Clinical and Structural Markers Associated with Cognitive Impairment in Non-Demented Parkinson's Disease Patients

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Sara Becker
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Contents

Zusammenfassung

Die Parkinson-Krankheit (PD) geht mit motorischen sowie einer Vielzahl nicht-motorischer Symptome (NMS) einher. Kognitive Störungen sind eines der häufigsten NMS bei der PD und verringern die Lebensqualität der Patienten. Patienten mit einer leichten kognitiven Störung (PD-MCI) haben ein erhöhtes Risiko an einer Parkinson-Demenz (PDD) zu erkranken, jedoch entwickeln nicht alle PD-MCI Patienten letztendlich eine PDD. Bislang kann kein einzelner Marker die Entwickelung einer PDD innerhalb kurzer Zeit vorhersagen. Daher bleibt die Identifizierung von Risikofaktoren für die Progredienz kognitiver Störungen eine wichtige Forschungspriorität. Ziel der vorliegenden Arbeit war es Zusammenhänge zwischen möglichen Risikomarkern bei nicht dementen PD-Patienten zu untersuchen.

Die Beeinträchtigung in der Ausführung der Aktivitäten des täglichen Lebens (ADL) im Zusammenhang mit kognitiven, aber nicht motorischen, Funktionen ist das Kernkriterium einer PDD-Diagnose. In der ersten Publikation konnten anhand neu entwickelter Scores, basierend auf dem Functional Activities Questionnaire (FAQ), kognitiven von motorischen Einflüssen auf die ADL-Funktion unterschieden werden. PD-MCI Patienten mit kognitiv-assoziierten ADL-Beeinträchtigungen zeigten stärkere Defizite in den kognitiven Domänen Aufmerksamkeit und Sprache als PD-MCI Patienten mit primär motorisch bedingten ADL-Dysfunktionen. Basierend auf diesen Studienergebnissen zielte die zweite Veröffentlichung darauf ab den Zusammenhang zwischen kognitiven Störungen und weiteren Prodromalmarkern der PDD (Depressionen, Angstzustände, Schlafstörungen und Halluzinationen, DASH) zu untersuchen. Der DASH-Score konnte zwischen kognitiven Gruppen unterscheiden und wies signifikante Assoziationen mit kognitiv-assoziierten ADL-Beeinträchtigungen, definiert durch den FAQ, auf. Eine Kombination aus der DASH-Belastung und kognitiven ADL-Beeinträchtigungen erscheint vielversprechend, um eine Risikogruppe für PDD unter PD-MCI Patienten zu identifizieren.

Da auch bei der PD eine Alzheimer Pathologie bestehen kann, befasste sich die letzte Veröffentlichung mit dem Hippocampus als ein struktureller Prodromalmarker und den Biomarkern Amyloid-β und Tau im Liquor bei PD-Patienten. Obwohl beide eine Rolle bei der PDD spielen, ist deren Zusammenhang mit der kognitiven Progression noch unklar. Die Studienergebnisse legen nahe, dass die Hippocampal-Amygdaloid Transition Area das Potenzial hat den kognitiven Status bei PD-Patienten zu differenzieren. Dahingegen waren die Hippocampus-Teilfelder mit den kognitiven Domänen Gedächtnis, Sprache, räumliches Arbeitsgedächtnis und exekutiven Funktionen assoziiert. Es wurde keine Assoziation zwischen

den Hippocampus-Teilfeldern und Amyloid-β 1-42 gefunden, jedoch korrelierten die Tau Werte mit kleineren Hippocampus-Volumen.

Insgesamt unterstreichen die Ergebnisse dieser Arbeit, dass die Kombination von verschiedenen Demenzrisikomarkern (insbesondere ADL-Funktion und DASH-Symptome) Assoziationen mit der kognitiven Funktion aufweisen können, auch im prodromalen Stadium der PDD. Längsschnittstudien sind erforderlich, um festzustellen, ob bei diesen identifizierten Gruppen tatsächlich ein erhöhtes Risiko besteht eine PDD zu entwickeln.

Summary

Parkinson's disease (PD) is associated with motor as well as a variety of non-motor symptoms (NMS). Cognitive disorders are one of the most common NMS in PD and reduce patients' quality of life. Patients with mild cognitive impairment (PD-MCI) are at higher risk of developing Parkinson's disease (PDD), but not all eventually develop PDD. Currently, no single marker can predict the development of a PDD in a short time. Therefore, identifying risk factors for the progression of cognitive disorders remains an important research priority. The aim of the present thesis was to investigate the relationships between possible risk markers in non-demented patients.

Loss of the ability to perform activities of daily living (ADL) related to cognitive, but not motor, functioning is the core criterion for diagnosing PDD. In the first publication we were able to differentiate cognitive from motor influences on ADL function based on newly developed scores from the Functional Activities Questionnaire (FAQ). PD-MCI patients with cognitive-driven ADL impairments exhibited stronger deficits in the attention and language domains than those with motor-driven ADL dysfunction. Based on these study results, the second publication aimed to investigate the relationship between cognitive disorders and other prodromal markers of PDD (depression, anxiety, sleep disorders and hallucinations, DASH). The DASH score was able to differentiate between cognitive groups and was significantly associated with cognitive ADL impairment, as defined by the FAQ. A combination of DASH burden and cognitive ADL impairment shows promise in characterizing a risk group for PDD among PD-MCI.

The last publication was primarily concerned with coexisting Alzheimer's pathology in PD, namely the hippocampus as a structural marker and Alzheimer's pathology (amyloid-β and tau) in cerebrospinal fluid as a biomarker. Although both play a role in PDD development, their association with cognitive progression is still unclear. Study results suggest that the hippocampal amygdaloid transition area has the potential to differentiate cognitive status in PD, while hippocampal subfields were associated with memory, language, spatial working memory, and executive functions. No association was found between hippocampal subfields and amyloid-β 1-42; however, tau values correlated with smaller hippocampal volumes.

The results of this work emphasize that combinations of dementia risk markers (especially ADL function and DASH symptoms) show associations with cognitive function in the prodromal stage of PDD. Longitudinal studies are now needed to determine whether the groups identified are at a high risk for developing dementia.

Abbreviations

Aβ42	Amyloid-beta 1-42 protein
ABC-PD	Amyloid-Beta in cerebrospinal spinal fluid as a risk factor for cognitive dysfunction in Parkinson's Disease
AD	Alzheimer's Disease
ADL	Activities of Daily Living
CA	Cornu Ammonis
CANTAB	Cambridge Neurological Test Automated Battery
CSF	Cerebrospinal Fluid
DASH	Depression, Anxiety, Sleep Disturbances, and Hallucinations
DASH-NMS	Depression, Anxiety, Sleep Disturbances, and Hallucinations Score from the Non-Motor Symptoms-Scale
DASH-PDQ	Depression, Anxiety, Sleep Disturbances, and Hallucinations Score from the Parkinson's Disease Questionnaire-39
FAQ	Functional Activities Questionnaire
FAQ_C	Functional Activities Questionnaire cognitive subscore
FAQ_M	Functional Activities Questionnaire motor subscore
FAQ_Q	Functional Activities Questionnaire quotient
GC-DG	Granule Cell layer of the Dentate Gyrus
HATA	Hippocampal-Amygdaloid Transition Area
ICV	Intracranial Volume
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NMS	Non-Motor Symptoms
PD	Parkinson's Disease
PD-CN	Parkinson's Disease Cognitively Normal
PDD	Parkinson's Disease Dementia
PD-MCI	Parkinson's Disease with Mild Cognitive Impairment
PDQ-39	Parkinson's Disease Questionnaire – 39
p-tau	phosphorylated tau
REM	Rapid Eye Movement
t-tau	total tau
UPDRS-III	Unified Parkinson's Disease Rating Scale Part III

List of Publications

Parts of this thesis have previously been published elsewhere. This thesis consists of 2 published manuscripts and 1 manuscript that is currently under review.

Accepted Publications:

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Submitted Manuscripts:

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1. Introduction

With the continual rise in the aging population, age-related neurodegenerative disorders are becoming more common, presenting serious health problems in the elderly. Parkinson's Disease (PD) is the second most common neurodegenerative disease after Alzheimer's Disease (AD), affecting approximately 1% of individuals over the age of 65 (Miller & O'Callaghan, 2015; Thomas, 2009). PD presents clinically with a complex motor disorder known as parkinsonism, which worsens following the pathological deposition of misfolded α-synuclein protein aggregates (McCann, Stevens, Cartwright, & Halliday, 2014; Smith et al., 2019). Patients also present with various non-motor symptoms (NMS) that have a substantial impact on PD patients and their quality of life (Balzer-Geldsetzer et al., 2011; Kramberger et al., 2010).

One of the most debilitating NMS in PD is cognitive dysfunction, which can range from mild cognitive impairment (PD-MCI) to dementia (PDD). While patients with PD-MCI are at greater risk of developing PDD, not all will eventually develop dementia. Some will remain stable or even revert back to normal cognition (Kehagia, Barker, & Robbins, 2013; Lawson et al., 2017). No specific factor has been able to predict conversion to dementia in the short term. There is a critical need for the identification of specific factors and sub-groups of patients that are at a high risk for cognitive deterioration and PDD. Identification of such a risk group is paramount in order provide early treatment and rehabilitation therapies, in the hopes of maintaining patients' quality of life for as long as possible. Therefore, this thesis will be concerned with examining different clinical and structural markers and their association with each other and with cognitive impairment in PD.

1.1. Parkinson's Disease

First described by James Parkinson in 1817, PD affects millions of people worldwide, with the prevalence of the disease expected to increase substantially in the future (Kramberger et al., 2010; Parkinson, 2002). In Germany, the incidence is 100-200 new diagnoses per 100,000 inhabitants per year (Waldthaler & Timmermann, 2019), with a prevalence of 1,800 cases per 100,000 inhabitants over the age of 65 (Schroder et al., 2011). The risk of developing PD increases with age: 1.8% at 65 years, 2.4% at 70 years, and 2.6% for all over 85 years (de Rijk et al., 2000). The average age of onset lies between 50 and 60 years, and life expectancy is around 15 years post diagnosis (de Rijk et al., 2000).

1.1.1. Motor symptoms

Symptoms of PD arise from the degeneration of the nigrostriatal dopamine system, characterized by the loss of dopamine-producing neurons within the s*ubstantia nigra pars compacta* (Dickson, 2012; Schulz-Schaeffer, 2015). Once the concentration of dopamine falls below 60-70%, cardinal motor symptoms begin to present themselves (Rodriguez-Oroz et al., 2009). Idiopathic PD presents with four cardinal motor features: bradykinesia, (i.e., a slowness of movement), rest tremor, rigidity, and postural instability, which manifests in advanced PD (Beitz, 2014; Berardelli, Rothwell, Thompson, & Hallett, 2001; Massano & Bhatia, 2012; Postuma et al., 2015). PD can be diagnosed clinically by neurologists with considerable accuracy when robust criteria are used (Hughes, Daniel, Ben-Shlomo, & Lees, 2002; Postuma et al., 2015), with an autopsy necessary for disease confirmation (Miller & O'Callaghan, 2015). There is no cure for PD, and existing therapies have not been able to slow or reverse progression of the disease (Rao, Hofmann, & Shakil, 2006). While levodopa therapy remains the gold standard of symptom management in PD (Zappia, Colosimo, & Poewe, 2010), other available pharmacological treatments include: dopamine agonists, indirect dopamine transmission enhancers, anticholinergics, and glutamine antagonists (Kaakkola, 2000; Magennis, Lynch, & Corry, 2014; Rascol, Ferreira, Thalamas, Galitsky, & Montastruc, 2001). However, treatment is still difficult, due to the number of motor and non-motor symptoms combined with the progressive nature of the disease.

