopamine agonist medication (Winge et al. 2004). We computed a possible adverse effect of medication-as well parkinsonian as non-parkinsonian, expressed by the anticholinergic risk scale (ARS), as suggested by Crispo and colleagues (Crispo et al. 2016). Patients taking anticholinergics, which can have a negative influence on cognition, were excluded from further analyses. Motor function was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Fahn et al. 1987) and the modified Hoehn-Yahr scale.

Presence and severity of UD was scored on a 5 point scale (0- normal urinary function, 1-increase in urgency and/or frequency, no drug treatment required, 2- urgency and/or frequency, drug treatment required, 3- urge incontinence and/or incomplete bladder emptying needing intermittent catheterization, and 4- incontinence needing indwelling catheter) (Wenning et al. 2004). A scale score ≥ 1 was defined as UD. Patients with a catheter (score ≥ 3) were excluded from further analyses (for demographic data see Supplementary Table 1) as this treatment is only rarely needed in PD and therefore suggests a urologic condition as the cause (Sakakibara et al. 2012).

To assess the major areas of subcortical-frontal and cortical mediated functions affected in PD, a comprehensive test battery was used (Dubois et al. 2007) (see Table 2 for details). Parkinson's disease dementia (PDD) was diagnosed according to the Level II criteria of the Movement Disorder Society (MDS) Task Force (Emre 2007). As the language domain was only assessed with one test, diagnosis of mild cognitive impairment (PD-MCI) was made by use of the Level I criteria of the MDS Task Force criteria (Litvan et al. 2012). Based on the neuropsychological test data, PD-MCI patients were further subdivided into those with single domain MCI (one test within one cognitive domain ≤ 1.5 standard deviation below the population norm described in the handbooks of each test) or multiple PD-MCI (at least two tests in two different cognitive domains below cut-off, see Table 1 for further details). Additionally, self-reported memory status was evaluated using the Memory Assessment Clinical Self-Report (subscales: retention, long term memory, digit memory, daily memory, verbal skill and constructive skills) (Crook and Larrabee 1992). The total score of the Beck Depression Inventory-I (BDI) (Hautzinger et al. 1995) was used to identify depressive symptoms. Presence and severity of neuropsychiatric symptoms was assessed by the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994). Activities of instrumental daily living impairment (IADL) were investigated by using the total score of the Lawton Instrumental Activities of Daily Living (Lawton-IADL)(Graf 2009) and the Nürnberger-Alters Aktivitäten Inventory (NAA-IADL) (Oswald 1999).

Statistical analysis

Data were analysed using SPSS 22 for Windows (SPSS Inc, Chicago, IL, USA). Motor and demographic characteristics and prevalence of cognitive diagnosis of all UD subgroups were analysed using either Mann-Whitney-Tests or χ^2 -statistics ($p < 0.05$ indicating differences between groups). A Mann-Whitney-U Test was used for the comparison of cognition and IADL functions between UD and no-UD groups. For the UD positive groups (treatment vs. no treatment), a binary regression with cognitive test or IADL test as the dependent variable and group membership as the independent variable was used. Gender and education years were included into the model as cofounders. Post-hoc testing was done with the Holm-Bonferroni adapted alpha level ($p = .006$ for Lawton IADL and $p = .004$ for NPI). A non-parametric Mann-Whitney-U test was performed to identify the association between IADL impairment and the cognitive diagnosis (no cognitive impairment (PD-NC) vs. PD-MCI vs. PDD). Further, a non-parametric regression analysis was performed to specify the primary cause on IADL impairment including the cognitive diagnosis (PD-NC vs. PD-MCI vs. PDD) as independent variables, and the UD score, UPDRS-III score, gender and education years as covariates.

Results

Hundred PD patients fulfilled the criteria for PD and were recruited into the study. Mean age was 71 (range: 56-89 years), with 52 (55.3%) patients reporting UD. Sixteen (17%) of examined patients received drug treatment of UD. Four patients (4.3%) had a catheter (score ≥ 3 , all female) and two received anticholinergic medication, which is known to influence cognitive performance in negative matter, were therefore excluded from further analyses. Data of 94 patients were included into the final analysis.

Of all 94 PD patients, 74 (78.7%) were medicated with dopamine agonists-of whom 8 (10.8%) received dopamine agonists as a monotherapy. Twenty (21.3%) of all patients received MAO-inhibitors, of whom 9 (45.0%) as monotherapy; and 78 (83.0%) received levodopa, out of whom 11 (87.0%) with a combination of other dopaminomimetics. Regarding the level of LEDD, MAO-inhibitors and dopamine agonist, we found no significant difference between our study groups (see Table 1 for details).

The study groups differed significantly in gender distribution and educational level (Table 1). Therefore, these were included as confounders for further analyses. In our population, only higher educated males were more likely to receive UD drug treatment, including antispasmodic agents ($n=3$), herbal medications ($n=5$) or alpha blockers ($n=8$). Our groups did not differ in the number of patients diagnosed as PD-MCI or PDD ($p > .05$, see Table 1). Also PD-MCI subtype classification did not differ statistical significantly ($p > .05$) between our study groups, with the following prevalence: PD-MCI single

(19.0% of PD no-UD, 16.6% of UD-non medicated and 18.7% of UD-medicated); PD-MCI multiple (47.7% of PD no-UD, 47.2% of UD-non medicated and 56.3% of UD-medicated).

Patients who reported UD showed lower cognitive performances as reflected by the Parkinson Neuropsychometric Dementia Assessment (PANDA, $p=.05$), Nuernberger Altersinventar (NAI) subtest Figure Test ($p=.03$), and the Praxis subtest of the Consortium to establish a Registry of Alzheimer Disease (CERAD) plus battery, ($p=.03$) compared to patients with no UD. They had lower scores in the Lawton-IADL scale than in those without UD ($p=.03$). Post-hoc comparisons (Holm-Bonferroni method) of the IADL item profile between patients who reported UD and those without UD revealed differences in financial management ($p=.005$).

The comparison analysis for patients who reported UD (patients with/without urological medication) showed following results: patients with medical treatment showed lower cognitive performance reflected by PANDA ($p=.02$), Praxis subtest of CERAD ($p=.05$) and for the Praxis Recall ($p=.05$). An overall effect in IADL or NPI scale was not found. No statistical group differences were found for the self-reported memory complains assessed by the MAC-S scale.

In our post-hoc analysis we found that PD-NC had higher scores (median 23, 14-24 points) on the Lawton IADL scale than both PD-MCI (median 22, 11-24, $p=.008$) and PDD patients (median 18, 10-24 points, $p<.001$). Moreover, PD-MCI and PDD patients differed in their Lawton IADL scores ($p=.004$). To evaluate if the effect on IADL functions was primarily caused by cognitive or bladder dysfunction, we performed a non-parametric regression analysis with cognitive groups as independent variable, the UPDRS III Score, the UD score, gender and education years as covariates; and the total Lawton IADL total as dependent variable. As expected, performance of the three groups differed in their total Lawton IADL scores as follows: $p=.04$ for PD-NC vs. PD-MCI, $p=.001$ for PD-NC vs. PDD and $p=.004$ for PD-MCI vs. PDD. We found that even if the cognitive impairment was a strong predictor of IADL function, also motor performance ($p<.001$) as well as gender ($p=.02$) were significantly associated to the total Lawton IADL score. UD did not achieve significance level ($p=.06$).

Discussion

Urinary dysfunction in PD has received increasing attention in the past years, due to the better knowledge of non-motor symptoms. Our data confirms the high UD prevalence in PD population – 55% reported UD, with 17% receiving UD drug treatment (Araki and Kuno 2000; Winge and Fowler 2006). Our prevalence rate is in accordance with previous data, confirming that UD is recognized as a common, non-motor problem of PD. However the limited sample size should be acknowledged when reviewing the results.

To examine the UD symptoms, we used self-report questionnaires, which are often used to assess urinary problems in PD (Wenning et al. 2004; Winge and Fowler 2006; Winge and Nielsen 2012). Even though our groups did not differ in the motor scale scores (UPDRS III and H&Y Scales), we cannot rule out that the reported urinary problems might be, at least partly, caused by motor, especially gait disorders or other concomitant diseases. Future studies should assess the potential influence of these factors. To exclude other physical causes leading to UD, urological examinations should be taken into account.

It is known that PD medication may influence bladder function in PD patients. Previous findings reported a vast, yet unpredictable influence of dopamine agonists on urodynamic parameters. As our study groups did not differ in their daily dose of varying dopamine agonists, MAO- inhibitors or levodopa levels, we did not control for medication intake. Since no statistical difference was found, we assume that the type of medication was not the primary cause of UD in our sample.

As studies have shown that use of anticholinergic medication may affect cognitive function in PD (Ehrt 2010), we decided to exclude this small group of PD patients from our analysis. However, latter findings (Crispo et al. 2016; Rudolph et al. 2008) show that also the adverse effects related to anticholinergic medication use may cause negative effects in older patients. In our study we compared all medications in our cohorts, using the ARS-Scale as recommended by Crispo and colleagues (Crispo et al. 2016). We did not find significant differences between our study groups. These findings strengthen our assumption that there is an association between bladder dysfunction and cognition in PD.

In our explorative analysis, patients who reported UD performed worse in global cognition (executive and visuo-constructive functions), than patients with no UD complaints. Moreover, patients who received UD drug treatment showed more impairment in global cognitive, as well as in executive, visuo-constructive and IADL functions, compared to patients without UD. It has been shown that different cortical regions and parts of the frontal lobe, which are involved in modulating aspects of cognition and emotions, are also involved in the control processes of bladder control (Fowler and Griffiths 2010). In general, urinary function is influenced by a complex neural system, located in the brain, spinal cord, and peripheral autonomic ganglia. The forebrain's activation of a voluntary voiding is being modulated by the basal ganglia and brain stem circuitry (de Groat et al. 2015; Kitta et al. 2016). In PD, central nervous system pathology is clearly related to UD problems and should be further examined on a cortical as well as a subcortical level.

Depression and anxiety are also known to worsen bladder function (Sakakibara et al. 2013), however our study could not confirm these findings. Within our study population, no difference was found for neuropsychiatric symptoms, neither for the total score, nor for the individual subscale comparisons. Further examinations are required, as the associations could build a more heterogenic phenotype of PD (Fereshtehnejad et al. 2015).

Our findings show that there is a connection between impairment in cognitive functions and UD in PD. The link between autonomic dysfunction (orthostatic hypotension) and cognition has been explored in previous studies (Pillari et al. 2013). Since autonomic dysfunction might appear before PD onset, or during the disease course, whilst cognitive dysfunction rate increases with disease duration (Liepelt-Scarfone et al. 2015), it is important for future studies to explore if this complex relationship is associative or causative. In our group, UD was associated with cognitive dysfunction, independent of disease duration and anti-cholinergic effects. A higher UD impairment was associated with higher impairment in cognition, which implies that UD itself might be an important marker for PDD. To specify the analyses, we divided our cohort as mentioned earlier. Although we included cofounders such as gender and education years, we could not completely exclude that other concomitant medical conditions influenced UD in our sample; therefore our pilot data need to be confirmed in future studies.

Previous studies show that PD patients may experience abnormal urodynamic functions without reporting UD (Araki and Kuno 2000; Uchiyama et al. 2011). In these findings, patients did not contribute to any impairment in IADL. However, in order to score on the questionnaire, patients must acknowledge and/ or be bothered by a given symptom, and /or need to be stressed by the compensatory mechanisms (Winge et al. 2004). As group classification in this study was primarily based on patients' reports, we cannot exclude the possibility that presence of asymptomatic UD might affect cognitive performance. Future studies should therefore, include urological examinations to exclude possible concomitant factors of UD in PD.

In general, patients with UD reported having more problems in their activities of daily living than those with no UD. Hence, impairment of IADL function might be an indicator for accompanying cognitive worsening. It was shown that even mild cognitive impairment, which precedes PDD in many cases, is associated with IADL problems (Leroi et al. 2012). In our post hoc analysis we found that only cognitive and motor impairment influence the perceived worsening of IADL in a negative matter. Our analysis therefore showed that severity of UD did not additionally contribute to the reported IADL problems. Our findings are in accordance with results from Uchiyama and colleagues (Araki et al. 2000; Uchiyama et al. 2011), who also found that asymptomatic urinary problems did not affected IADL function in PD. However, more research is needed to clarify the link between cognitive performance, urinary functions and the profile of IADL complaints in PD.

Our study groups did not differ in age, disease duration, or motor severity. Previous studies showed correlations between UD and either disease stage, motor severity (Araki and Kuno 2000; Yamamoto et al. 2009), or age (Campos-Sousa et al. 2003), while others failed to do so (Winge et al. 2006). Higher educated males were more likely to report UD drug treatment in our sample, which, even if statistically corrected, is a limitation of our study. Presence and severity of UD might be of great heterogeneity, unfortunately, the origin and UD disease onset were not assessed in the present cohort. Since we compared parkinsonian medication, we can surely rule out its influence on UD in our sample. Future studies should distinguish in more detail whether the occurring symptom can be related to other primary causes.

Our explorative analysis suggests that cognitive function may be different in PD patients with and without UD. Since urinary autonomic dysfunctions are often difficult to medicate, a deeper understanding of the association between cognitive worsening and UD and its possible causality can help to define a more holistic model of urinary dysfunction in PD.

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Table 1: Demographic and clinical characteristics of subjects with and without self-reported urinary dysfunction (UD)

| Variables | Total | No UD | UD | <i>p</i> value no-UD vs. UD | UD without treatment | UD with treatment | <i>p</i> value for both UD groups |
|-----------------------------|-------------------|-----------------------|--------------------|-----------------------------------|-------------------------|----------------------|---|
| Number of Subjects, n(%) | 94 (100%) | 42 (44.7%) | 52 (55.3%) | | 36 (38.3%) | 36 (38.3%) | |
| Male gender, n (%) | 60 (63.8%) | 23 (54.8%) | 36 (69.2%) | .10 | 20 (55.5%) | 16 (100%) | .003 |
| Years of Age | 71.0 (56/89) | 71.1 (56/83) | 70.93(58/89) | .86 | 69.6 (58/84) | 72.7 (62/89) | .25 |
| Years of Education | 12.0 (8/20) | 12.0 (8/19) | 12 (8/20) | .77 | 11.0 (8/19) | 13.5 (11/19) | .01 |
| Years of Disease duration | 6.4 (1.2/24.4) | 7.8 (1.2/19.4) | 5.86 (2.6/24.4) | .88 | 5.8 (2.6/22.9) | 6.4 (4.2/24.4) | .82 |
| PD-MCI, n (%) | 46 (48.9%) | 26 (50.0%) | 20 (47.6%) | .48 | 17(47.2%) | 9 (56.3%) | .81 |
| PDD, n (%) | 13 (13.8%) | 3 (7.1%) | 10 (19.2%) | .10 | 5 (13.9%) | 5 (31.3%) | .23 |
| LEDD | 615 (0/4273.5) | 552.5 (100/4273.5) | 620 (0/1661) | .66 | 620 (0/1650) | 655 (297/1661) | .68 |
| MAO Daily Dose | 0 (0/203.5) | 0 (0/203.5) | 0 (0/151) | .75 | 0 (0/150) | 0 (0/151) | .87 |
| Dopamine Agonist | 74 (78.7%) | 33 (78.6%) | 41 (97.6%) | .85 | 29 (90.1%) | 12 (75%) | .87 |
| Dopamine Agonist Daily Dose | 0 (0/203.5) | 0 (0/203.5) | 0 (0/150) | .78 | 0 (0/150) | 0 (0/52.5) | .82 |
| Pergolide | 0 (0/600) | 0 (0/0) | 0 (0/600) | .23 | 0 (0/600) | 0 (0/0) | .12 |
| Ropinirole | 0 (0/0) | 0 (0/0) | 0 (0/0) | .17 | 0 (0/480) | 0 (0/160) | .93 |
| Cabergoline | 0 (0/533) | 0 (0/533) | 0 (0/533) | .39 | 0 (0/0) | 0 (0/533) | .19 |
| Bromocriptine | 0 (0/0) | 0 (0/0) | 0 (0/0) | | 0 (0/0) | 0 (0/0) | |
| COMT Inhibitor | 0 (0/0) | 0 (0/0) | 0 (0/0) | .49 | 0 (0/1) | 0 (0/1) | .16 |
| Selegeline | 0 (0/2) | 0 (0/2) | 0 (0/2) | .83 | 0 (0/2) | 0 (0/2) | .52 |
| ARS, n (%) | | | | .41 | | | .17 |
| 1 | 21 (22.3%) | 7 (16.7%) | 14 (26.8%) | | 12 (33.3%) | 2 (12.5%) | |
| 2-3 | 59 (62.8%) | 29 (69.0%) | 30 (57.8%) | | 18 (50.0%) | 12 (75.0%) | |
| 4+ | 14 (14.9%) | 6(14.3%) | 8 (15.4%) | | 6 (16.7%) | 2 (12.5%) | |
| Beck Depression Inventory | 9.0 (0/34) | 7.5 (0/34) | 9 (1/30) | .48 | 9.0 (1/20) | 6.0 (1/30) | .56 |
| Motor performance | | | | | | | |
| UPDRS III | 31 (10/73) | 27.0 (10/73) | 34 (14/58) | .50 | 34 (15/53) | 33 (14/58) | .81 |
| Hoehn & Yahr n (%) | | | | .16 | | | .49 |
| 1 | 1 (1%) | 1 (2.4%) | 0 (0%) | | 0 (0%) | 0 (0%) | |
| 1.5 | 5 (5.3%) | 3 (7.1%) | 2(3.8%) | | 2(3.8%) | 1 (6.2%) | |
| 2 | 34 (36.9%) | 15 (35.7%) | 19 (36.5%) | | 19 (36.5%) | 4 (25%) | |
| 2.5 | 14 (14.7%) | 2 (4.8%) | 12 (23.1%) | | 12 (23.1%) | 4 (25%) | |
| 3 | 30 (31.6%) | 16 (38.1%) | 14 (26.9%) | | 14 (26.9%) | 5 (31.3%) | |
| 4 | 10 (10.5%) | 5 (11.9%) | 5 (9.4%) | | 5 (9.4%) | 2 (12.5%) | |

If not other indicated values were given in Median (range); post-hoc comparison: ^ano UD vs. UD without treatment, ^bno UD vs. UD with treatment, ^cUD without vs. UD with treatment; *LEDD*: Levodopa equivalence daily dose; *UPDRS III*: Unified Parkinson Disease Rating Scale, *ARS*: Anticholinergic Risk Scale

Table 2: Neuropsychological test results.