1.1.2. Non-Motor Symptoms

The focus of research has long been on understanding and treating the motor symptoms in Parkinson's Disease, yet it is becoming increasingly evident that NMS are an integral part of the disease spectrum and considerably influence patients' quality of life (Bonnet, Jutras, Czernecki, Corvol, & Vidailhet, 2012; Kramberger et al., 2010). These NMS are often reported as more disabling than motor symptoms (Chaudhuri & Martinez-Martin, 2008), and can increase the patient's loss of independence (Hermanowicz, Jones, & Hauser, 2019), socioeconomic burden (Vossius, Larsen, Janvin, & Aarsland, 2011), placement in nursing homes (Aarsland, Larsen, Tandberg, & Laake, 2000), and risk of mortality (Levy et al., 2002).

NMS in PD are numerous and include: cognitive impairment, depression, anxiety, sleep disorders and dysfunctions (e.g., excessive daytime sleepiness), fatigue, sensory symptoms (e.g., pain or olfactory dysfunction), hallucinations, orthostatic hypotension, gastrointestinal dysfunction (e.g., constipation), increased salivation, and dopamine dysregulation syndrome

(Bonnet et al., 2012; Chaudhuri & Martinez-Martin, 2008; Chaudhuri, Odin, Antonini, & Martinez-Martin, 2011; Kadastik-Eerme et al., 2016; Kramberger et al., 2010; Miller & O'Callaghan, 2015; Rodriguez-Oroz et al., 2009; Titova & Chaudhuri, 2018; Zhang, Liu, Ye, Cohen, & Zhang, 2015). Some NMS, such as loss of smell, gastrointestinal problems, and rapid eye movement (REM) sleep behavior disorder, can even be regarded as the earliest clinical symptoms of PD as they can occur years before the motor manifestation (Berg et al., 2015; Bonnet et al., 2012; Pellicano et al., 2007). Previous studies have shown 97% to 100% of patients present with at least one NMS (Barone et al., 2009; Bugalho et al., 2016; Kim et al., 2013; Salari et al., 2017). These NMS increase in terms of occurrence and severity throughout the disease course of PD, reflecting a widespread pathology of the central and peripheral nervous systems (Erro et al., 2016; Mou, Ding, & Fernandez-Funez, 2019).

1.1.3. Neuropathology of PD

The Braak staging model has been proposed to explain the spread of α-synuclein pathology throughout the disease course (Braak et al., 2003). Pathogenesis begins gradually in the brainstem and continues to spread through the limbic cortex into the neocortex, following a caudal-to-rostral pattern (Figure 1). In stages 1 and 2, Lewy neurites form in the *medulla oblongata* and the olfactory system, affecting sense of smell and REM sleep. Pathology spreads upwards to the midbrain in stage 3, involving the formation of Lewy bodies in the *substantia nigra* and leading to the characteristic motor symptoms in PD. Neuropathological alterations

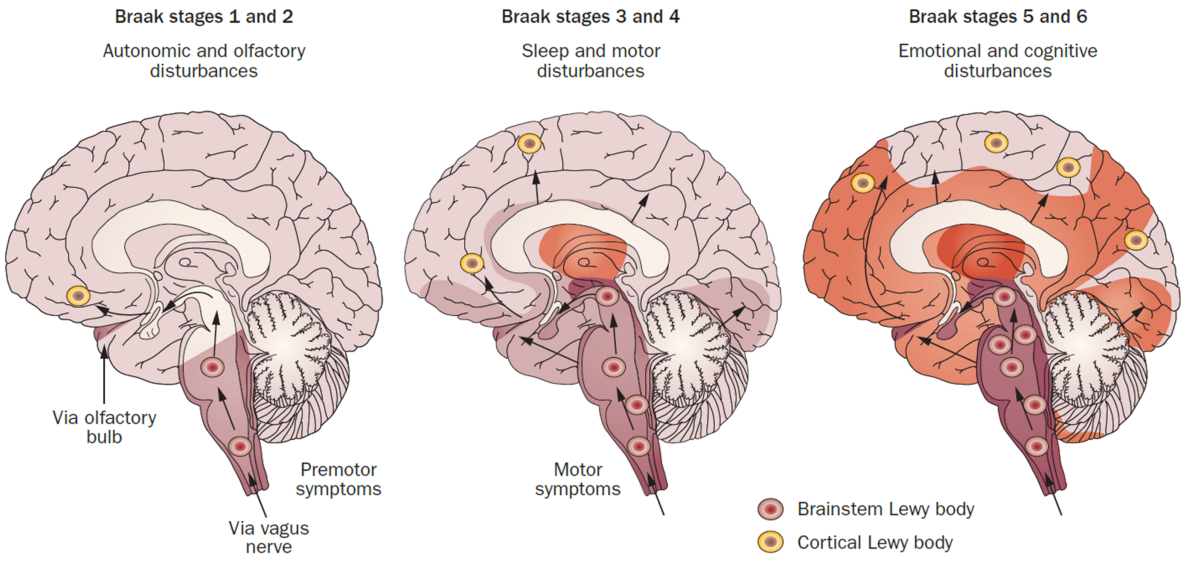

Figure 1. The Braak staging system of Parkinson's Disease, showing the initiation sites in the olfactory bulb and the medulla oblongata, through to the later infiltration of Lewy pathology into cortical regions. Reprinted by permission from Springer Nature: Springer, Nature Reviews Neurology, (Doty, 2012), Copyright 2012.

continue to spread upwards to the paralimbic cortex and hippocampus in stage 4, possibly manifesting as early cognitive dysfunction (Braak, Rub, Jansen Steur, Del Tredici, & de Vos, 2005). Stages 5 and 6 show widespread pathology in the neocortex, manifesting as the full range of symptomatology seen in PD patients.

Apart from degeneration of the nigrostriatal dopamine system, PD is now being recognized as a multisystem disorder. Further degeneration has been shown in various neuronal systems, including the dopaminergic mesolimbic and mesocortical pathways, the cholinergic system of the basal nucleus of Meynert, the serotonergic system of the dorsal raphe nuclei, and the noradrenergic system of the locus coeruleus (Jellinger, 2012; Tibar et al., 2018; Uc et al., 2005). The involvement of multiple neurotransmitter systems supports the range of NMS seen from the pre-motor to the final stages of PD, most notably cognitive impairment, and aids in the understanding of their pathophysiology (Zis et al., 2014).

1.2. Cognitive Impairment in PD

One of the most common and debilitating NMS in PD is cognitive impairment, which is associated with shorter life expectancy (Marder et al., 1991), and contributes to significant caregiver distress and placement in a nursing home (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999). Cognitive impairments in PD can range from normal cognition (PD-CN) or slight deficits (PD-MCI) to PDD (Jellinger, 2013). Recently, PD-MCI has been defined as an intermediate stage of cognitive dysfunction and a prodromal stage of PDD (Goldman & Litvan, 2011). The prevalence of PD-MCI ranges between 20-50% in epidemiological studies (Aarsland et al., 2010; Foltynie, Brayne, Robbins, & Barker, 2004; Muslimovic, Post, Speelman, & Schmand, 2005), and longitudinal studies report that between 39-50% of PD-MCI patients progress to PDD within 5 years (Domellof, Ekman, Forsgren, & Elgh, 2015; Pedersen, Larsen, Tysnes, & Alves, 2017). However, PD-MCI is a heterogeneous concept; while some patients progress to PDD, others remain cognitively stable or revert back to PD-CN (Lawson et al., 2017). Diagnosis necessitates dysfunction to be present in at least two cognitive domains, with preserved activities of daily living (ADL) function. The most common domains affected include executive functions (decision making and planning), memory (retrieval rather than encoding deficits), visuospatial skills, and attention, whereas language and procedural learning are usually less affected (Aarsland et al., 2009; Barone et al., 2011). Table 1 provides an overview of the diagnostic criteria for both PD-MCI and PDD according to recent consensus criteria.

Table 1. *Diagnostic criteria for PD-MCI and PDD*

PD-MCI (Litvan et al., 2012**)**	**PDD (**Emre et al., 2007**)**
I. Core Features	
PD Diagnosis according to United Kingdom Brain Bank Criteria	PD Diagnosis according to United Kingdom Brain Bank Criteria
Gradual decline in cognition reported by patient, informant, or clinician	Dementia syndrome with subtle onset (>1 year after PD diagnosis) and slow progression
Cognitive deficits observed on neuropsychological testing or a global cognitive assessment	Impairment in at least one cognitive domain, representing a decline from premorbid levels
Cognitive deficits do not interfere with activities of daily living, although mild functional impairments may be present	Cognitive deficits are severe enough to interfere with daily life (social, occupational, or personal care), unrelated to motor or autonomic symptoms
II. Associated Clinical Features	
	Cognitive features - Impaired attention, executive functions, memory, and visuo-spatial functions - Language functions are mostly preserved
	Behavioral features (e.g. apathy, depression and anxiety, hallucinations and delusions, excessive daytime sleepiness)
III. Exclusion Criteria / Features making diagnosis of PDD uncertain	
Diagnosis of PDD	Unknown time interval between the onset of motor symptoms and cognitive dysfunctions
Comorbid conditions interfering with cognitive testing (e.g. severe anxiety, depression, psychosis)	Diseases that also result in cognitive impairments (e.g. vascular abnormalities), but are not the primary reason for dementia
Other explanations for cognitive impairment (e.g. traumatic brain injury, stroke, major depression)	
IV. Features making reliable diagnosis of PDD impossible	
	Cognitive symptoms or behavioral problems occurring only in the context of other diseases or accompanying circumstances (e.g. acute confusion due to intoxication or systemic diseases)
	Features compatible with "Probable Vascular dementia" criteria
Subtype Classification	
<u>Single domain PD-MCI</u> - Deficits on two tests within a single cognitive domain	<u>Probable PDD</u> - Core features present, typical profile of cognitive deficits, presence of at least one behavioral symptom - No group III or IV features present
<u>Multiple domain PD-MCI</u> - Deficits on two tests in two or more cognitive domains	<u>Possible PDD</u> - Core features present, atypical profile of cognitive deficits, behavioral symptoms can be exhibited - Or, one or more group III features present, no group IV features present

PD, Parkinson's Disease; PD-MCI, Parkinson's Disease with Mild Cognitive Impairment; PDD, Parkinson's Disease Dementia

In PDD, impairment is more widespread, affecting multiple cognitive domains and representing a decline from premorbid levels, with functional impairments severe enough to impact ADL (Emre et al., 2007). PD patients have a four-to-six-fold increase in their risk of developing dementia compared to healthy elderly persons (Aarsland, Zaccai, & Brayne, 2005; Janvin, Aarsland, & Larsen, 2005; Williams-Gray et al., 2009). The mean duration between disease onset and development of dementia is 10 years (Hughes et al., 2002), with the cumulative prevalence of PDD in patients surviving more than 10 years at 75% (Buter et al., 2008; Hely, Reid, Adena, Halliday, & Morris, 2008). As the presence of PDD is a burden not only to the patient but also to their caregivers, the identification of risk factors for progression to PDD is of the utmost importance (Anang et al., 2014; Janvin et al., 2005).

1.3. Risk Markers for Cognitive Impairment and Dementia in PD

Although various demographical factors have been associated with the conversion to dementia in PD, the clinical, neuropathological, and structural mechanisms underlying cognitive impairment still are not well understood (Aarsland, 2016; Arnaldi et al., 2017). Diffuse cortical and subcortical Lewy body pathology (as detailed in section 1.1.3.) has been shown to drive the progression of cognitive impairment (Aarsland, Perry, Brown, Larsen, & Ballard, 2005; Irwin et al., 2012). However, its influence has been debated and studies argue for the involvement of other factors (Farlow & Cummings, 2008). A number of risk markers for PDD have been proposed, which will be explained in further detail in the following sections.

1.3.1. Demographical Markers

Presence of PD-MCI and older age (over 60 years) are the most established risk factors for PDD (Aarsland et al., 2001a; Anang et al., 2014; Delgado-Alvarado, Gago, Navalpotro-Gomez, Jimenez-Urbieta, & Rodriguez-Oroz, 2016; Hanganu & Monchi, 2016; Kulisevsky et al., 2013; Litvan et al., 2011; Pagonabarraga & Kulisevsky, 2012). Other demographic risk factors reported include disease duration (Litvan et al., 2011), the severity of motor symptoms (Williams-Gray, Hampshire, Barker, & Owen, 2008), postural instability/gait difficulty phenotype (Kelly et al., 2015), lower educational level (Kandiah et al., 2013), and male sex (Szewczyk-Krolikowski et al., 2014). However, it is important to note that both older age and lower educational level are risk factors for dementia in the general population and therefore not specific to PD (Marinus, Zhu, Marras, Aarsland, & van Hilten, 2018).

1.3.2. Activities of Daily Living

The core criterion for diagnosing dementia is the loss of the ability to perform activities necessary for independent living. Impairment in ADL results in increased caregiver burden, with patients ultimately requiring alternative care or placement in a nursing home (Desai, Grossberg, & Sheth, 2004; Tabert et al., 2002). In patients with PDD, ADL impairments correlate with global deterioration in daily functioning skills (Sabbagh et al., 2007), as well as deterioration in higher skills, for example making medical decisions (Griffith, Dymek, Atchison, Harrell, & Marson, 2005). There are two types of ADL that can be defined: basic ADL, which include self-maintenance skills (e.g. toileting, dressing, and eating), and instrumental ADL, which are more complex activities (e.g. shopping, preparing meals, and managing finances or medication) (Marshall et al., 2015; Sikkes, de Lange-de Klerk, Pijnenburg, Scheltens, & Uitdehaag, 2009).

As instrumental ADL require more complex processes, they are more likely to be susceptible to early cognitive decline and are affected earliest in the disease compared to basic ADL (Rosenthal et al., 2010; Sikkes et al., 2009). While it is possible that cognition and ADL function decline in parallel (Leroi, McDonald, Pantula, & Harbishettar, 2012; Reginold et al., 2012), there has been limited attention directed towards understanding this relationship (Martin et al., 2013). Recent studies have demonstrated that PD-MCI patients already show the first signs of ADL dysfunction, which may be indicative of a risk group for PDD development (Beyle et al., 2018; Cheon, Park, & Kim, 2015; Fellows & Schmitter-Edgecombe, 2019; Foster, 2014; Glonnegger et al., 2016; Pirogovsky et al., 2014). The association between PD-MCI and ADL dysfunction needs to be evaluated in further studies to understand their relationship and whether their combination presents a high-risk group.

It is important to note that the diagnosis of dementia necessitates that ADL dysfunction is caused by cognitive deficits. This is a particular challenge in PD, as there are many sources of functional deficits. Most notably, the motor symptoms of PD interfere with virtually all ADL (Brod, Mendelsohn, & Roberts, 1998). The combination of progressive motor dysfunction in PD and aging often leads to a poorer ability to perform ADL tasks (Lee et al., 2014b; Skinner, Lee, Roemmich, Amano, & Hass, 2015). A previous study found that independence loss was predicted by advanced age, shorter disease duration, higher motor disability, and presence of PD-MCI at diagnosis (Bjornestad, Tysnes, Larsen, & Alves, 2016). This suggests that early functional deficits in ADL are caused by both motor and cognitive impairment, becoming more prominent with disease progression.

To date, no validated measure is able to distinguish cognitive from motoric influences on ADL in PD (Holden et al., 2018). The breakdown of motor and cognitive processes may also affect ADL differentially, as cognitive and motor dysfunction in PD do not share the same neuropathological substrates (Cahn et al., 1998; Slachevsky et al., 2019). It is of utmost importance to develop diagnostic measures able to differentiate between these two sources of ADL impairment to avoid false dementia classifications (Almeida et al., 2017; Benge & Balsis, 2016). Moreover, ADL function in different cognitive impairment levels should be studied, so as to understand the progression of ADL impairment and its association with cognition (Weintraub, Moberg, Duda, Katz, & Stern, 2004).

1.3.3. NMS Burden

Another important feature used in the diagnosis of PDD is the presence of additional behavioral NMS, such as mood disorders (depression or anxiety), hallucinations or delusions, apathy, and excessive daytime sleepiness (Emre et al., 2007). Presence of one of these features strengthens the diagnosis from possible to probable PDD, as detailed in Table 1. These behavioral features have also been commonly associated with PD-MCI (Aarsland et al., 2007; Delgado-Alvarado et al., 2016; Monastero, Di Fiore, Ventimiglia, Camarda, & Camarda, 2013). Presence of visual hallucinations (Uc et al., 2009) and sleep disturbances (excessive daytime sleepiness or REM sleep behavior disorder) (Levy et al., 2002; Pagonabarraga & Kulisevsky, 2012) have been shown to be associated with subsequent PDD development. However, these NMS have only been studied independently of one another. A novel study by Naismith and Lewis (2011) examined a specific cluster of NMS, namely: depression, anxiety, sleep disturbances, and hallucinations, summing up their presence into a "DASH" score. They found that a higher DASH score was associated with poorer working memory and executive functions, even in non-demented patients, which could provide a simple measure for identifying patients who might progress to PDD.

The symptoms of the DASH score have been shown to significantly affect health related quality of life (Huang et al., 2018; Pfeiffer, 2016; Prakash, Nadkarni, Lye, Yong, & Tan, 2016), however their association with cognition in PD has hardly been studied. Previous research studies have looked at the individual symptoms of the DASH score separately with respect to the relationship with cognition in PD (Fenelon, Mahieux, Huon, & Ziegler, 2000; Gjerstad, Alves, & Maple-Grodem, 2018). One study found that the most common neuropsychiatric symptoms associated with PD-MCI are depression, apathy, anxiety, and hallucinations

(Aarsland et al., 2007), while another study concluded that depression, sleep disorders, apathy and anxiety were associated with the presence of PD-MCI (Monastero et al., 2013). It is therefore important to determine whether individual NMS or the combination (DASH score) are possible markers for subsequent cognitive impairment or dementia in PD.

1.3.4. Hippocampal Atrophy

Apart from clinical features, pathological changes assessed using imaging biomarkers can assist with the prediction of dementia in PD. Atrophy of the hippocampus is one of the most established early neuroimaging marker for conversion to dementia in AD (Apostolova et al., 2012), with greater reductions in volume correlating with steeper cognitive decline (Leow et al., 2009; van de Pol et al., 2006). Hippocampal atrophy also occurs in a number of other dementias (Aybek et al., 2009; Laakso et al., 1996), and has been suggested as a biomarker of early cognitive decline in PD (Weintraub et al., 2011). Greater hippocampal atrophy has been found in demented compared to non-demented PD patients (Bouchard et al., 2008; Burton, McKeith, Burn, Williams, & O'Brien, 2004; Lin & Wu, 2015; Nagano-Saito et al., 2005; Rodriguez-Oroz et al., 2015; Summerfield et al., 2005; Xia et al., 2013). Compared to healthy controls, more severe atrophy has been shown in PD (Camicioli et al., 2003; Jokinen et al., 2009; Junque et al., 2005; Noh et al., 2014; Tam, Burton, McKeith, Burn, & O'Brien, 2005) as well as PDD patients (Ibarretxe-Bilbao et al., 2008; Summerfield et al., 2005). Even newly diagnosed drug-naïve PD patients have more hippocampal atrophy in comparison with healthy controls (Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004; Lee et al., 2014a), and this atrophy is associated with cognitive decline (Apostolova et al., 2012; Beyer et al., 2013b). Other studies have found no difference in hippocampal size between PD-MCI and PD-CN patients (Beyer et al., 2013a; Xu, Yang, Hu, & Shang, 2016) or between PD patients and controls (Carlesimo et al., 2012; Femminella et al., 2016; Lee et al., 2013).

It has been suggested that hippocampal volume in PD-MCI patients shows an accelerated, age-related decline, preceding the onset of dementia (Schneider et al., 2017). However, presence of hippocampal atrophy is more variable and its association with specific cognitive domains and predictive value for cognitive progression and PDD development is still unclear (Femminella et al., 2016). Different factors can account for divergent results in hippocampal atrophy, namely the methods used (e.g. manual vs. automated segmentation), varying imaging analyses (e.g., region of interest vs. voxel-based morphometry analyses), small sample sizes, differences in neuropsychological tests used, or poorly matched patient groups. The

classification of cognitive impairment is also different among studies; some have grouped PD-CN and PD-MCI into a combined "non-demented" group, blurring the distinction between mild and no cognitive impairments.

Importantly, most researchers to date have only considered the hippocampus as a whole structure, instead of as distinct sub-structures that are differently affected by Lewy body pathology (La et al., 2019). Previous magnetic resonance imaging (MRI) studies in healthy controls have demonstrated that different hippocampal subfields are involved in the various stages of memory processing (Mueller, Chao, Berman, & Weiner, 2011). Each subfield has a distinct effect on memory, with complex interactions between the subfields possibly influencing both the pathophysiological and the cognitive processes in PD (Foo et al., 2017). Examining the relationship between hippocampal subfields and cognition in PD patients, especially in PD-MCI, is important to determine their predictive value as a marker for progression of cognitive decline.

1.3.5. Cerebrospinal Fluid Biomarkers

While the motor symptoms in PD are due to the spreading of α-synuclein pathology, concurrent AD pathology, namely amyloid-beta plaques and neurofibrillary tau tangles, also plays a role in PD. Cerebrospinal fluid (CSF) levels of Amyloid-β 1-42 (Aβ42), phosphorylated tau (p-tau), and total tau (t-tau) are the most established biomarkers of AD, and have promise as biomarkers of PD, showing associations with cognitive decline and dementia in PD (Modreanu et al., 2017; Yousaf, Pagano, Niccolini, & Politis, 2019).

Aβ42 pathology in the brain increases with age, and can be found in approximately 30-50% of PDD patients (Berlyand et al., 2016; Boller, Mizutani, Roessmann, & Gambetti, 1980; Braak et al., 2005). Smith et al. (2019) did not find an association between PDD and Aβ42, however their results showed that severity of deposition was linked to rapid cognitive decline, which has been replicated in other studies (Blennow & Hampel, 2003; Compta et al., 2009; Halliday & McCann, 2008; Siderowf et al., 2010). Low levels of Aβ42 have been linked to impaired cognitive performance and PDD in both cross-sectional (Aarsland et al., 2017; Beyer et al., 2013a; Carlesimo et al., 2012; Hanagasi, Tufekcioglu, & Emre, 2017) and longitudinal studies (Alves et al., 2014; Backstrom et al., 2015; Brockmann et al., 2015; Hall et al., 2015; Parnetti et al., 2014). In contrast to these straightforward findings, a few studies have not been able to demonstrate an association between lower Aβ42 levels and cognitive decline (Buddhala, Campbell, Perlmutter, & Kotzbauer, 2015; Mollenhauer et al., 2016).

Research examining the association between tau pathology and cognitive decline in PD is less consistent. Some studies have shown higher levels of tau in PDD compared to non-demented patients (Hall et al., 2012; Modreanu et al., 2017; Mollenhauer et al., 2006), while others do not demonstrate any difference in tau levels in these patients (Montine et al., 2010; Parnetti et al., 2008; Prell, Witte, & Grosskreutz, 2019; Vranova et al., 2014). Elevated tau levels have been associated with poorer memory and naming performance (Compta et al., 2009; Siderowf et al., 2010), with pathology predominantly affecting the entorhinal cortex and hippocampus (Smith et al., 2019). More research is still needed to determine what role both Aβ42 and tau pathology play in cognitive progression in PD.