| Assessments | Total | no-UD | UD | p value no-UD vs. UD | UD without treatment | UD with treatment | p value for both UD groups |
|---------------------------------------|-----------------|-----------------|------------------|----------------------------|-------------------------|----------------------|----------------------------------|
| Cognitive Screening Assessments | | | | | | | |
| Global Cognition: | | | | | | | |
| PANDA | 21 (4/30) | 23 (5/30) | 19 (4/30) | .05 | 19 (4/30) | 16.5 (8/27) | .02 |
| MMSE | 27 (19/30) | 28 (19/30) | 27 (20/30) | .42 | 27 (20/30) | 26.5(22/30) | .98 |
| Executive Domaine: | | | | | | | |
| Tower of London | 41 (0/100) | 36 (0/99) | 42 (0/100) | .81 | 42 (0/100) | 31 (13/80) | .90 |
| CERAD-Verbal Fluency | -.60 (-3.7/1.3) | -.65 (-1.9/0.9) | -.6 (-.37/1.3) | .55 | -.70 (-3.7/1.3) | -.50 (-1.7/1.2) | .59 |
| Trail Making Test-Part B | -.50 (-3.1/3.3) | -.45 (-3.1/2.8) | -.50 (-3.0/3.3) | .99 | .20 (-3.0/3.1) | -1.2 (-3.0/3.3) | .25 |
| Working Memory: | | | | | | | |
| WMSR-Digit Span forward | 53 (2/99) | 53 (2/98) | 53 (5/99) | .58 | 53 (5/99) | 53 (11/98) | .85 |
| WMSR-Digit Span backwards | 27 (2/94) | 45.5 (2/85) | 27 (2/94) | .12 | 27 (2/93) | 27 (2/94) | .60 |
| Attention: | | | | | | | |
| TAP-Go/No Go, Median RT | 42 (0/ 99) | 46 (0/ 99) | 31 (0/99) | .51 | 34 (0/94) | 31 (2/99) | .96 |
| Trial Making Test Part A | -.50 (-3.3/3.2) | -.50 (-3.3/1.9) | -.70 (-3.1/3.2) | .52 | -.60 (-3.3/3.2) | -1.5 (-3.1/.60) | .27 |
| Memory: | | | | | | | |
| -Word-List Learning | -.80 (-3.7/2.1) | -.30 (-3.7/1.9) | -.60 (-3.3/2.1) | .66 | -.90 (3.6/ 2.1) | -1.2 (-3.4/ 1.7) | .38 |
| -Word-List Recall | -.50 (-3.3/2.2) | -.10 (-2.5/1.9) | -.60 (-3.3/ 2.2) | .18 | -.60 (-3.3/2.2) | -.50 (-2.1/ 1.6) | .21 |
| -Word-List Recognition | .50 (-3.2/1.4) | .50 (-3.1/1.4) | .40 (-3.2/ 1.4) | .79 | .50 (-3.2/1.1) | -.75 (-2.2/1.0) | .75 |
| -Logical Memory I | 18 (0/98) | 13 (2/98) | 25 (0/98) | .42 | 13 (1/98) | 23.5 (0/85) | .27 |
| -Logical Memory II | 22 (0/99) | 12 (2/99) | 25 (0/97) | .22 | 22 (0/97) | 39(0/77) | .15 |
| Language: | | | | | | | |
| CERAD-Boston Naming Test | -.30 (-3.0/1.6) | -.05 (-3.0/1.4) | -.50 (-3.0/ 1.6) | .07 | -.30 (-3.0/1.6) | -.50 (-2.1/1.1) | .94 |
| Visuo-Construction: | | | | | | | |
| CERAD-Praxis | -1.1 (-4.7/1.5) | -1.0 (-3.6/1.3) | -1.0 (-4.7/ 1.5) | .03 | -1.4 (-4.7/1.5) | -2.0 (-4.2/.09) | .05 |
| CERAD-Praxis Recall | -.80 (-4.1/2.2) | -.50 (4.1/2.2) | -1.0 (-3.5/ 1.8) | .08 | -1.0 (-3.5/1.8) | -0.8 (-4.1/2.2) | .05 |
| Object decision | 38.1(0/100) | 39.7(0/91) | 38.1(2/100) | .27 | 38.1(5/100) | 38.1(2/76) | .77 |
| Figure test | 56(0/95) | 65(0/95) | 45 (3/92) | .03 | 45(5/88) | 40.5(0/92) | .63 |
| Berlin Apraxia Test | 34(17/24) | 33(20/40) | 34 (17/ 42) | .78 | 34(17/24) | 35.5(25/41) | .78 |
| Activity of Daily Living Assessments: | | | | | | | |
| Lawton IADL scale | 23 (10/24) | 23(11/24) | 22 (10/24) | .03 | 23(15/24) | 19.5(10/24) | .09 |
| NPI Total | 7 (0/50) | 6 (0/45) | 7 (0/50) | .74 | 7(0/34) | 7.5 (0/50) | .14 |
| Delusion | 0 (0/12) | 0 (0/9) | 0 (0/12) | .87 | 0 (0/2) | 0 (0/12) | .29 |
| Hallucination | 0 (0/12) | 0 (0/9) | 0 (0/12) | .80 | 0 (0/12) | 0 (0/12) | .99 |
| Arousal | 0 (0/9) | 0 (0/9) | 0 (0/9) | .29 | 0 (0/2) | 0 (0/9) | .04 |
| Depression | 0 (0/9) | .50 (0/9) | 0 (0/8) | .08 | 0 (0/8) | 0 (0/8) | .97 |
| Anxiety | 0 (0/9) | 0 (0/9) | 0 (0/8) | .09 | 0 (0/8) | 0 (0/2) | .69 |
| Euphoria | 0 (0/3) | 0 (0/1) | 0 (0/3) | .46 | 0 (0/3) | 0 (0/0) | .51 |
| Apathy | 0 (0/9) | 0 (0/8) | 0 (0/9) | .72 | 0 (0/8) | 0 (0/9) | .19 |
| Disinhibition | 0 (0/4) | 0 (0/3) | 0 (0/4) | .02 | 0 (0/4) | 0 (0/2) | .82 |
| Irritability | 0 (0/12) | 0 (0/12) | 0 (0/9) | .35 | 0 (0/9) | 0 (0/6) | .60 |
| Motor movement | 0 (0/8) | 0 (0/8) | 0 (0/3) | .69 | 0 (0/3) | 0 (0/0) | .32 |
| Sleep | 0 (0/8) | 0 (0/12) | 0 (0/3) | .25 | 0 (0/8) | 2 (0/12) | .36 |
| Appetite | 0 (0/12) | 0 (0/12) | 0 (0/8) | .49 | 0 (0/8) | 0 (0/8) | .31 |

All values are given as median and range; Berlin Apraxia Test (Liepelt-Scarfone, I. (2007). Der Berliner-Apraxie-Test für ideomotorische und ideatorische Apraxie - Bestimmung der Itemkennwerte. *Zeitschrift für Neuropsychologie*, 18(3), 193-206); Consortium to Establish Registry for Alzheimer's Disease (CERAD-plus, Memory Clinic-NPZ (2005). The Consortium to Establish a Registry of Alzheimer's Disease CERAD-Plus. Basel: Memory Clinic-NPZ); *Lawton IADL*: Lawton Instrumental Activity of Daily Living Function scale; *MMSE*: Mini-Mental State Examination (Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*, 12(3), 189-198.); *NAA*: Nürnberger-Alters-Aktivitäten-Scale. Das Nürnberger Altersinventar (kurz: NAI). Göttingen: Hogrefe); *PANDA*: Parkinson Neuropsychometric Dementia Assessment (Kalbe, E. (2007). Sensitivity and Specificity of the "Parkinson Neuropsychometric Dementia Assessment" (PANDA): Results of the GEPAD-Study. *Aktuelle Neurologie*, 34, 140-146); Test for Attentional Performance (TAP- Zimmermann, P., Fimm, B. (2002). Testbatterie zur Aufmerksamkeitsprüfung (Version 1.7): Psytests, Herzogen; Tower of London (ToL, Toucha, L. (2004). Turm von London - Deutsche Version TL-D. Göttingen: Hogrefe; Object decision (Warrington, E., James, M. (1992). VOSP - Testbatterie für visuelle Objekt- und Raumwahrnehmung. Göttingen: Hogrefe Verlag; RT. Reaction time, Wechsler Memory Scale revised (WMS-R,- Härting, C., Markowitsch, H.J., Neureld, H., Calabrese, P., Deisinger, K. & Kessler, J. (2000). Wechsler Gedächtnistest - Revidierte Fassung (WMS - R): Joseph Kessler (Hrsg.)); CERAD values are given as z-values, WMS-R, ToL, Figure test, TAP are given as percentage range, BAXT and PANDA scores are given as raw values. If available we chose norms

Supplementary Table 1. Demographic and clinical characteristics of subjects with self-reported urinary dysfunction, excluded from further analysis.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---------------------------|-----------|-----------|-----------|-----------|
| Gender | w | w | w | w |
| Years of Age | 70 | 78 | 65 | 70 |
| Years of Education | 8 | 9 | 9 | 9 |
| Years of Disease duration | 8.25 | 12.25 | 11.83 | 19.5 |
| LEDD | 590 | 710 | 1030 | 320 |
| Beck Depression Inventory | 13 | 11 | 22 | 13 |
| UPDRS III | 35 | 29 | 48 | 43 |
| Hoehn & Yahr | 2 | 2.5 | 4 | 4 |
| MMSE | 28 | 28 | 15 | 23 |

LEDD: Levodopa equivalence daily dose; UPDRS III: Unified Parkinson Disease Rating Scale; MMSE: Mini-Mental State

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Validation of a novel Montreal Cognitive Assessment scoring algorithm in non-demented Parkinson's disease patients

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Abstract

Introduction: The early diagnosis of mild cognitive impairment (PD-MCI) in Parkinson's disease (PD) is essential as it increases the future risk for PD dementia (PDD). Recently, a novel weighting algorithm for the Montreal Cognitive Assessment (MoCA) subtests has been reported, to best discriminate between those with and without cognitive impairment in PD. The aim of our study was to validate this scoring algorithm in a large sample of non-demented PD patients, hypothesizing that the weighted MoCA would have a higher diagnostic accuracy for PD-MCI than the original MoCA.

Methods: In 202 non-demented PD patients, we evaluated cognitive status, clinical and demographic data, as well as the MoCA with a weighted and unweighted score. Receiver Operating Characteristic (ROC) curve analysis was used to evaluate discriminative ability of the MoCA. Group comparisons and ROC analysis were performed for PD-MCI classifications with a cut-off ≤ 1 , 1.5, and 2 standard deviation (SD) below appropriate norms.

Results: PD-MCI patients scored lower on the weighted than the original MoCA version ($p < 0.001$) compared to PD patients with normal cognitive function. Areas under the curve only differed significantly for the 2 SD cut-off, leading to an increased sensitivity of the weighted MoCA score (72.9% vs. 70.5%) and specificity compared to the original version (79.0% vs. 65.4%).

Conclusions: Our results indicate better discriminant power for the weighted MoCA compared to the original for more advanced stages of PD-MCI (2 SD cut-off). Future studies are needed to evaluate the predictive value of the weighted MoCA for PDD.