1.4. Association between PDD Risk Markers

Identification of risk factors and prodromal markers for progression to PD-MCI and PDD remains a key research priority (Svenningsson, Westman, Ballard, & Aarsland, 2012). Evidence suggests that neither clinical, imaging, or biomarker assessments alone can reliably detect which patients will progress to PDD (Biundo, Weis, & Antonini, 2016), due to the heterogeneity of PD-MCI patients (Delgado-Alvarado et al., 2016; Kalia, 2018) and the nature of the various underlying neuropathological and neurotransmitter deficits (Park et al., 2019). It has been suggested that distinct PD-MCI subtypes exist, each with different underlying pathologies and outcomes (Monchi, Hanganu, & Bellec, 2016). In AD, risk models combining clinical features and biomarkers exist to aid in the prediction of dementia (Schrag, Siddiqui, Anastasiou, Weintraub, & Schott, 2017). This emphasizes that the combination of various risk markers may substantially increase the likelihood of developing dementia, yet only a few studies have examined such combined marker models in PD (Delenclos, Jones, McLean, & Uitti, 2016). Identifying specific associations characterizing those patients at high-risk for developing PDD would allow tailored treatments and therapeutic interventions aimed at delaying cognitive decline and maintaining patients' quality of life for as long as possible (Hogue, Fernandez, & Floden, 2018).

2. Objectives

The main aim of this thesis was to explore the onset, severity, and associations between various potential PDD risk markers in the prodromal stage of dementia in PD. Evaluating symptom patterns and co-occurrence of risk markers can be beneficial for classifying patients

at high risk of subsequent PDD conversion within a short time period, however not enough studies have investigated this in PD. Using cross-sectional studies, we examined various associations between cognition, ADL, NMS burden, hippocampal atrophy, and CSF biomarkers in non-demented PD patients.

2.1. Publication 1

"*Assessment of cognitive-driven activity of daily living impairment in non-demented Parkinson's patients"*

The goal of this study was to use the Functional Activities Questionnaire (FAQ), a widely implemented ADL questionnaire, to identify a combination of items that could differentiate cognitive- from motor-related influences on ADL function. It is important to be able to separate these two impacts on daily function, as only cognitive-driven ADL impairment is a requirement for the diagnosis of dementia. As it has been shown that even non-demented PD patients present with mild ADL disabilities, the profile of both cognitive and motor ADL dysfunction was compared between PD-CN and PD-MCI patients. Lastly, the association between cognitive-driven functional ADL impairment in PD-MCI patients and neuropsychological tests performance was examined, to determine whether these patients pose a risk group to be evaluated in future longitudinal studies.

a. Can we differentiate cognitive and motor influences on ADL using the FAQ?
b. Do PD-MCI patients have more cognitive-driven ADL impairment compared to PD-CN patients?
c. Is there a difference in the cognitive profile between PD-MCI patients with more cognitive ADL impairment compared to those with more motor ADL impairment?

2.2. Publication 2

"Association of Cognitive Activities of Daily Living (ADL) Function and Nonmotor Burden in Nondemented Parkinson's Disease Patients"

This publication examined the DASH score and its relation to cognitive impairment and mild ADL dysfunction in a large cohort of non-demented PD patients. All three markers are important diagnostic criteria for probable PDD, and so their combination may characterize a risk group for development of dementia in the short-term. We first aimed to replicate the

original DASH score in our larger cohort and compared its performance to a second score developed using a different NMS scale. On a cross-sectional level we investigated the association of both DASH scores to the presence of PD-MCI and mild cognitive-driven ADL impairment, defined based on the results of the first study. Additionally, the association of DASH scores and ADL impairment was examined only in the PD-MCI group, to determine whether a specific accumulation of prodromal symptoms is associated with lower cognitive function.

a. Can the DASH score be replicated using a more validated NMS scale as its basis?
b. What is the association between the DASH scores, cognition, and ADL impairment?
c. Is there a specific profile of NMS burden and ADL impairment in PD-MCI patients?

2.3. Publication 3

"Hippocampal Subfields, Cognition and CSF Biomarkers in Non-Demented Parkinson's Disease Patients"

In this last publication, we examined hippocampal volume loss in non-demented PD patients, as its presence is variable and the associations with specific cognitive domains is still undetermined. As it is currently unclear whether hippocampal volume loss is primarily associated with cognitive impairment or pathological Aβ42 levels, we compared hippocampal subfield volumes between patients stratified by both cognitive group and by Aβ42 status. Additionally, the association between prevalence and severity of clinical symptoms related to hippocampal atrophy in the total sample was evaluated by investigating the relationship between hippocampal subfield volumes, neuropsychological test performance, CSF biomarker profiles, and ADL impairment.

a. Are there differences in hippocampal subfield volumes between PD-CN and PD-MCI patients?
b. Do hippocampal subfield volumes differ between Aβ42 positive and negative patients?
c. How are hippocampal subfield volumes associated with other risk markers for PDD development (cognitive performance, CSF biomarker profiles, and ADL impairment)?

3. Results and Discussion

Specific progression markers for cognitive decline and PDD have been identified, including the presence of PD-MCI and older age. However, not all factors can predict a definite conversion within a short time period. This highlights the importance of identifying risk factors or combinations of different markers to characterize those PD patients at risk for cognitive decline. While many previous markers have been determined for AD where cognitive progression is straightforward, it is unknown how these markers also affect PD patients and whether they are applicable for studying this disease. Moreover, the identification of a risk group for dementia in PD is also difficult, due largely to the heterogeneous nature of the PD-MCI construct (Lawson et al., 2017). The Braak staging model emphasizes the concept that PD is a multisystem neurodegeneration, affecting both motor and non-motor systems, instead of being solely a dopaminergic disease (Braak et al., 2003). It is therefore necessary to explore different and novel areas of symptoms and examine specific aggregations of markers in relation to cognitive changes in PD, specifically to define a high-risk group for PDD. Identification of these prognostic factors is imperative to allow clinicians to plan and initiate treatment strategies to delay the progression of cognitive decline and maintain patient's quality of life for as long as possible.

3.1. Influence of ADL Impairment on Cognition in PD

A diagnosis of PDD necessitates that cognitive impairment is severe enough to impact daily activities. Assessing the impact of cognitive dysfunction on ADL is a challenge in PD, due to the interacting effect of motor impairment on severity of daily function (Benge & Balsis, 2016; Beyle et al., 2018; Cahn et al., 1998; Cheon et al., 2015). Commonly, ADL is assessed though an informant, such as a family member or close friend, who can reliably give information regarding the patients' level of functioning (Cahn-Weiner et al., 2007). However, it is important to note that caregivers and patients cannot accurately distinguish cognitive and motor influences on ADL function, reflected in either over- or underreporting ADL functions (Shulman et al., 2006). Moreover, most ADL assessments used for PD patients have been designed for use in other neurodegenerative diseases (such as AD) and do not take into account motor impairments. When using simple ADL measurements, unadjusted for physical ability, ADL impairment might be overstated (Benge & Balsis, 2016), highlighting the need to differentiate cognitive from motor influences on ADL.

3.1.1. Results of Publication 1

Data from 216 non-demented PD patients enrolled in the cross-sectional "Amyloid-Beta in cerebrospinal spinal fluid as a risk factor for cognitive dysfunction in Parkinson's Disease" (ABC-PD) study were analyzed. All patients underwent comprehensive motor and neuropsychological assessments, and the FAQ was used to assess ADL impairments (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982). The FAQ is a short, 10-item questionnaire that assesses instrumental ADL, and has been shown to have the highest discriminatory power to discriminate between demented and non-demented elderly patients among ADL self-reported scales (Juva et al., 1997).

Regression analyses using the FAQ items, the Montreal Cognitive Assessment (MoCA) and the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) were conducted to differentiate subscores of the FAQ primarily reflecting patients' global cognition (FAQ_C) or PD-related motor severity (FAQ_M). By dividing the cognitive by the motor subscore, a quotient (FAQ_Q) was calculated where values >1 indicated more cognitive-driven compared to motor-driven ADL impairment.

Results showed PD-MCI patients had more impairment on measures assessing motor, cognitive, and ADL function than PD-CN. Compared to PD-CN, both the FAQ_C and FAQ_M subscores were significantly higher in PD-MCI patients. A subgroup analysis was conducted only in PD-MCI patients (n=89), using the FAQ_Q cutoff of 1 to split patients into two groups. PD-MCI patients with an $FAQ_{Q>1}$ demonstrated more impairment tests assessing attention (p=0.019) and language (p=0.033) compared to those with an $FAQ_{Q<1}$. Overall, this publication was able to differentiate cognitive and motor influences on daily function as well as characterize a PD-MCI group with more cognitive- compared to motor-driven ADL impairments as a possible risk group for conversion to PDD.

3.1.2. Differentiation of Cognitive and Motor Influences

In this first study we aimed to differentiate the cognitive and motor influences on ADL in PD patients using items from the FAQ. Items most associated with the MoCA included financial capabilities (accounting, and assembling tax records), as well as remembering appointments and important events. Marshall et al. (2015) demonstrated that the FAQ items remembering appointments and assembling tax records were best able to distinguish between PD-CN and PD-MCI patients, and were also able to predict conversion to PD-MCI over time. Results are also in line with a previous study in PD that found keeping appointments, following recent

events, managing finances, and using a telephone were specific ADL items unaffected by motor dysfunction, but able to identify dementia (Cheon et al., 2015). Financial abilities have been shown to be impaired in PD-MCI patients (Pirogovsky et al., 2014), and greater difficulties in keeping track of events for the PD-MCI group may suggest an early memory deficit affecting ADL function. Memory is known to be affected early in PD (Muslimovic et al., 2005), even in the prodromal phase of PD (Fengler et al., 2017; Liepelt et al., 2008; Yilmaz et al., 2016), possibly driving this association between keeping track of current events and cognitive ADL impairment.

The items significantly associated with disease-related motor severity in PD included using appliances, shopping alone, engaging in skills and hobbies, travelling out of the house, and meal preparation. As these items can be significantly affected by motor impairment (e.g. inability to use household appliances due to rigor or tremor), these associations can be expected (Shulman et al., 2008; Skinner et al., 2015; Stella, Banzato, Quagliato, Viana, & Christofoletti, 2008; Stewart, Fernandez, Okun, Jacobson, & Hass, 2008). Previous studies determined that motor symptoms interfere with ADL to a different extent than cognitive dysfunction (Benge & Balsis, 2016; Rasovska & Rektorova, 2011), which is confirmed through the current findings. This is an important step to aid in accurately identifying and diagnosing PDD, as well as helping to develop instruments to focus solely on cognitive-driven ADL dysfunction.

This current publication stands out from a study by Almeida et al. (2017) that proposed eliminating two items from the FAQ considered by the authors to be particularly vulnerable to motor severity. Using their modified (8-item) questionnaire, a cut-off of 3.5 (sensitivity of 47% and a specificity of 88%) differentiated between PD patients with and without ADL impairments. The claim that the two items using household appliances and preparing a balanced meal were triggered by motor influences was based on a hypothesis instead of previous literature. The authors also chose to validate their modified FAQ and new cut-off using a second informant-based questionnaire that measures changes in ADL impairment over two years, instead of using motor and cognitive scales as confirmation. Contrary to this approach, we chose a data-driven method that included all FAQ items in the analyses to enable a more systematic separation of cognitive and motor contributions, using associations with validated scales for measuring cognition and motor severity. Being able to attribute ADL impairment to the correct source is a considerable challenge for both clinicians and researchers, and this research has taken a considerable step towards distinguishing cognitive and motor influences.

3.1.3. Cognitive Profiles Associated with ADL Impairments

Beyond differentiating influences on ADL, we wanted to examine whether PD-MCI patients had more cognitive-driven ADL impairment compared to PD-CN patients**.** There is growing evidence that even non-demented patients with PD can demonstrate functional impairment (Manning et al., 2012; Young, Granic, Yu Chen, Haley, & Edwards, 2010), which may be a potential marker for faster progression to PDD. In general, PD patients are four times more likely to lose their independence in ADL than healthy controls, and this loss is irreversible in most patients (Bjornestad et al., 2016). In our study, PD-MCI patients showed greater cognitive and motor ADL impairments than PD-CN patients, possibly reflecting how increasing PD-related disease severity is associated with greater impairments in cognition (Lawson et al., 2014) as well as ADL (Holden et al., 2018). Both the FAQ_C and the FAQ_M were higher in PD-MCI patients, showing that the progressive nature of the disease affects both cognitive function and motor severity (Domellof et al., 2015). However, as disease duration was comparable between the two groups, it can be stated that both cognitive and motor ADL impairments are more severe in PD-MCI than PD-CN.

In PD-MCI, deficits in ADL function have also been shown to be related to worsening cognition and increased risk for PDD in cross-sectional (Cheon et al., 2015; Fellows & Schmitter-Edgecombe, 2019; Foster, 2014; Glonnegger et al., 2016; Pirogovsky et al., 2014), and longitudinal studies (Beyle et al., 2018). Current results demonstrated that one-third of the PD-MCI group showed more cognitive ADL impairments than motor-related ADL impairment, the percentage of which is very similar to the number of PD patients (26-39%) who converted to PDD within five years in previous studies (Broeders et al., 2013; Pedersen et al., 2017). PD-MCI patients with mild ADL deficits may therefore correspond to a high-risk group for conversion to PDD. Interestingly, we also found that 17% of PD-CN patients demonstrated more cognitive compared to motor ADL impairments. It is possible that this group represents a pre-MCI stage, indicating possible conversion to PD-MCI within a few years, however this needs to be evaluated further in longitudinal studies. In AD, a higher incidence of dementia was shown for patients who had increased ADL impairments at baseline (Di Carlo et al., 2016). For PD, a longitudinal study found that after 31 months, 21.7% of PD-CN patients had converted to PD-MCI (Gasca-Salas et al., 2014). These results again hint that the PD-CN group with ADL impairments could progress to PD-MCI in the short term. Further research into newly diagnosed PD patients has shown that even untreated PD patients demonstrate impaired ADL function compared to age-matched controls (Hariz & Forsgren, 2011), where approximately 15% of patients were functionally dependent at diagnosis (Bjornestad et al., 2016). However, loss of

independence was assessed using interviews in these patients, limiting the interpretation of these findings in relation to ADL scales. It would be interesting to examine both cognitive and motor ADL impairments PD patients longitudinally, to examine whether cognition and cognitive ADL, as well as disease severity and motor ADL, develop in parallel.

As PD-MCI has been defined as an important risk factor for PDD development (Aarsland et al., 2001a; Hanganu & Monchi, 2016; Litvan et al., 2011; Pedersen, Larsen, Tysnes, & Alves, 2013), we wanted to examine the differences in cognitive and motor ADL influences specifically in this group. Our results showed that PD-MCI patients with more cognitive-driven ADL impairment exhibited stronger deficits in the attention/working memory and language domains than those with predominantly motor-driven ADL impairment. These results are in line with a previous study that found that attentional deficit was the single strongest predictor of ADL performance related to dementia in PD, even after they controlled for sex, age, educational level, motor impairment, and cognitive functions (Bronnick et al., 2006). In our study cohort, attention also contributed to cognitive ADL skills when controlling for age, sex, educational level, and motor functions, emphasizing the role of attention in cognitive impairment. Recent studies have demonstrated greater attention deficits in PDD patients, emphasizing attention as a possible marker for conversion to PDD in PD-MCI (Biundo et al., 2014; Miura, Matsui, Takashima, & Tanaka, 2015; Pedersen et al., 2013). This attentional deficit may be explained by increased impairment in cholinergic and noradrenergic pathways, affecting the control of arousal and vigilance of PD patients. Stage 3 of the Braak model notes that pathology affects the basal nucleus of Meynert, a cluster of acetylcholine-rich neurons that project to various regions in the cortex affecting arousal, vigilance, and selective attention (Braak et al., 2003; Bronnick et al., 2006; Perry & Perry, 2004). In PDD patients, cholinergic deficit is severe, and can be improved using cholinesterase inhibitors. Rivastigmine, for example, has been shown to have a positive effect on ADL, attention, and verbal fluency in PDD patients (Emre et al., 2004; Meng, Wang, Song, & Wang, 2019), with the best response shown in patients with severe deficits in attention (Wesnes, McKeith, Edgar, Emre, & Lane, 2005). Therefore, attention plays an important role in PDD, and, as this study shows, in PD-MCI patients as well. Together with mild ADL deficits, they may pose a risk group for patients at risk of developing PDD.

Deficits in language were also shown in the PD-MCI group with cognitive ADL impairments, in line with previous studies demonstrating that language problems arise during conversion to dementia (Bastiaanse & Leenders, 2009; Chung et al., 2019; Hobson & Meara, 2004). The dual-syndrome hypothesis proposes that cognitive deficits such as semantic fluency,

language, and picture copying are predictors for conversion to PDD, as their posterior-cortical basis is related to impairment in multiple neurotransmitter systems, while fronto-striatal deficits including working memory and executive functions, related to dopaminergic dysfunction, are not predictors (Martinez-Horta & Kulisevsky, 2011; Williams-Gray et al., 2009; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). However, discrepancies have been noted in other studies demonstrating that cortical thinning in frontal regions predicted conversion to dementia (Chung et al., 2019; Compta et al., 2013). Our study agrees with the dual-syndrome hypothesis, as no differences were found in executive function between the two PD-MCI groups. While an earlier study also did not find a relationship between ADL and executive functions (Liepelt-Scarfone et al., 2013), other studies have shown efficient performance of ADL in PD relies on executive functions, which are affected early in the disease (Barbosa et al., 2017; Cahn et al., 1998; Higginson, Lanni, Sigvardt, & Disbrow, 2013). However, the validity and use of tests measuring executive functions have been debated in the literature, with studies claiming their inability to represent cognitive abilities in real-world situations (Chaytor & Schmitter-Edgecombe, 2003). A previous study found a relationship between instrumental ADL performance and memory, executive functions and processing speed, suggesting impairment these domains may predict PDD (Beyle et al., 2018). They specifically noted that worsening instrumental ADL function was characterized by trial and error behavior, which reflects executive functioning. However, this was a study using performance-based measures of ADL and therefore may assess different aspects of instrumental ADL than questionnaires. Longitudinal studies are therefore needed to examine this relationship in more detail.

3.1.4. Limitations of ADL Assessment and the FAQ

There are some limitations of the ADL assessment used in this study that need to be addressed. Patient-reported questionnaires are frequently used to provide insight into how cognitive impairment in PD affects their daily life (Foster & Hershey, 2011; Koerts, Van Beilen, Tucha, Leenders, & Brouwer, 2011). However, there are downsides to using patients' report of impairment, namely that PD patients have been shown to rate themselves as less impaired on measures of ADL than their caregivers (Christ et al., 2013; Leritz, Loftis, Crucian, Friedman, & Bowers, 2004; Shulman et al., 2006; Wadley, Harrell, & Marson, 2003). For the ABC-PD study, it was not specified a-priori who should fill out the FAQ. If a caregiver was not available, patients were asked to fill out the FAQ themselves. This potential bias was controlled for by examining the relationship between cognitive group and who filled out the FAQ, categorized

as either subjective (patient) or objective (spouse, child, close friend, or another informant), before conducting data analyses. As the relation between both was not significant, it was concluded that there was no difference in self vs. informant assessment between groups and therefore the groups were not separated in further analyses. These results are in line with other studies that have not found differences in how caregivers and patients report ADL disabilities (Brown, MacCarthy, Jahanshahi, & Marsden, 1989; Liepelt-Scarfone et al., 2013). It cannot be ruled out that some over-reporting of ADL dysfunction may have still occurred, as both patients and informants may have rated based on motor abilities instead of cognitive function (Kulisevsky et al., 2013). However, as the aim was to separate cognitive and motor influences, it is likely that this potential bias would have been eliminated through the analyses.

Shortcomings of the FAQ should also be mentioned, specifically that it was not originally designed for use in pathological aging or even as an informant-based measure. The FAQ has been found in older adults to be dependent on age and education, where functional dependence declined especially in adults over 85 years (Bezdicek, Stepankova, Martinec Novakova, & Kopecek, 2016). To overcome this potential bias age, sex, and disease duration were included in the individual FAQ item regressions. Using these covariates, any gender bias that may have affected the ADL domains would also have been eliminated. It has been shown that, out of different ADL domains, only shopping and cleaning were shown to be more severely impacted by disease severity in women than in men, possibly due to the general gender differences in these activities (Sperens et al., 2020).

In conclusion, this first study was able to differentiate the cognitive from motor influences on ADL impairment in PD using a validated ADL assessment. It was further shown that PD-MCI patients were more impaired on measures of cognition and ADL function than PD-CN patients. Moreover, PD-MCI patients with more cognitive ADL impairments showed significantly worse attention and language deficits compared to those with more motor-driven ADL dysfunction. A specific profile of cognitive impairment, namely deficits in attention and language, combined with mild ADL dysfunction could contribute to an accelerated cognitive decline resulting in PDD development. This is an association which further longitudinal studies need to examine.

3.2. NMS Burden as a Risk Factor for Cognitive Impairment

Based on results of the first study, the second publication aimed to further our understanding of clinical markers potentially predicting dementia in PD. PDD patients present

with widespread cognitive impairment, typically affecting multiple domains, as well as a decline from premorbid levels, with functional impairments severe enough to impact ADL (Emre et al., 2007). Further classification as probable PDD requires at least one behavioral feature to be present. These NMS, which have also been commonly associated with PD-MCI (Aarsland et al., 2007; Delgado-Alvarado et al., 2016; Monastero et al., 2013), have generally been studied independently of one another instead of as a combination of symptoms potentially influencing conversion to dementia. Naismith and Lewis (2011) showed that patients with greater severity of DASH symptoms had worse cognitive functioning, postulating this score could provide a simple measure for identifying patients who might progress to PDD.

3.2.1. Results of Publication 2

Two-hundred twenty-six PD patients recruited through the aforementioned ABC-PD study were included into the analyses. As with Publication 1, a comprehensive motor and neuropsychological examination was conducted in all patients, and the FAQ was used to calculate cognitive (FAQ_C) and motor (FAQ_M) ADL impairment. Using the Parkinson's Disease Questionnaire (PDQ-39) which assesses quality of life in PD (Peto, Jenkinson, & Fitzpatrick, 1998), we replicated the DASH score developed by Naismith and Lewis (2011). To determine validity of this questionnaire as the basis, we constructed a second DASH score based on questions from the NMS-Scale (Chaudhuri et al., 2007), which was developed specifically for the assessment of NMS in PD. NMS-Scale items were chosen based on close similarity to the original questions from the PDQ-39, to form the DASH-NMS and DASH-PDQ scores, respectively.

Correlation analyses tested the relationships among DASH scores and other PDD risk factors, including cognitive status and ADL impairments. Binary logistic regressions analyses further compared PD-CN and PD-MCI in relation to both DASH scores. Results of the Spearman correlation showed that the DASH-PDQ was associated with the levodopa-equivalent daily dose of anti-parkinsonian medication intake, disease duration, the MoCA score, as well as both FAQ subscores. In contrast, the DASH-NMS was significantly associated with a variety of different neuropsychological assessments, specifically with the MoCA and the scores of the attention/working memory, visuospatial functions, and language domains. Additionally, the DASH-NMS was correlated to the cognitive and motor subscores of the FAQ, but not to other clinical or demographical disease variables. The binary logistic regression showed the FAQ_C was the only statistically significant predictor of the DASH-NMS (p=0.01).