Keywords: Parkinson's disease, cognition, screening assessment, MoCA

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in Europe [1]. First described as a movement disorder, it is now known PD patients also suffer from a variety of non-motor symptoms. Loss of cognitive functions is very common in PD, even in the early disease stages [2,3]. In the non-demented PD population, around 27% show signs of mild cognitive impairment (PD-MCI) [4]. Early and valid detection of PD-MCI is increasingly regarded as very important in clinical practice, due to its predictive value for Parkinson's disease dementia (PDD) [5]. Furthermore, cognitive decline has a strong effect on patients' quality of life [6], often leading to nursing home placement and increased risk of mortality [7]. Therefore, an early and valid diagnosis of cognitive impairment in the daily clinical routine is crucial. However, identifying PD-MCI accurately in a clinical interview alone seems to be inadequate [8]. A sensitive test, economic in time, is needed.

Several screening tools exist, and one of the most favored cognitive screening tools to identify PD-MCI is the Montreal Cognitive Assessment (MoCA) [9]. However, the MoCA was originally designed as a global cognitive assessment to detect mild cognitive impairment in Alzheimer's disease (AD). There are studies validating the MoCA in PD, showing a clear benefit of the MoCA for detecting PD-MCI and PDD compared to the Mini-Mental State Examination (MMSE) [10-12]. Compared to the initial validation study in AD, some studies with PD cohorts suggest a different cut-off score for the MoCA to classify cognitive impairment [11,10]. Though, there are also limitations to the MoCA regarding its application to a PD patient group. Fengler et al. [13] criticized that the scoring system of the MoCA does not consider subtest discriminant power to distinguish between cognitive impairment and no cognitive impairment in PD. Considering the importance of executive dysfunctions in PD, it should be noted that the three subtests of visuospatial and executive functions only represent 30% of the total score, compared to orientation, which represents 20%. However, it is known that executive functions are the most prominent and often the first cognitive deficits noticeable in PD [14]. Therefore, it is a crucial domain to diagnose cognitive impairment in PD. Fengler et al. [13] developed a weighting system for the MoCA subtests by addressing the diagnostic accuracy of each subtest for cognitive impairment in PD (PD-MCI and PDD) with a receiver operating characteristic (ROC) analysis. By calculating the area under the curve (AUC) for each subtest, the authors weighted visuospatial and executive functions higher than before. For example, the Trail Making Test received only one point on the original MoCA and now four points, and word list learning performance is scored with three points, whereas it did not receive any points on the original MoCA. In contrast, orientations' weight was reduced from six points to one point out of 30 compared to the original version. When testing their weighted scoring system in a small PD patient group, they found that the sensitivity of the weighted MoCA was higher than the original version, without loss of specificity for discriminating PD patients with any cognitive impairment from those with normal cognition.

Based on their low sample size, which included patients with PDD, it is still unclear whether this novel weighted MoCA score discriminates between PD-MCI and PD patients with no cognitive impairment. Thus, the aim of this present study was to validate the weighted MoCA scoring algorithm in a large non-demented PD cohort. We hypothesized that the weighted MoCA score would have a better diagnostic accuracy for PD-MCI and would be more highly correlated to results in other neuropsychological assessments than the unweighted original version.

Methods

Participants

Two hundred and forty-one PD patients were recruited from the outpatient clinic of the University of Tübingen as part of the “Amyloid-Beta in cerebrospinal spinal fluid as a risk factor for cognitive dysfunction in Parkinson’s Disease” (ABC-PD) study. Patients between 50 and 85 years of age diagnosed with PD according to the United Kingdom PD Brain Bank criteria [15], who agreed to a lumbar puncture, were recruited. Exclusion criteria for the ABC-PD study participation were: diagnosis of PDD according to Level II consensus guidelines [16], severe concomitant diseases affecting patients’ judgement for informed consent, and history of substance abuse (except for nicotine). In addition, patients with deep brain stimulation (DBS) were excluded. In the present study, only patients with a complete MoCA assessment were analyzed; data of 12 (5%) patients with a missing MoCA were excluded from the analysis. Furthermore, 7 (2.9%) patients with concomitant neurological diseases (e.g. history of stroke, epilepsy) and 23 (9.5%) PD patients with a moderate or severe depression as defined by a cut-off ≥ 20 points on the Beck Depression Inventory II (BDI-II) [17], were also excluded to ensure that cognitive dysfunctions were primarily caused by PD [18,19]. In total, 202 PD patients were included in the present data analysis. The study was approved by the local ethics committee of the University of Tübingen. All patients gave written informed consent.

Assessments

Demographics and medication intake to express the levodopa equivalent daily dose (LEDD) [20] were collected. The Unified Parkinson’s Disease Rating Scale part III (UPDRS-III) and the Hoehn and Yahr Stage (H&Y) were used to rate severity of PD-related motor symptoms. The Beck Depression Inventory II was applied to screen for signs of depression [17].

The MoCA is a cognitive screening tool developed to define mild cognitive impairment, assessing executive and visuospatial functions, abstraction, naming, orientation, attention, language, and memory

performance. In this study, the original subtest scoring of the MoCA [9], as well as a new weighted scoring algorithm, was calculated [13]. The new scoring algorithm evaluates each domain by its individual discriminant power for PD with cognitive impairment. A maximum of 30 points can be reached in both versions. The MoCA was conducted before the neuropsychological test battery on the same day.

To distinguish between patients with and without cognitive impairment, a comprehensive neuropsychological battery was applied. Executive functions were assessed by semantic and phonemic fluency, and the Trail Making Test part B of the Consortium to Establish a Registry for Alzheimer's disease - Plus (CERAD-Plus) [21]. Memory performance was tested using the following three CERAD-Plus subtests: word list learning, word list recall, and praxis recall. Scores of the Praxis (CERAD-Plus) and the Fragmented Words test (Leistungsprüfsystem, LPS 50+) [22] constituted visuospatial abilities. Attention was assessed with the Digit-Number and Letter-Number-Sequencing subtest of the Wechsler Adult Intelligence Scale (WIE) [23]. The Boston Naming Test (CERAD-Plus) and the Similarities subtest of the WIE evaluated language function. The CERAD-Plus corrects for education, age, and gender, while the LPS 50+ and WIE are normed for age.

Diagnosis of PD-MCI was made according to the MDS Level-II criteria [24]. Impairment in at least two neuropsychological tests (≤ 1.5 standard deviations (SD) from the population mean reported in the test handbooks) either in one or two cognitive domains was required for diagnosis of PD-MCI. PD patients who did not meet these criteria were classified as having normal cognitive function (PD-NC). Additionally, we classified PD-MCI with a cut-off of 1 SD and 2 SD equal or below the population mean to classify cognitive impairment in an early and advanced stage in PD.

Statistical Analysis

Study data were collected and managed using REDCap electronic data capture [25]. Data analysis was performed by use of the IBM SPSS Statistics version 23 and the statistical software MedCalc (Version 17.1, MedCalc Software). Figures were created using Microsoft Excel 2013. Except for the UPDRS-III score, data were not normally distributed, as verified by the Shapiro-Wilk test. Therefore, the Pearson chi-squared test (gender and Hoehn & Yahr stage), independent-samples *t*-test (UPDRS-III score) and the Mann-Whitney-*U*-test (all other variables including MoCA) were conducted for between-group comparisons of PD-NC and PD-MCI. The Wilcoxon-Test was used to compare the original and weighted MoCA scores in all PD patients and cognitive subgroups. We also calculated the score difference of the two MoCA versions by subtracting the weighted MoCA scores from the original MoCA scores. With the Mann-Whitney-*U*-test we compared the MoCA score difference between PD-NC and PD-MCI.

A ROC analysis was conducted to validate the diagnostic accuracy of the original and weighted MoCA by means of sensitivity and specificity. The Youden's index was calculated to define the optimal cut-off for the original and weighted MoCA for PD-MCI.

All group comparisons and ROC analyses were applied independently to each of the three PD-MCI classifications by using a cut-off of either ≤ 1 SD, 1.5 SD, or 2 SD below the appropriate norms. The Spearman correlation coefficient (r_s) was used to evaluate the strength of the association between the two MoCA scores. To identify the congruent validity of both MoCA scores, the scores were correlated with the average z-values of all neuropsychological tests assigned to their respective cognitive domain.

Results

All 202 PD patients were classified according to the three differing PD-MCI classification approaches. The 1 SD cut-off led to 74 PD-NC (36.6%) and 128 (63.4%) PD-MCI patients, the 1.5 SD cut-off to 125 (61.9%) PD-NC and 77 (38.1%) PD-MCI patients, and the 2 SD cut-off to 162 (80.2%) PD-NC and 40 (19.2%) PD-MCI patients. In general, the PD-MCI patients suffered from more severe motor problems (see Table 1 for details) and showed significantly lower test performances on all neuropsychological tests and cognitive domains than PD-NC patients ($p \leq 0.001$) (for details we refer to Online Resource Table 1). According to the 1, 1.5, or 2 SD cut-off, 93.8%, 93.5%, and 95.0% respectively, of all PD-MCI patients were classified as multi domain PD-MCI.

The correlation between the original and weighted MoCA score was high ($r_s = 0.89$, $p < 0.001$). In the total PD sample, the score range of the original MoCA varied between 16 and 30 (Median, Mdn = 26) points and on the weighted MoCA score between 11 and 30 (Mdn = 26) points.