PD-MCI patients were then split according to the 50th percentile of the DASH-NMS into low vs high DASH burden groups, and those with high DASH burden were further divided into subgroups with high and low cognitive ADL impairment. The high-risk group (PD-MCI with high DASH-NMS burden and cognitive ADL dysfunctions) showed the lowest MoCA scores (p=0.036), indicating a lowered global cognitive function. This difference was statistically significant between the high-risk group and patients with a low DASH burden (adjusted p=0.045). Overall, these results demonstrate that the combination of these two prodromal markers (increased DASH burden and cognitive-driven ADL impairment) may present a risk group within PD-MCI patients who are at risk for conversion to PDD within a short time.

3.2.2. DASH Score Reproducibility

NMS burden was examined using the two DASH scores, constructed from the NMS-Scale and the PDQ-39. We found that the DASH-NMS scale could distinguish PD-CN from PD-MCI, while the DASH-PDQ could not. Results also showed that the DASH-PDQ was associated with demographic variables primarily reflecting certain motor parts of the disease, notably showing a stronger association with motor-driven ADL impairment (FAQ_M) than the DASH-NMS. This correlation reflects the high association of the DASH-PDQ with motor parts of the disease. The DASH-NMS was unaffected by these and therefore can be seen as being independent of motor influences, similar to the FAQ_C described in the first study.

These findings can be further explained by the main differences between the scales. First, the PDQ-39 is a self-rated questionnaire, while the NMS-Scale is interview-based. Second, both scales are scored differently; while the PDQ-39 is rated on a scale of 0-4, the items of the NMS-Scale are classified according to severity (0-3) and frequency (1-4) and then multiplied to obtain a total score (0-12). Third, each scale has a different aim: the PDQ-39 assesses quality of life associated with Parkinson's Disease symptoms, while the NMS-Scale examines specific non-motor symptoms occurring in Parkinson's Disease. Taken together, the PDQ-39 is self-rated with a smaller item score range than the NMS, which is scored by an experienced interviewer and has been designed to specifically quantify NMS (Chaudhuri et al., 2007). As the goal was to develop an instrument that is primarily associated with cognitive functions, we propose the NMS-Scale is a superior questionnaire than the PDQ-39 to construct the DASH score. Future studies should continue to examine both DASH scores in relation to cognitive decline to confirm this suggestion.

3.2.3. Relation of DASH Scores to Cognition and ADL Impairments

Associations between both DASH Scores and cognition were examined in detail. The DASH-NMS score was highly correlated with attention/working memory, visuospatial functions, and language domains. Impairment in these specific domains has been associated with conversion to dementia (Bastiaanse & Leenders, 2009; Biundo et al., 2014; Bronnick et al., 2006), as discussed in section 3.1.3. of this thesis. Moreover, attention and language deficits were also more prominent in the PD-MCI patients with cognitive-driven ADL dysfunctions identified by the first study of this thesis. These results demonstrate that a greater DASH burden affects cognitive domains implicated in PDD, strengthening the hypothesis that a specific combination of NMS may lead to a higher risk for conversion to dementia in PD.

Similar to the comparison of ADL dysfunctions in PD-MCI, the DASH-NMS did not show a significant relationship with executive functions, which are often noted to be the earliest functions impaired in PD (McKinlay, Grace, Dalrymple-Alford, & Roger, 2010). Along with findings supported by the data of our first study, the current results again argue in favor of the dual-syndrome hypothesis describing that functions with a posterior-cortical basis may better predict conversion to PDD than dopaminergic-dependent frontal functions. NMS in PD have been shown be driven by a multisystem neurotransmitter dysfunction, in addition to the ongoing dopaminergic degeneration. Depression in PD results as changes in serotonergic pathways, presenting even as early as the second stage in the Braak model, where deposition of Lewy bodies affects the brainstem, notably in the dorsal raphe nucleus and locus coeruleus (Simuni et al., 2018; Zhang et al., 2016). The serotonergic dorsal raphe nucleus is known to play a role in sleep/wake cycles, whereas the noradrenergic locus coeruleus is involved in attention and response to stress or panic and additional neuronal loss in adrenergic neurons throughout the brain may cause anxiety (Jellinger, 2015). Visual hallucinations, emerging as a result of cortical Lewy body deposition in the temporal-occipital regions, also predict accelerated cognitive deterioration and development of dementia in PD patients (Aarsland, Ballard, Larsen, & McKeith, 2001b; Harding, Broe, & Halliday, 2002). Interestingly, presence of visual hallucinations has been linked with executive dysfunctions in previous studies (Schapira, Chaudhuri, & Jenner, 2017), although the current data was not able to confirm this association. However, the results suggest a strong association between cognition and the combination of these specific NMS, promoting their usefulness in examining cognitive decline in PD. The spread of pathology and additional degeneration of various neurotransmitter systems early in the disease course drives the development of NMS and cognitive dysfunction.

Differing from the original study (Naismith & Lewis, 2011), the DASH-PDQ did not show any associations with cognition in our cohort. This can be attributed to the difference in sample size (53 vs. 226 patients), and the more extensive neuropsychological testing applied in our cohort. It is also notable that the DASH-PDQ, which only measures frequency of NMS, could not differentiate cognitive status. In contrast, the DASH-NMS was significantly correlated with cognitive domains shown to have a higher PDD risk, and significantly distinguished PD-MCI from PD-CN patients. Perhaps the important aspect of the DASH score that needs to be examined is not frequency of symptoms, but their severity. Increasing severity of NMS is also reflected in the spread of pathology through the peripheral and central nervous systems (Erro et al., 2016; Mou et al., 2019). Few studies to date have examined how the severity of specific NMS progresses in PD, focusing instead on their frequency in different diseases stages. Overall, the current findings highlight the role of severity of DASH symptoms in cognitive decline, which is a good starting point for future studies.

The additional study of ADL impairments in relation to cognitive dysfunction is important, as they are crucial for the differential diagnosis of PDD. Santos-Garcia et al. (2018) even found that patients with a higher NMS burden and lowered autonomy to carry out ADL, among other factors, were at a higher risk of death in the short term. In the second publication, both DASH scores showed a high association with ADL function, which would be expected as PD patients report that NMS have a significant negative impact on their daily life and social activities (Hermanowicz et al., 2019). A further analysis showed that cognitive-driven ADL impairment was the most significant predictor of the DASH-NMS score. This is a relatively novel finding, as the relationship between individual DASH symptoms and ADL impairment has been sparsely investigated, and studies examining this have solely focused on depression and ADL. One study found that patients with more severe depression scored lower on ADL measures than patients without depression (Piccinni et al., 2012), while another noted the negative impact of depression was stronger than the severity of motor impairment on ADL function (Dissanayaka et al., 2011). In contrast to these findings, results from other studies could not confirm a significant link between depression and ADL in PD (Foster, 2014; Laatu, Karrasch, Martikainen, & Marttila, 2013; Lawrence, Gasson, Kane, Bucks, & Loftus, 2014). In fact, one study has even shown that problems with ADL increase the risk of developing depression in PD (Marinus et al., 2018). This calls attention to the fact that the influences of the individual DASH symptoms on ADL function are unclear and need to be studied further. As motor and cognitive impairment as well as NMS burden and severity increase with disease duration, it is probable that a combination of these factors will lead to poorer ability to perform

ADL (Benge & Balsis, 2016). Furthermore, the combination of higher burden of DASH symptoms and mild cognitive-related ADL impairment in PD patients may define a group at risk for subsequent PDD development, which longitudinal studies need to verify.

3.2.4. Profile of PD-MCI Patients with both DASH Burden and ADL Impairment

As it has been shown that prodromal features of PD are more meaningful when combined (Liepelt-Scarfone et al., 2017), it may be beneficial to also examine the associations between varying risk markers. This was the rationale behind examining both the DASH-NMS score and ADL impairments (both independent criteria for the diagnosis of dementia) together, and how they relate to cognitive function (another criterion for PDD). The association of the DASH-NMS and ADL impairment was examined only in the PD-MCI group, which has previously been defined as the risk group for PDD (Anang et al., 2014). Only the DASH-NMS score was used for these analyses, as it showed significant correlations with cognitive function, whereas the DASH-PDQ did not. It was postulated that patients with a high DASH burden (DASH-NMS Score >1) would be those who had increased risk of developing PDD. Using this median split allowed for the simplification of analyses between the two groups, by using an unbiased, artificial cut-off. Alternatively, quartiles could have been used to divide the sample, yet this would have been disadvantageous as the sample size per group would have been too small for further analyses.

Results showed that a higher burden of DASH-NMS symptoms corresponded to a more affected global cognitive status, as assessed by the MoCA. This effect remained when stratifying the groups according to both non-motor burden and the FAQ_Q. Specifically, this association was significant between patients with a combined high DASH burden and cognitive-driven ADL impairment, compared to patients with only a low DASH burden. The MoCA is a validated screening tool for cognitive impairment in PD, and studies have confirmed that the MoCA is sensitive for assessing early cognitive impairment (Sulzer et al., 2018; Zadikoff et al., 2008). However, its prognostic ability for predicting cognitive decline seems to be rather low (Faust-Socher et al., 2019). In the regression, the MoCA did not predict the DASH-NMS score, showing that cognitive impairment per se does not increase the risk for higher NMS burden. Rather, this association is modulated by the severity of cognitive-driven ADL impairment, reflected by the addition of the FAQ_C score. Based on the results of the present cross-sectional study, we are not able to conclude if cognitive impairment is the main cause of ADL impairment, and whether it also facilitates progression of NMS in PD.

Longitudinal studies should therefore aim to further investigate this relationship and whether there is a causal relationship between NMS burden, ADL function, and cognitive decline.

If specific risk factors for PDD conversion can be specified, appropriate therapeutic measures can be taken to improve functioning and hopefully prevent conversion to PDD or slow down worsening of both cognitive and ADL dysfunction. Non-pharmacological treatments aiming to improve ADL functions such as cognitive training (Hindle, Petrelli, Clare, & Kalbe, 2013) have been described to be effective in maintaining cognitive status in the short- and long-term in PD (Nousia et al., 2020). Other methods for training both cognition and ADL function focus on endurance and coordination, such as Exergames, physiotherapy, Nordic walking, and dancing (Barry, Galna, & Rochester, 2014; Bombieri et al., 2017; Schenkman et al., 2012). Improving cognitive function could also concurrently improve NMS, however this needs to be examined in further studies (Leung et al., 2015; Petrelli et al., 2015). Targeted treatment of the separate DASH symptoms would also be beneficial, as both pharmacological (Chaudhuri, Healy, Schapira, & National Institute for Clinical, 2006; Schapira et al., 2017; Titova & Chaudhuri, 2018) and non-pharmacological (Cusso, Donald, & Khoo, 2016) treatments exist to ameliorate these symptoms. It is unclear whether addressing these symptoms has the potential to delay or prevent cognitive decline, yet targeted treatment should at least lead to an overall improved quality of life.

3.2.5. Limitations of the DASH Scores

The most important limitation that needs to be mentioned is that the presence and severity of anxiety, depression, and sleep disturbances are not independent from each other in PD. Depression and anxiety are often comorbid in PD (Menza, Marin, Kaufman, Mark, & Lauritano, 2004; Yamanishi et al., 2013), and have been shown to be associated with the occurrence and progression of excessive daytime sleepiness over time, possibly reflecting the spreading of pathology within the brainstem (Amara et al., 2017). A recent cluster analysis was able to distinguish six different subtypes of NMS in early and untreated PD patients: cognition, apathy, depression/anxiety, REM sleep behavior disorders (including visual hallucinations), lower limb pain, and olfactory disturbance (Sauerbier, Jenner, Todorova, & Chaudhuri, 2016). This suggests that while depression and anxiety might be too related to be examined as separate entities in the DASH score, they are still distinct from both sleep disturbances and cognition. Thus, our findings that DASH and cognition are separate and can influence each other remains a valid assumption. Also, there is a significant benefit to this interaction, specifically that the

amelioration of symptoms becomes easier. Treatment of the central symptom (e.g. depression) can lead to improvements seen in associated symptoms (e.g. sleep disturbances and anxiety) (Engels et al., 2019). Perhaps treatment of the DASH symptoms can lead to improvements in cognition and ADL functioning, however this is purely speculative and would need to be examined in future studies.

It should also be noted that NMS can also be largely influenced by dopaminergic drugs or even emerge as side-effects of these medications (Zis et al., 2014). Sleep disorders in PD are thought to result from an interplay between neurodegeneration, side effects of PD medications, nightly persistence of motor symptoms, and other comorbid diseases (such as sleep apnea) (Salawu & Olokoba, 2015). Hallucinations are not only an expression of PD pathology, but can also be induced or enhanced by dopamine replacement therapy (Schaeffer & Berg, 2017). Depressive symptoms have been shown to significantly improve one year after time of diagnosis (Larsen, Dalen, Pedersen, & Tysnes, 2017), with the authors attributing this to an improvement of psychological and social factors after receiving a diagnosis, as well as initiation of dopaminergic medications. However, previous studies did not find that NMS improved with the initiation of dopamine therapy (de la Riva, Smith, Xie, & Weintraub, 2014), nor that progression of NMS was associated with the dosage or type of dopaminergic medication (Simuni et al., 2018). A factor analysis showed cognitive impairment, depression, excessive daytime sleepiness, and psychosis did not improve when patients were given dopamine replacement therapy (van Rooden et al., 2010). Based on these conflicting results, it is not possible to determine whether treatment with dopaminergic medication would have affected our PD sample. While patient groups did not differ in the daily dosage of antiparkinsonian medications, the effects that medication may have had up until the point of testing cannot be ruled out. Future studies should therefore not only examine the predictive value of the DASH score, but also how these symptoms are associated with dopamine replacement therapy and whether these have a positive or negative influence on cognition.

In conclusion, in the second study we were able to construct a novel DASH-NMS score based on the original DASH score developed by Naismith and Lewis (2011). We assume the DASH-NMS to be a more viable score for assessing NMS burden as it could differentiate between PD-CN and PD-MCI patients, and demonstrated significant associations with specific cognitive domains and cognitive-driven ADL impairment. PD-MCI patients with a high NMS burden and more cognitive ADL impairment showed worse global cognitive functioning, as assessed by the MOCA, than PD-MCI patients with only a low DASH burden. Therefore, the combination of DASH burden and cognitive ADL impairment may characterize a risk group of

PD-MCI patients who will progress to PDD in the short-term. Longitudinal studies are needed to investigate whether these patients are indeed a high-risk group and to further examine the relationship between NMS burden, ADL function, and cognitive decline.

3.3. The Hippocampus as a Structural Marker for Cognitive Impairment

In recent years, there has been a shift in the view that the hippocampus is not affected in PD. Grey matter atrophy in various brain structures, including the bilateral hippocampal formation, has been shown to occur in PD-MCI patients, with neuronal loss in these regions correlating with global cognition as well as motor impairment (Melzer et al., 2012). Hippocampal atrophy has also been linked to CSF Aβ42 levels, which have been shown to be lowered in PD patients compared to controls and are associated with a rapid cognitive decline (Backstrom et al., 2015; Buddhala et al., 2015). The hippocampus, especially its subfield volumes as a potential imaging marker for cognitive impairment, and its association CSF biomarkers, cognition, and ADL impairments has only been sparsely studied in PD patients.

3.3.1. Results of Publication 3

Data of 45 patients was collected as part of the baseline visit of the longitudinal study "Non-demented patients with Parkinson's Disease with and without low Amyloid-beta 1-42 in cerebrospinal fluid" (ABC-PD Longitudinal). All patients underwent a neurological and neuropsychological examination, MRI imaging, as well as a lumbar puncture to determine CSF Aβ42, phosphorylated tau (p-tau), and total tau (t-tau) levels. The cohort was stratified according to either cognitive diagnosis or CSF Aβ42 biomarker status. According to the Level I criteria recommended by the Movement Disorder Society (Litvan et al., 2012), the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) score was used to define the PD-CN (≥26 points) and PD-MCI (<26 points) groups. For the biomarker analyses, an Aβ42 cut-off of 600 pg/mL (Lerche et al., 2019) divided the sample into two groups: Aβ42+ (<600 pg/mL) and Aβ42– (≥600 pg/mL). Freesurfer image analysis suite 6.0 (Iglesias et al., 2015) was used to segment the hippocampus of each patient into 12 distinct subfields: hippocampal tail, subiculum, Cornu Ammonis (CA) 1, hippocampal-fissure, presubiculum, parasubiculum, molecular layer, granule cell layer of the dentate gyrus (GC-DG), CA2-3, CA4, fimbria, and the hippocampal-amygdaloid transition area (HATA).

Linear regression models were used to compare hippocampal subfield volumes in the two study groups (cognition and Aβ42 status), correcting for estimated intracranial volume (ICV). Partial correlations assessed the association between neuropsychological tests, CSF biomarkers, FAQ subscores and hippocampal subfields, while controlling for ICV. PD-MCI patients performed worse than PD-CN patients on a number of neuropsychological tests, which confirmed an accurate division of the cognitive groups. The linear regression showed PD-MCI patients had smaller HATA (p=0.04) and a trend towards smaller CA1 (p=0.05) volumes than PD-CN. No significant differences were found for hippocampal subfield volumes or cognitive tests after group stratification according to CSF Aβ42 levels. Results of the correlation analyses revealed smaller hippocampal subfield volumes were associated with worse memory, language, spatial working memory and executive functioning as well as higher CSF tau levels. Interestingly, greater severity of ADL impairment, measured by the FAQ and its subscores, was associated with larger hippocampal subfield volumes. Overall, our results show that the HATA can differentiate cognitive groups, and that hippocampal subfield volume, but not CSF Aβ42, is a promising marker for cognitive decline.

3.3.2. Hippocampal Structures Differentiating Cognitive Groups

Studies investigating the association between hippocampal atrophy and cognition in PD have been inconclusive. While some studies demonstrate greater hippocampal atrophy in cognitively impaired patients, especially in PDD compared to non-demented patients (Nagano-Saito et al., 2005), others could not replicate this finding (Xu et al., 2016). Heterogeneity in these previous studies may arise from researchers regarding the hippocampus as a whole structure, instead of as consisting of many separate substructures with distinct characteristics. In our study, there was also no difference in the volume of the whole hippocampus between PD-CN and PD-MCI patients, but study groups differed in the volumes of the HATA region. The results showed that only the HATA region was smaller in PD-MCI patients than in PD-CN. While this was an unexpected finding, a previous longitudinal study also found an involvement of the HATA in PD cognition (Foo et al., 2017). They demonstrated that the right HATA, along with left fimbria and right CA1 volumes, was smaller in PD-MCI patients than PD-CN at baseline. Furthermore, left HATA volume at baseline was among the most significant predictors of conversion to PD-MCI after 18 months. Combined with our current results, this highlights the role of the HATA in both differentiating cognitive impairment, as well prediction potential for cognitive decline.

Research into hippocampal subfields has proposed that smaller CA1 and subiculum regions are associated with an increased risk of conversion from mild cognitive impairment to AD (Apostolova et al., 2006). This general pattern of neurodegeneration seen in AD has been associated with the progression of cognitive dysfunction in PD (Weintraub et al., 2012), with studies reporting smaller CA1 volumes in PD-MCI patients compared to PD-CN (Beyer et al., 2013b; Foo et al., 2017; Low, Foo, Yong, Tan, & Kandiah, 2019). While this could not be replicated in our results, a trend that almost reached significance was noted in CA1 volume between PD-CN and PD-MCI. As the CA1 is one of the output regions of the hippocampus, it has been suggested to play a role in attention (Muzzio, Kentros, & Kandel, 2009), and atrophy of this region could aggravate further cognitive decline. This would be in line with the previous publications of this thesis, highlighting attentional deficits as a possible risk factor for cognitive deterioration. More longitudinal studies are needed to examine its role in cognitive progression, as it has been sparsely studied in relation to PD and our current research only allows us to make inferences from cross-sectional data.

It is possible that so few differences were found between our two cognitive groups as hippocampal atrophy has been shown to be present in PD-CN as well as PD-MCI patients (Apostolova et al., 2012). The Braak staging model postulates that in stages 3 to 4, Lewy bodies and neurites spread to involve the amygdala, entorhinal cortex, and hippocampus (Braak et al., 2005), which may be reflected as hippocampal atrophy on MRI. In stage 3, pathology also affects the *substantia nigra*, resulting in the onset of motor symptoms in PD. Concurrent involvement of both these structures may be found early in the disease course, possibly reflecting hippocampal atrophy as an early marker of cognitive progression (Aybek et al., 2009). This is a plausible explanation for the similar hippocampal volumes, as our patient groups did not differ in terms of disease duration. There has also been considerable divergence in how PD-MCI was diagnosed between studies examining the hippocampus. Different studies have compared different cognitive groupings: all PD patients compared to controls, non-demented (combining both PD-CN and PD-MCI) vs. demented patients, or PD-CN and PD-MCI. This heterogeneity hinders the interpretation of our data, as we cannot compare with results using different diagnostic criteria. It is possible that our cognitive groups would show more hippocampal atrophy compared to controls, or more compared to PDD patients, yet this was not examined in our study. It is also unclear whether grouping PD-CN and PD-MCI patients would be advantageous. Further studies should therefore examine atrophy in specific cognitive groups while aiming to maintain a standardized diagnosis of PD-MCI. Nevertheless, mean hippocampal volume has been previously found to be a significant predictor for the progression

from PD-CN to PD-MCI, and from PD-MCI to PDD (Kandiah et al., 2014). This also highlights the importance of longitudinal studies. Examining the extent of atrophy in PD patients compared to both healthy controls and PDD patients would be extremely beneficial to determine whether there is a spectrum of atrophy in PD that correlates with cognitive decline.

3.3.3. Associations Between Hippocampal Subfields and Neuropsychological Tests

Besides examining the profile of PD-CN and PD-MCI patients, we wanted to determine how hippocampal subfields were related to neuropsychological test performance in our sample. Atrophy of medial temporal lobe structures has been assumed to run in parallel and may even give rise to the memory impairment seen in PD (Ibarretxe-Bilbao, Tolosa, Junque, & Marti, 2009). The organization of the hippocampal subfields forms a unidirectional circuit (Pereira et al., 2013). After receiving input from the entorhinal cortex, the GC-DG projects to the CA2-3 region, which in turn projects to the CA1. The CA1 then sends its projections to the major output region, the subiculum, which branches out into numerous cortical and subcortical regions (Duvernoy, Cattin, & Risold, 2013). Complex interactions between each subfield may influence both the pathophysiological and the cognitive processes in PD (Foo et al., 2017). Hippocampal volumes correlated with memory tests, supporting the notion that atrophy of these structures runs in parallel to cognitive decline (Ibarretxe-Bilbao et al., 2009). The Paired Associates Learning subtest of the computer-based Cambridge Neurological Test Automated Battery (CANTAB) was shown to correlate with almost all hippocampal structures, most importantly the CA1, CA2-3, CA4, and DG regions. Previous studies have shown that input hippocampal regions, such as the CA2-3 and DG, are associated with learning and encoding, output regions including the subiculum are related to recall, and the CA1 region is responsible for consolidation and later retrieval (Carr, Viskontas, Engel, & Knowlton, 2010; Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Mueller et al., 2011; Pereira et al., 2013). Our results reflect these findings, with errors made on the PAL test encompassing all aspects of memory. This specific subtest has even been shown in AD patients to be strongly associated with hippocampal volume (Nathan et al., 2017), characterizing hippocampal-dependent memory loss in the earliest stages of AD.