For all PD-MCI classifications in both the original and weighted MoCA scores, PD-MCI patients had significantly lower values than the PD-NC group ($p < 0.001$). In the PD-MCI groups, the weighted MoCA had significantly lower values than the original MoCA across all classifications ($p < 0.001$) (see Figure 1 for details). In the PD-NC patient groups, the original and weighted MoCA did not differ (1 SD: $p = 0.06$; 1.5 SD: $p = 0.13$), except for the 2 SD cut-off, where PD-NC patients showed a significantly lower MoCA score in weighted MoCA compared to the original MoCA (Mdn = 27, range: 14-30 vs. 27, 18-30, $p = 0.005$) (see Figure 1 for details). Comparing the score difference between the original and weighted MoCA revealed significantly higher differences for PD-MCI than PD-NC for all classifications (1 SD: Mdn: 1 vs. 0; $p = 0.029$; 1.5 SD: 1 vs. 0; $p < 0.001$; 2 SD: 2 vs. 0; $p < 0.001$). Both MoCA versions were moderately associated with each cognitive domain ($0.38 \leq r_s \leq 0.52$) and did not statistically differ in the strengths of association to each cognitive domain ($p > 0.05$) (see Table 2 for details).

AUC values of the original (0.76, 95% confidence interval, CI: 0.70 – 0.82) and weighted (0.81, CI: 0.75 – 0.86) version varied significantly in the 2 SD classification ($p = 0.044$), but not for the classification of

PD-MCI according to the 1 SD ($p = 0.32$) and 1.5 SD cut-offs ($p = 0.15$). The ROC analysis identified different cut-offs maximizing both sensitivity and specificity for the original and weighted MoCA for the diagnosis of PD-MCI (Table 3). For both MoCA versions, an optimal cut-off of 26 was revealed using the 1 SD cut-off to define PD-MCI. Sensitivity showed a tendency to increase from 57.8% to 64.1% and specificity decreased slightly from 86.5% to 77.0% because of the weighted MoCA, leading to a slightly increased positive predictive value (PPV) from 54.2% to 55.3% and decreased negative predictive value (NPV) from 88.1% to 82.8% compared to the original version. With the 1.5 SD cut-off for defining PD-MCI, an optimal cut-off of 27 was revealed for the original MoCA and 26 for the weighted version. Here, due to the weighted MoCA, sensitivity slightly decreased from 77.9% to 75.32% and specificity showed a tendency to increase from 60.8% to 67.2% compared to original MoCA. The PPV remained stable (81.7 vs. 81.6%) and the NPV increased from 55.0% to 58.6% with the weighted MoCA. By using a 2 SD cut-off to classify PD-MCI, an optimal cut-off of 26 was revealed for the original MoCA and 24 for the weighted version. Sensitivity slightly increased from 70.0% to 72.5% due to the weighted MoCA and specificity also increased from 65.4% to 79.0% compared to original MoCA. Therefore, the PPV increased from 89.8% to 92.1% and the NPV increased from 33.3% to 46.0%.

Discussion

The purpose of the present study was to validate a novel weighted MoCA scoring algorithm for the diagnosis of PD-MCI in a large sample of non-demented PD patients.

The main results are that (i) both the original and the weighted MoCA scores differed significantly between PD-NC and PD-MCI patients, (ii) within PD-MCI patients, the weighted MoCA scores were significantly lower than those for the original MoCA, (iii) diagnostic accuracy of the two MoCA versions was found to be highly dependent on the cut-off score used to classify PD-MCI, and (iv) the association of both MoCA scores to the neuropsychological domain scores was comparable.

In the present study the cut-offs for the original and weighted MoCA score were determined by maximizing the ratio of sensitivity and specificity (defined by the Youden's index). For each version, the optimal cut-off was analysed to ensure the highest diagnostic accuracy for PD-MCI of each MoCA score. With a cut-off ≤ 1.5 SD to define PD-MCI, we found an optimal cut-off of 26 for the weighted MoCA and 27 for the original MoCA. Therefore, our proposed cut-off for the original MoCA version is slightly higher than that of Nasreddine et al. [9], who recommended a score of 26. However, their suggestion applies to AD patients and is therefore not necessarily applicable to PD patients. Other studies have already discussed an optimal cut-off in PD. Using a 1.5 SD cut-off to identify patients with any cognitive impairment, Hoops et al. [11] found a cut-off score of 25, which is two points lower than ours. However, the cut-off was not only defined for PD-MCI but also PDD patients (summarized as any cognitive impairment), which might explain the lowered cut-off score. Dalrymple-Alford et al. [10], suggest a cut-

off at 26 points for PD-MCI (also defined by a 1.5 SD cut-off). Our results for the original MoCA do not support these findings, as our results suggest a slightly higher MoCA cut-off at 27 points. Defining PD-MCI in our sample with a 1 SD cut-off, revealed optimal cut-off scores of 26 for both the original and weighted MoCA. With a 2 SD cut-off, for the original MoCA a cut-off 26 was identified, and for the weighted MoCA a distinctly lowered cut-off of 24. However, there are no studies confirming this cut-off for early and later stages of PD-MCI. More studies in large PD samples are needed to confirm the diagnostic cut-off of the MoCA.

With a 1.5 SD cut-off for PD-MCI, we did not find a significant difference between the AUC of the ROC analysis for the two MoCA versions. Due to the weighted MoCA, sensitivity was slightly lowered by 2.6% and specificity increased by 6.4 % compared to the original MoCA. Compared to the initial study, sensitivity and specificity are altogether lowered for the weighted MoCA. We also did not find a significant difference of the AUC with a 1 SD cut-off. This does not support the notion of a superior discriminant power of the weighted MoCA score. However, with a 2 SD cut-off to define PD-MCI, the weighted MoCA seems to be advantageous to the original MoCA. The AUC level of the weighted MoCA was significantly higher than the AUC of the original version (AUC: 0.81 vs. 0.76; $p = 0.044$), which led to an increased sensitivity (70.0% vs. 72.5%) and specificity (65.4 vs. 79.0%). This improvement is also represented by a high PPV of 92.1% and moderate NPV of 46.3%. This was an unexpected finding as the weighted MoCA places a higher priority on executive function, which is considered to be highly frequent in early stages of PD-MCI. However, the weighted MoCA takes visuospatial deficits more into account. Lower visuospatial cognitive function has been found to be associated to a faster cognitive decline and progression to PDD.

The fact that patients with PD-MCI not only scored significantly lower on the weighted than the original MoCA version, but that the score differences between the original and weighted version were substantially larger in PD-MCI than PD-NC, further indicates that the weighted MoCA score reflects cognitive impairment associated to PD-MCI to a greater degree. This effect was found to be independent of the applied PD-MCI classification cut-off. Cognitive impairment in PD is highly heterogeneous and its severity might reflect a continuum rather than a sudden onset of dysfunction. So far, progression of the cognitive decline is only partly understood; while some patients develop PDD within a short time period, others remain stable or even return to a non-impaired level [26,27,2]. However, no reliable, purely cognitive predictor, has been identified to encircle a risk group for PDD among PD-MCI. In summary, our findings show that the weighted MoCA detects cognitive dysfunction in PD-MCI to a greater degree, especially in more advanced stages of cognitive impairment. It is possible that PD-MCI patients scoring lower on the weighted MoCA version might be at higher risk for conversion to PDD than PD-MCI patients scoring higher on the weighted MoCA. In the PD-NC group, the weighted MoCA did not differ significantly from the original for the 1 SD and 1.5 SD cut-off for PD-MCI. However, at a 2 SD cut-off, PD-NC patients scored significantly lower in the weighted MoCA than in the original MoCA. By application of this cut-off we suggest that there are at least some patients with cognitive impairment at a mild stage in the PD-NC group. In our sample, deficits of those persons could be better detected by the weighted than the original

MoCA. To further investigate the notion of a possible risk group, longitudinal studies are needed to monitor patients' disease progression in large PD samples. In our study, the low MoCA scores pose the question of whether those patients might already have PDD. However, patients did not show any signs of activity of daily living dysfunctions, which is the core criteria for PDD diagnosis.

Correlations between both MoCA versions and each cognitive domain also ranged at a moderate level and did not differ significantly, indicating that both versions reflect cognitive domains well.

As a limitation, the present study did not include patients with PDD; therefore, we do not know whether we could not replicate the results from the validation study due to these missing PDD patients, or because of a possible invalidity of the scoring algorithm. Another important difference compared to the study of Fengler et al. [13] is the exclusion of patients with moderate or severe depression in our analysis. In PD, depression is very common [28] and it is well-known that occurrence of depression has a negative influence on cognitive functions [18]. Hence, it is possible that the development of the new weighted scoring algorithm was, at least partly, affected by the presence and severity of depression. In our cohort, cases of moderate and severe depression were excluded and BDI-II total scores did not differ significantly between the remaining PD-NC and PD-MCI patients. Therefore, we concluded that cognitive functions could not be ascribed to severity of depression in our sample. Also compared to the initial study, we excluded patients with DBS. Cognitive decline after DBS surgery in PD has been controversially discussed [29,30]. To diminish this possible cause of cognitive impairment we did not include patients with DBS.

It is important to mention that differences in the data between Fengler et al. [13] and our study might result from differences in the neuropsychological test assessments utilized to classify PD-MCI. Both studies used the CERAD-Plus test battery to assess memory, executive functions, and, to some extent, visuospatial and language impairment. However, some tests differ, especially in the attention domain. For more details see Online Resource Table 2. This might lead to varying interpretation of cognitive impairment in patients, even though both studies used the MDS Level II criteria to identify PD-MCI patients. Another noteworthy difference to the study by Fengler and colleagues (2017) is that they used a 1.28 SD cut-off for the CERAD subtests as suggested by the test manual and a percentile rank for the two tests not related to the CERAD test battery. In our study the diagnostic value of different cut-offs (1, 1.5 and 2 SD) for PD-MCI were compared, therefore we cannot compare our study and the initial study entirely.

All neuropsychological tests applied were standardized, however subtests of the WIE and LPS 50+ only correct for age whereas the CERAD-Plus additionally corrects for education and gender. Therefore, we cannot rule out that education and gender status may have, at least partly, affected our PD-MCI classification. As the proportion of males in our PD-NC and PD-MCI groups was comparable and the educational level did not differ statistically between groups, we conclude that between groups effect of the MoCA can be interpreted in our sample. Furthermore, our cohort did differ in motor symptoms

which might partly influence some test results. There is also some evidence regarding the influence of dopaminergic therapy on cognitive test performances [26]. Normative values, especially for the MoCA, that take such confounders into account would be valuable for the assessment of cognitive impairment in PD. This also applies to the use of the MoCA in clinical routine as a screening tool for a first impression of patients' cognitive status. Further comprehensive, diagnostic Level II testing can then be applied after the noticeable MoCA score. In our study, the MoCA was conducted separately before the neuropsychological tests. However, we cannot exclude the influence of variabilities concerning the individual investigators or the time during the day of the assessment on test performances.

In summary, we conclude that the weighted MoCA has an advantage for detecting cognitive impairment in more advanced stages over the original version. However, we can only confirm a better overall discriminant power due to the novel scoring algorithm for PD-MCI patients classified with a 2 SD cut-off, leading to a high PPV and increased NPV compared to the original version. Therefore, the application of the weighted MoCA might have a higher potential to encircle those PD patients at risk for future conversion to PDD, which needs to be verified with longitudinal studies.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained prior to inclusion from all individual participants included in the study.

Conflict of interest

Maarten Timmers, Luc van Nueten, Giacomo Salvatore and Johannes Streffer are employed by Janssen Pharmaceutica N.V which sponsor the ABC-PD study. The funding of the ABC-PD study is pre-competitive. All of these aspects do not alter the authors' adherence to the journals' policies on sharing data and materials.

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Figure 1 Clustered boxplots for original and weighted Montreal Cognitive Assessment (MoCA) total scores for both Parkinson's disease patients. Divided by the three classification cut-offs with different standard deviations (SD). Part a) refers to the PD-NC and part b) to the PD-MCI patient group with no cognitive impairment (PD-NC). * referring to a significant difference with $p < 0.01$.

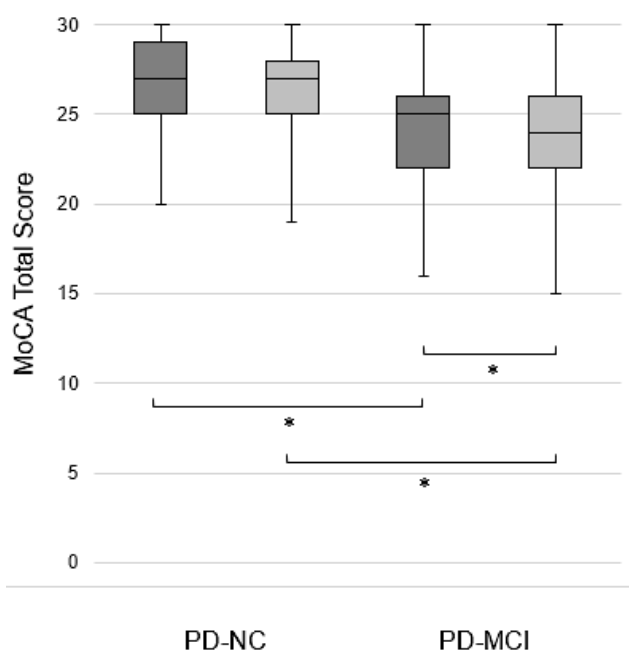


Table 1 Characteristics of Parkinson's disease patients with normal cognition (PD-NC) and mild cognitive impairment (PD-MCI)

| | Total Sample | PD-NC | PD-MCI | <i>p</i> -value |
|-------------------------------------|------------------|------------------|------------------|-----------------|
| Number | 202 | 117 | 85 | |
| Male <i>n</i> (%) | 133 (65.8) | 78 (66.7) | 55 (64.7) | 0.77 |
| Age | 66.1 (48.1-82.2) | 66.0 (48.1-79.9) | 66.7 (50.6-82.2) | 0.12 |
| Education Years | 13 (8-21) | 13 (8-21) | 12 (8-21) | 0.08 |
| Age at Onset | 60.8 (36.4-79.5) | 60.4 (36.4-77.6) | 61.2 (45.5-79.5) | 0.28 |
| Disease Duration Years | 4.1 (0-18.4) | 3.8 (0.1-18.4) | 4.8 (0-15.4) | 0.39 |
| LEDD | 480.0 (0-1574.0) | 436.8 (0-1574.0) | 510.0 (0-1380.0) | 0.036* |
| UPDRS-III <i>Mean</i> (<i>SD</i>) | 25.4 (10.7) | 23.7 (10.44) | 27.7 (10.68) | 0.009* |
| H & Y <i>n</i> (%) | | | | 0.039* |
| 1 | 28 (13.9) | 20 (17.1) | 8 (9.4) | |
| 2 | 112 (55.4) | 70 (59.8) | 42 (49.4) | |
| 3 | 60 (29.7) | 26 (22.2) | 34 (40.0) | |
| 4 | 2 (1.0) | 1 (0.9) | 1 (1.2) | |
| BDI-II Score | 7 (0-19) | 6 (0-19) | 7 (0-19) | 0.22 |
| Weighted MoCA Score | 26 (11-30) | 27 (14-30) | 23 (11-30) | <0.001* |
| Original MoCA Score | 26 (16-30) | 27 (20-30) | 25 (16-30) | <0.001* |

Note. If not other indication, values are given as Median (range); LEDD = Levodopa Daily Dose; UPDRS-III = Unified Parkinson's Disease Rating Scale part III; H & Y = Hoehn & Yahr stage, BDI-II = Beck Depression Inventory II; MoCA = Montreal Cognitive Assessment

Table 2 Spearman rank correlations coefficients (r_s) between each of the two MoCA total and cognitive domain scores including statistical comparison between these two correlation coefficients.

| Cognitive Domain Score (z-value) | r_s | | p -value |
|----------------------------------|---------------------------|---------------------------|------------|
| | Original MoCA total score | Weighted MoCA total score | |
| Executive functions | 0.42 | 0.44 | 0.20 |
| Memory | 0.41 | 0.41 | 0.50 |
| Visuospatial functions | 0.38 | 0.42 | 0.09 |
| Attention | 0.50 | 0.50 | 0.50 |
| Language | 0.48 | 0.43 | 0.05 |

Note. * significant difference with $p < 0.05$

Executive function is related to urinary urgency in non-demented patients with Morbus Parkinson

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Short title: Urinary Urgency and cognition in Parkinson's Disease.

Keywords: Parkinson's Disease, bladder dysfunction, urge incontinence, cognition, dementia

Abstract

INTRODUCTION: Evidence suggests urinary urgency is associated with cognitive impairment in a subtype of Parkinson's disease (PD) patients. This study investigates if cognitive impairment independently predicts the presence of urinary dysfunction.

METHODS: We report data of 189 idiopathic PD patients, excluding those with concomitant diseases or medication interacting with bladder function. A standardized questionnaire was used to define presence of urinary urgency. All patients underwent a comprehensive motor, cognitive non-motor and health-related quality of life (HRQoL) assessment. Multivariable linear regression analysis was performed to identify independent predictors of urinary urgency (PD-UU), which were applied as discriminant features to estimate their individual contribution to the phenotype of PD-UU group.

RESULTS: Of 189 PD patients, 105 (60.8%) reported PD-UU. Among cognitive domains, only executive function (EF) ($p = .04$) was associated with PD-UU. In a second model, scores of the Montreal Cognitive Assessment (MoCA) significantly differentiated between study groups ($p = .007$) and with non-motor symptom (NMS) burden ($p < .001$). The third model consisted of reports of HRQoL, of which stigma was the only subscale of the Parkinson's Disease Questionnaire (PDQ-39) differentiating between patients with and without PD-UU ($p = .02$). Linear discriminant analysis provided evidence that the combination of EF, NMS impairment, and stigma differentiated between groups with 72.4% accuracy.

CONCLUSION: In our large, non-demented PD cohort, urinary urgency was associated with executive dysfunction, supporting a possible causative link between both symptoms. A combination of neuropsychological and non-motor aspects identified patients with PD-UU with high discriminative accuracy.

Introduction

Urinary urgency is a common non-motor symptom in Parkinson's disease (PD) [1-3]. Presence of urinary urgency in PD (PD-UU) lowers patients' health-related quality of life (HRQoL) [4, 5] and its frequency is higher as among older healthy individuals [6, 7]. To date, no effective treatment of PD-UU exists. The influence of dopaminergic medication is not predictable [8] and standard anticholinergic medication should be avoided, for its negative impact on cognition [9]. Therefore, novel treatment approaches are necessary.

Bladder dysfunction has been linked to a variety of clinical PD-related symptoms, including cognition [10-12]. Contrary, recent study found no association between PD-UU and cognitive impairment [12]. In this study, applied cognitive screening assessment, did not provide insight into domain specific characterization of cognitive functions. In vascular dementia, as well as in healthy elderly adults, the loss of EF has been reported to be related to urinary incontinence [13, 14]. The impairment in EF is a common feature in PD [15], which raises the question if these specific function associates with PD-UU in a subtype of PD patients, independent from the presence of dementia.

Our primary aim was to verify the role of domain specific cognitive impairment, independent from the effect of other symptoms, in the occurrence of PD-UU in a large, non-demented PD sample. We hypothesized that especially EF would be associate to the presence of PD-UU. Taking limitations of previous studies into account, we excluded patients with intake of medication or presence of concomitant diseases interacting with bladder function.

Methods

Patients

As a part of the ongoing "Amyloid-beta in CSF as risk factor for cognitive dysfunction in PD (ABC-PD)" study, 262 PD patients diagnosed according to the United Kingdom Brain Bank criteria [16] were recruited. Inclusion criteria of the ABC-PD study were age between 50 and 85 years, adequate or corrected hearing/visual abilities, German as mother tongue, no history of substance abuse except for nicotine, and no further neurological diseases affecting the central nervous system. As a premise for the ABC-PD study, informant consent for a lumbar puncture was mandatory. All patients were examined during the "on" state after taking their regular optimized dopaminergic treatment.

For the data analysis reported here, 73 (27.9%) PD patients were excluded due to the presence of concomitant diseases affecting bladder control (see Figure 1 for details). Therefore, data of 189 PD patients were included into the final analysis. The study was approved by the local ethics committee. All patients gave written informed consent for study participation.

Classification of PD-UU vs. PD-NUU

Item 8 of the validated Parkinson's Disease Non-motor Symptoms Questionnaire (PDNMS-Quest) [17] was used to differentiate between PD patients with (PD-UU, score = 1) and without (PD-NUU, score = 0) urinary urgency.

Demographics, medication, and motor symptoms

Demographics and a full drug history, including the total daily dose of all dopaminomimetics [expressed by the levodopa equivalent daily dose (LEDD)] and the total daily dose of dopaminergic agonists medication (DAEDD) were obtained. Since medications with anticholinergic effects have been identified as a risk factor for cognitive decline, the anticholinergic risk score (ARS) for medication with additional anticholinergic properties was calculated. Severity of motor symptoms was assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) part III and the Hoehn-Yahr (H & Y) scale, while falls were assessed with item 13 of the UPDRS part II.

Neuropsychological test battery

To assess major areas of cognitive function, a standardized neuropsychological test battery was applied. The MoCA was used to screen for patients' global cognitive status. The Consortium to Establish a Registry of Alzheimer's Disease Plus (CERAD-PLUS) test battery and subtests of the Wechsler Intelligence Test for adults (WIE) as well as the Performance Evaluation for Seniors (Leistungsprüfsystem, LPS-50+) were assigned to the following cognitive domains: EF (CERAD-PLUS: lexical and phonemic fluency, Trial Making Test B); Attention/working memory (WIE: Digit Symbol Test, Letter Number Sequencing Task); Memory (CERAD-PLUS: Word List Learning, Word List Recall, Word List Recognition, Praxis Recall); Visuo-constructive abilities (CERAD-PLUS: Praxis, LPS-50+: Fragmented Words) and Language (CERAD-PLUS: Boston Naming Test, WIE: Similarities).

For all subtests, z-scores were computed, corrected for age (all), gender (CERAD-PLUS), and education (CERAD-PLUS) where possible. For each of the above-mentioned cognitive domains, a mean z-score was calculated. PD-related mild cognitive impairment (PD-MCI) was diagnosed based on recommendations by the Level II criteria of the Movement Disorder Society Task Force [18].

Further non-motor function scales

Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II) [19]. Total HRQoL was assessed using the Parkinson's Disease Questionnaire total score (PDQ-39)[20]. The total score was built out of 39 questions, divided into 8 domains: Mobility (10 items); Activities of daily living (ADL, 6 items); Emotional well-being (6 items); Stigma (4 items); Social support (3 items); Cognitions (4 items); Communication (3 items); and Bodily discomfort (3 items). Other non-motor symptoms were evaluated by the German version of the PD Non-Motor Symptom Questionnaire (NMSQuest) [21]. Moreover, instrumental ADL (iADL) were measured by the Functional Activities Questionnaire (FAQ) [22].

Statistics

Data were collected and managed using REDCap electronic data capture tools [23] and analyzed using SPSS 22 for Windows (SPSS Inc, Chicago, IL, USA). Descriptive values are presented as mean, standard deviation (SD), number, and percentage (%). Comparisons between groups were performed using chi-squared and student's t-tests, as appropriate (Table 1). To analyze the possible predictors of PD-UU, a linear regression analysis with group status (PD-UU vs. PD-NUU) as the dependent variable was applied, controlling for potential confounders (disease duration and LEDD). To test the link between motor, non-motor, and cognitive symptoms and PD-UU, three independent regression models were conducted. *Model A* consisted of all five cognitive domain scores in addition to the covariates. In *model B*, the PDQ-39 summary index, NMS-Quest, FAQ, MoCA total score, and falls incidence (UPDRS-II) were considered to evaluate the association between cognition and PD-UU among other symptoms. Given the covariance between total score and the subscales scores of the PDQ-39, we created *model C*, in which all subscales were included as independent variables. Based on significant results from the linear regression models, a blockwise discriminant function was performed to confirm if the identified variables contributed to the classification of PD-UU. Wilks' lambda was used to test significance of the model fit for prediction of PD-UU, and the Box-M test evaluated variance homogeneity between both groups. To validate the results of the blockwise model, a stepwise discriminant function was calculated. Results are presented as mean and 95% confidence intervals.

Data Availability Statement

Due to ethical restrictions imposed by the Ethics Committee of the Medical Faculty of the University of Tuebingen related to approved patient consent procedure and protecting patient privacy, all relevant data should be requested at Dr. Inga Liepelt-Scarfone or Prof. Dr. Thomas Gasser directly using the email address inga.liepelt@uni-tuebingen.de or in case of unavailability thomas.gasser@uni-tuebingen.de. The Ethical Committee decided how data of this particular study should be handled by the researchers; however, the Ethical Committee does not have access to the actual data.

Results

An overview of demographic and clinical characteristics of all 189 PD patients (93 males, 49.2%) is reported in Table 1. Mean age of all PD patients was 64.7 ± 7.9 years, with 115 patients (60.8%) reporting PD-UU. Patients reporting PD-UU had longer disease durations ($p = .02$) and higher LEDDs ($p = .01$) compared to PD-NUU. In contrast, the DAEDD ($p = .37$) and ARS ($p = .35$) scores did not significantly differ between study groups. Frequency of patients with diagnosis of PD-MCI did not statistically differ between groups.

Regarding the linear regression, among all cognitive domains (*model A*), PD-UU patients performed worse on tests assessing EF ($p = .04$), but not on other domains compared to PD-NUU. In *model B*, the MoCA score ($p = .007$) and the total score of NMSQuest ($p < .001$) significantly differentiated between study groups, whereas the FAQ, PDQ-39 total score, and falls rate did not statistically contribute to the prediction of PD-UU. Values of the Stigma subscale of the PDQ-39 (*model C*) were lower among PD-UU patients compared to PD-NUU ($p = .02$) and was considered as the only subscale associated with the presence of urinary urgency. The cofounders did not reach significance level in any of the regression models.

To predict group membership of PD-UU, we executed a discriminant analysis. Predictor variables were the z-score of the EF domain, MoCA total score, NMSQuest total score, and the PDQ39- Stigma scale score. Based on the blockwise model, PD-UU patients were classified with an accuracy of 72.4% for group discrimination and 69.9% of variance explained by the variables. Box's M ($p = .78$) and Wilks' lambda ($\lambda = 0.67, \chi^2 = 57.5, df = 4, p < .001$) confirmed a high quality of model fit resulting in the following discriminant function (DF): $DF = (0.59 \times EF) + (0.31 \times NMSQuest) + (-0.65 \times PDQ-39 \text{ Stigma}) - 2.79$; ($p < .001$). Due to its low discriminant power, the MoCA score was not included in the DF. In the discriminant model, the pooled within-groups correlations between discriminating variables and standard canonical discriminant function built the following hierarchy: NMSQuest score differentiated best between PD-UU and PD-NUU ($p < .001$), followed by EF ($p = .03$) and PDQ-39 Stigma ($p = .02$). The stepwise analysis confirmed that all variables together, apart from the MoCA, contributed significantly ($p < .001$) to group discrimination of PD-UU and PD-NUU.

Discussion

We here present results of a study investigating the link between urinary dysfunction and cognitive impairment in a selected cohort of PD patients controlled for the intake of concomitant medication and presence of age-related bladder symptoms. Our most important finding is the prediction of urinary

urgency with high accuracy, given the combination of non-motor symptom burden, executive dysfunction, and self-perceived stigma in PD.

During the course of the disease, non-motor symptoms start to predominate the clinical picture, which are often more troublesome for patients than the motor symptoms [24]. Hence, it is important to detect the casual relation of the non-motor burden to develop more specific adjuvant therapy forms.

Our data shows that cognitive impairment, especially EF, is an independent predictor of PD-UU among other motor and non-motor symptoms. Some reports suggest an interdependence between autonomic and cognitive symptoms, which was shown for orthostatic hypotension and cognitive worsening [25]. However, the association between PD-UU and cognition is only sparsely investigated despite a high prevalence rate of urinary urgency in some forms of dementia or late stages of PD [26-29]. PD-UU can be caused by the neurodegenerative processes of the prefrontal cortex since the frontal cortex-basal ganglia circuit plays a prominent role not only in modulating EF and goal-directed behavior [30] but also in suppressing micturition [31]. Neuroimaging studies identified that the prefrontal cortex is activated during bladder filling [32] and that progressive neurodegenerative changes in PD cause disruptions of these patterns [33, 34]. The causality of connection between EF and PD-UU should be considered as bidirectional, as executive impairment might prevent PD patients from planning or inhibiting physiological processes that lead to PD-UU. In our study, 60.8% of non-demented PD patients reported urinary urgency. This finding demonstrates that PD-UU is not limited to a subgroup of demented PD patients or PD-MCI, but can develop early and correlate with early cognitive deteriorations. The rate of patients with and without PD-MCI did not differ in our sample, which emphasizes that cognitive impairment per se does not lead to onset of PD-UU. Rather, our data suggests that a specific cognitive function is associated with the presence and severity of PD-UU, at least in a subtype of PD patients.

In our study, we used a comprehensive neuropsychological battery, including tests for the assessment of cognitive domains. This approach might have allowed us to detect prefrontal cognitive changes that other studies could not observe [12]. Performance in the MoCA did distinguish between our study groups, however it did not independently contribute to classification of PD-UU in a discriminant function analysis. The MoCA is a global cognitive assessment with a lower sensitivity for single cognitive domains and the substantial overlap with the assessed EF tests might have weakened its discriminative role in further analysis. Contrary to our findings, in the PRIAMO cohort, no association between urinary dysfunction and the global cognitive assessment, measured by Mini-Mental State Examination (MMSE), independently from the presence and severity of other non-motor symptoms, could be identified [12]. Further studies are necessary to specify the distinctive mechanism of executive dysfunction potentially causing PD-UU, specifically considering the prefrontal area as a control center for decision-making or inhibitory function in PD [13, 35]. The impairment in executive functioning is a common and early feature in PD [15], which raises the question if these specific functions might be associated with urinary urgency (with or without incontinence) in a subtype of PD patients. EF is only sparsely assessed within

the MMSE, which might explain divergent results among previous studies evaluating the association between cognition and PD-UU.

Apart from the more pronounced executive worsening, patients with PD-UU reported higher non-motor symptom burden. This confirms previous findings reporting non-motor symptoms as highly prevalent in PD patients [36] and that PD-UU patients experience higher rates of non-motor symptoms than PD-NUU [12, 31]. PD is considered a spectrum disorder, whereas non-motor symptoms have been recognized as a progression marker of the disease [37, 38]. The significantly higher prevalence of non-motor symptoms in the PD-UU subgroups in our study shows that PD-UU might influence the experienced effect on PD-UU and/or other non-motor symptoms [12]. Indeed, our findings are in line with previous studies that showed that autonomic dysfunction should be considered a risk factor for a more progressive course of PD [39, 40]. Hence, the assessment of various non-motor symptoms is needed to subtype the heterogeneity of PD patients.

In our non-demented sample, iADL function did not contribute to defining the status of PD-UU, indicating that iADL is equally intact in both groups. Previous studies have shown that presence and severity of urinary symptoms might have the potential to alter patients' everyday behavior, mainly due to withdrawal of their social activities [5]. Based on the assessment of the FAQ and the ADL subscale of the PDQ-39, we were not able to support these previous results [4]. However, HRQoL related to stigma differed between PD-UU and PD-NUU, but was contrary to our expectations. By engaging stigma arising from health-related symptoms, studies have shown that PD patients have a reduced interoceptive sensitivity [41] when compared to a healthy population. The reverse direction of the stigma outcome may imply that PD-UU patients might have difficulties perceiving the full consequences of urinary urgency or may tend to deny these symptoms. The interoceptive sensations seem to be modulated by the anterior cingulate cortex, a region that has been also associated with the performance in executive tasks [34, 42]. To gain further insight into this connection, more studies are required.

In line with previous findings using either questionnaires or urodynamic tests, our PD population presented a high prevalence of PD-UU [2, 12, 43]. Adjusting for factors relating to comorbidities that may play a role in developing age-related bladder symptoms, we minimized the possible misclassification and concentrated on urinary urgency as an independent medical condition caused by PD. In our cohort, presence of PD-UU was associated with a longer disease duration and higher dosage of LEDD, which has been previously reported [4, 31], but neither to age nor gender. To reduce the possible statistical bias, we corrected for potential confounders in all steps of our analysis. Even though LEDD and disease duration differentiated between our study groups, they did not contribute as independent traits of PD-UU, as their predictor value was not significant in any of our regression models. This argues for our assumption that PD-UU is a symptom strongly dependent upon the occurrence of other non-motor symptoms, characterizing a specific PD subtype. PD-UU, when diagnosed as an intrinsic PD symptom, rather than age-related comorbidity, can be an important diagnostic clue for the

disease progression and supports the existence of the autonomic PD subtype [37, 44]. However, the neuropathological pathway and its correlatives are not fully explained yet.

Our study has limitations. The cross-sectional study design does not allow exploration of the causative nature of the link between urinary urgency and cognition completely. Nevertheless, the applied statistical method allowed us to assess objective classification to a specific group, taking this limitation into concern. The non-demented patients were mostly recruited from a study that required a lumbar puncture, which could have biased the recruitment of the participants. In general, we could replicate previous reported prevalence rates of PD-UU and associations with these phenomena to more advanced disease stages. Secondly, the study had strict inclusion criteria, which led to a high number of exclusions. This design was needed to investigate the urinary urgency caused by PD and its neurodegenerative deterioration. Otherwise, the presence of concomitant, age-related diseases causing bladder dysfunction could bias the results.

In conclusion, to our knowledge, this is the largest study that investigates the role of cognitive impairment in PD-UU using a comprehensive neuropsychological test battery. Our findings emphasize that cognition should be taken into consideration as a predictor for urinary urgency, offering an alternative opportunity for intervention strategies.

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Table1 Demographics and clinical features of study patients

| | Total PD | PD-NUU | PD-UU | <i>p</i> -value |
|---------------------------|---------------|---------------|---------------|-----------------|
| Number of Subjects, n (%) | 189 (100) | 74 (39.2) | 115 (60.8) | |
| Male gender, n (%) | 93 (49.2) | 39 (52.7) | 54 (49.5) | .29 |
| Age, years | 64.7 (7.9) | 63.5 (8.3) | 65.5 (7.7) | .09 |
| Education, years | 13.4 (2.9) | 13.5 (2.9) | 13.3 (2.8) | .63 |
| Disease duration, years | 5.1 (3.8) | 4.3 (3.6) | 5.6 (3.9) | .02 |
| LEDD | 506.4(288.5) | 441.1 (273.6) | 548.9 (291.7) | .01 |
| DAEDD | 166.9 (152.8) | 154.6 (152.2) | 174.8 (153.0) | .37 |
| PD-MCI n (%) | 77 (40.7) | 35 (47.3) | 42 (36.5) | .21 |
| Motor Performance | | | | |
| UPDRS III | 24.5 (10.9) | 24.5 (12.7) | 24.6 (9.8) | .95 |
| Hoehn & Yahr, n (%) | | | | .06 |
| 1 | 28 (14.8) | 17 (22.9) | 11 (9.5) | |
| 2 | 110 (58.5) | 38 (51.4) | 72 (62.6) | |
| 3 | 50 (26.4) | 19 (25.7) | 31 (26.9) | |
| 4 | 1 (0.3) | 0 (0.0) | 1 (1.0) | |
| ARS, n (%) | | | | .35 |
| 0 | 66 (34.9) | 31 (41.9) | 35 (30.4) | |
| 1 | 54 (28.6) | 21 (28.4) | 33 (28.8) | |
| 2-3 | 45 (23.8) | 14 (18.9) | 31 (26.9) | |
| 4+ | 24 (12.7) | 8 (10.8) | 16 (13.9) | |
| BDI-II | 8.8 (7.22) | 7.7 (6.63) | 9.43 (7.53) | .13 |

If not other indicated, values are given as mean and standard deviation. ARS: Anticholinergic Risk Scale; BDI-II: Beck Depression Inventory II; LEDD: Levodopa equivalent daily dose; DAEDD: Dopaminergic antagonist equivalent daily dose UPDRS-III: Unified Parkinson Disease Rating Scale

Table 2 Cognitive performance and non-motor features of study patients

| <i>Domains</i> | Total PD | PD-NUU | PD-UU | Standardized beta | 95% CI | <i>p</i> -value |
|-----------------------------|--------------|--------------|--------------|-------------------|--------------|-----------------|
| <i>Model A*</i> | | | | | | |
| Executive function | -0.16 (0.92) | -0.03 (0.93) | -0.43 (0.90) | 0.51 | [0.84-2.16] | .04 |
| Attention | -0.11 (0.76) | -0.18 (0.75) | -0.11 (0.76) | -0.19 | [0.47-1.45] | .41 |
| Language | -0.21(0.78) | -0.18 (0.74) | -0.27 (0.79) | 0.19 | [0.87-2.23] | .25 |
| Memory | -0.25 (0.87) | -0.39 (0.76) | -0.16 (0.92) | 0.34 | [0.07,-1.89] | .68 |
| Visuo-constructive skills | -0.34 (0.86) | -0.43 (0.88) | -0.28 (0.79) | 0.04 | [0.67-1.61] | .73 |
| <i>Model B*</i> | | | | | | |
| PDQ-39 Total Score | 4.2 (3.6) | 3.8 (3.3) | 4.5 (3.7) | -.13 | [0.76-1.02] | .14 |
| FAQ | 2.1 (2.1) | 2.0 (2.9) | 2.2 (4.1) | -0.02 | [0.86-1.12] | .78 |
| MOCA | 26.30 (3.34) | 26.11 (3.18) | 24.14 (3.18) | 0.15 | [1.04-1.30] | .007 |
| NMSQuest | 7.7 (4.7) | 5.4 (4.3) | 9.2 (4.4) | .29 | [1.19-1.51] | .001 |
| UPDRS II: Falls | 0.25 (0.62) | 0.16 (0.46) | 0.34 (0.66) | 0.28 | [0.57-3.24] | .52 |
| <i>Model C*</i> | | | | | | |
| PDQ-39 Mobility | 17.2 (19.3) | 13.4 (17.3) | 19.6 (20.2) | .002 | [.98-1.02] | .89 |
| PDQ-39 ADL | 20.7 (18.3) | 16.7 (16.5) | 23.5 (19.2) | 0.02 | [.99-1.05] | .09 |
| PDQ-39 Emotional Well-Being | 17.2 (17.9) | 14.6 (19.5) | 18.7 (18.8) | .010 | [.98-1.04] | .48 |
| PDQ-39 Stigma | 14.7 (18.5) | 16.3 (20.6) | 13.6 (17.1) | -.029 | [.94-99] | .02 |
| PDQ-39 Social Support | 10.7 (18.5) | 9.6 (17.2) | 11.4 (19.3) | -.001 | [.98-1.02] | .96 |
| PDQ-39 Cognitions | 10.7 (18.4) | 15.2 (15.3) | 29.5 (17.9) | -.005 | [.98-1.04] | .64 |
| PDQ-39 Communication | 17.6 (19.3) | 15.8 (18.9) | 18.8 (19.5) | .013 | [.97-1.02] | .70 |
| PDQ-39 Bodily Discomfort | 23.7 (21.8) | 19.5 (20.2) | 26.3 (22.5) | -.758 | [.99-1.03] | .18 |

All values are given as z-values: median and standard deviation; ADL: Activity of Daily Living Function; FAQ: Functional Activities Questionnaire; MOCA: Montreal Cognitive Assessment Test; NMSQuest: Non-motor Symptoms Questionnaire; PDQ-39: Parkinson's Disease Questionnaire; UPDRS II: Unified Parkinson Disease Rating Scale II; *Every model also consisted of cofounders, which are not listed in the table

Figure 1 Recruitment Flowchart of study groups.