Verbal learning and recall have been associated with bilateral hippocampal atrophy in non-demented and demented PD patients (Bouchard et al., 2008; Ibarretxe-Bilbao et al., 2008; Junque et al., 2005; Noh et al., 2014), most notably in the CA1, CA3 and subiculum (Bouchard et al., 2008). We could not replicate these findings using paper-and-pencil based tests, possibly

reflecting that computerized tests are more sensitive than paper-and-pencil tests in relation to hippocampal volume. More research is necessary to examine sensitivity of both types of tests for detecting cognitive impairment and hippocampal atrophy in PD.

Our results in publication 3 also showed significant associations between the subfields and recognition memory. For the CANTAB recognition subtest, the strongest correlations were with the GD-DG and CA1 regions, with weak correlations also for the CA4 and HATA. The pencil-and-paper subtest showed weak correlations with the hippocampal tail, subiculum, and CA1 regions. This is an interesting finding, as PD patients generally demonstrate intact recognition memory (Aggleton & Brown, 1999; Bouchard et al., 2008; Cohn, Giannoylis, De Belder, Saint-Cyr, & McAndrews, 2016), although this notion has been debated (Das, Hwang, & Poston, 2019; Higginson, Wheelock, Carroll, & Sigvardt, 2005). Recognition scores have been associated with left hippocampal volume (Camicioli et al., 2003) as well as right subiculum and CA1 areas (Beyer et al., 2013b), in concordance with our findings. As there is no current agreement on the role of recognition memory in PD, further studies are needed to evaluate our study findings on the relationship between recognition memory and hippocampal volume.

Spatial working memory was negatively correlated to the parasubiculum, CA4, DG and fimbria, where a higher number of errors was related to smaller volumes. The fimbria has been shown to play a role in spatial working memory performance in rats (Sutherland & Rodriguez, 1989), with reduced volume in PD-MCI patients potentially characterizing an early marker of visuo-spatial dysfunction (Foo et al., 2017). While the deficit in spatial working memory in PD can be explained by disruption of visuo-spatial processing circuits involving the caudate nucleus (Possin, Filoteo, Song, & Salmon, 2008), the current study findings also emphasize the role of memory, specifically encoding, and the hippocampus. Future studies should examine whether fimbria volumes are predictive of cognitive decline and visuo-spatial dysfunction longitudinally. Based on these results, we would have also expected to find associations between hippocampal volumes and visuospatial functions. However, we did not, which is in contrast to previous studies (Aggleton, 2012; Rektorova et al., 2014; van Strien, Cappaert, & Witter, 2009). Moreover, this pattern does not reflect the dual-syndrome hypothesis supported by the earlier studies of this thesis, where posterior cortical changes reflect the progressive nature of cognitive decline. Instead, results from this hippocampal study reflect the notion of fronto-striatal dysfunction and dopamine loss in these regions in relation to cognitive impairment.

The extent to which working memory, including spatial working memory, is related to executive functions and mediated by frontal circuits (Kehagia et al., 2013) is unclear. A previous study has shown that tests measuring spatial working memory and set-shifting, which are mediated by fronto-striatal systems, are impaired in PD (Riekkinen et al., 1998). Others have been unable to show an association between hippocampal and frontal functions (Beyer et al., 2013b; Ibarretxe-Bilbao et al., 2009). In this study we identified significant correlations between a measure of executive function (Stockings of Cambridge task) and the molecular layer, the DG, and the fimbria. Correlations between an information sampling task, measuring impulsivity in reactions which is often affected in PD, and hippocampal volumes (DG, CA4, fimbria, HATA and whole hippocampus) were also detected in our study. It is possible that these executive dysfunctions, which have shown to be impaired in the earliest stages of cognitive decline, reflect impairment in fronto-striatal loops (McKinlay et al., 2010). Studies show that there is a gradient of neuropathology affecting the hippocampus (Summerfield et al., 2005), with the extent of cognitive impairment relating to the deposition of Lewy bodies and neurites (Churchyard & Lees, 1997). This study reflects an early cognitive impairment characterized by hippocampal atrophy and executive dysfunctions, which will, however, need to be replicated in longitudinal studies and cohorts with varying stages of cognitive decline. Overall, results emphasize the role of hippocampal subfield atrophy as a potential marker for cognitive decline in PD, showing associations with different memory functions as well as executive functions, which needs to be verified in future studies.

3.3.4. CSF Biomarker Profile in Relation to Cognition and Hippocampal Volume

Stratifying the sample based on Aβ42 levels (Aβ42+, <600 pg/mL; Aβ42–, ≥600 pg/mL) did not reveal any differences on demographical variables or neuropsychological test scores. This was a surprising result, as low Aβ values have previously been shown to be associated with cognitive decline (Brockmann et al., 2015; Zhang et al., 2013). Aβ42 pathology has been specifically related to deficits in attention/working memory (Leverenz et al., 2011), memory (Stav et al., 2015), visual memory (Yarnall et al., 2014), verbal fluency (Compta et al., 2009), and slowed processing speed (McMillan & Wolk, 2016). The current results did not support these previous findings. Moreover, longitudinal studies have emphasized that pathological Aβ42 levels predict development of PDD (Alves et al., 2014; Backstrom et al., 2015; Hall et al., 2015; Parnetti et al., 2014). Lower 42 levels were expected in the PD-MCI group, as they

are at risk for PDD development (Anang et al., 2014), yet this was also not replicated by the current research.

Some studies, however, have recently debated the influence of Aβ42 in PD patients, especially relating to cognitive decline (Melzer et al., 2019; Winer et al., 2018). Lower levels of Aβ42 were found in PD-MCI patients who subsequently developed PDD, yet Aβ42 levels were not significantly lower in PD-MCI patients compared to PD-CN in a cross-sectional analysis (Weil, Costantini, & Schrag, 2018). One study did not find a difference in Aβ protein accumulation between PD-CN and PD-MCI patients, however the baseline presence of pathological Aβ42 levels was weakly correlated with cognitive decline over three years (Gomperts et al., 2013). It is possible that the presence of Aβ42 does not reflect the severity of cognitive impairment, but rather predicts decline over time (Sasikumar & Strafella, 2020). Two previous studies have shown that patients with lower Aβ42 levels developed PDD within two years (Siderowf et al., 2010; Terrelonge, Marder, Weintraub, & Alcalay, 2016). It is possible that patients in the current study with low Aβ42 values may progress to PDD faster than those with normal levels, however our cross-sectional analyses impede this evaluation.

No differences were found in hippocampal subfield volumes between both Aβ42 groups. This is a novel finding, as very few studies have examined the relationship between hippocampal volume and CSF biomarkers in PD to date. A previous study did not find that mean hippocampal volume was a significant predictor of CSF biomarker levels (Beyer et al., 2013a). Their associations in the PD-CN group suggest that changes in CSF and brain structures develop before the manifestation of clinically relevant cognitive symptoms. However, only newly diagnosed drug-naïve patients were measured in this study. Aβ42 levels have been shown to be associated with ventricular enlargement (Beyer et al., 2013a), and with atrophy in frontal, parietal, and occipital cortices, but not with atrophy in the temporal lobe (Compta et al., 2012; Compta et al., 2013). It is possible that the hippocampus is not affected by Aβ42 pathology in PD, which our current results support. More research is still needed to determine the association between these two markers in PD.

Previous studies in both AD and PD suggest that some of the heterogeneity in the relationship between Aβ42 burden and cognitive function may be explained through other CSF biomarkers, such as total tau, phosphorylated tau and α-synuclein (Compta et al., 2009; Halliday, Holton, Revesz, & Dickson, 2011; Parnetti et al., 2014). Studies in AD show associations between greater hippocampal atrophy, lower Aβ42, and higher t-tau and p-tau (Tarawneh et al., 2015; Wang et al., 2012). Aβ42, t-tau and p-tau have previously been linked

to hippocampal atrophy and ventricular enlargement in AD (Apostolova et al., 2010b), yet in PD the results are more heterogeneous. Stav et al. (2016) did not find associations between CSF biomarkers and hippocampal volumes, even though subiculum volumes were reported to be smaller in PD patients compared to controls. We also identified a moderate correlation between lower subiculum volumes and higher values of total tau in our PD sample. While it still remains unclear whether neurodegeneration seen in PD is due to the underlying PD pathology, or AD pathology (Laakso et al., 1996), our findings argue for a greater role of tau pathology in hippocampal atrophy than Aβ42.

3.3.5. Associations Between Hippocampal Subfields and ADL Dysfunction

Beyond examining the relation between hippocampal volume and cognition, we looked at the correlation between subfield volumes and measures of ADL function, namely the FAQ and the subscores developed in the first publication. Interestingly, our study argued that greater severity of ADL impairment was associated with larger hippocampal subfield volumes. This may mirror compensation strategies of the hippocampus, to counteract already occurring daily relevant cognitive deficits in a vulnerable phase of the disease, however this is purely speculative. The relationship between hippocampal atrophy and ADL impairments has been sparsely studied in PD, and even in AD research studies are lacking. One cross-sectional study showed hippocampal volume independently predicted the severity of ADL deficits in AD patients (Brown, Devanand, Liu, Caccappolo, & Alzheimer's Disease Neuroimaging, 2011), another demonstrated associations between instrumental ADL and grey matter volume in the medial temporal lobe, predominantly the hippocampus, and the cingulate cortex (Jutten et al., 2019). Longitudinal studies in AD patients showed severity of atrophy in the hippocampus is correlated with deterioration of ADL deficits after one year (Choi et al., 2018), and baseline temporal atrophy predicts worsening of instrumental ADL function (Marshall et al., 2014). Both hippocampal and grey matter loss have been associated with a rapid decline in instrumental ADL function in AD (Cahn-Weiner et al., 2007; Slachevsky et al., 2019). A separate study only indirectly examined ADL and hippocampal atrophy; they found that in early AD, impaired cognition led to impaired ADL, attributing this to reductions in grey matter in the temporal and parietal cortices (Vidoni, Honea, & Burns, 2010).

As the current study sample only included non-demented PD patients, ADL impairment assessed with the FAQ was most likely at a mild stage and not severe enough to show negative correlations to hippocampal volume. We also did not examine the correlations separately

between PD-CN and PD-MCI patients, to determine whether there was a different association between cognition, hippocampal volume, and ADL function. For AD patients, it has been postulated that severity of both hippocampal atrophy and instrumental ADL dysfunction merely reflects the advanced disease state (Overdorp, Kessels, Claassen, & Oosterman, 2016). It would be imperative to separate patients based on cognitive status (PD-CN, PD-MCI, and PDD) in future studies. Moreover, it is possible that cross-sectional analyses are less reliable, and longitudinal studies are instead needed to determine whether baseline volumes of hippocampal atrophy are predictive of decline in ADL function in the long-term.

3.3.6. Limitations of Hippocampal Acquisition, Segmentation, and Analysis

There are some limitations that need to be addressed. Only a small sample of the study cohort were able to undergo MRI evaluation as not all patients are able to obtain MRI scans, due to various factors (e.g. implanted metal devices or severity of motor symptoms). This may cause inclusion bias and affect the reliability of findings, as more severely affected subjects are excluded. However, an important strength of the current study is that a 3 Tesla scanner was used, as a higher field strength has been shown to be associated with better segmentation results (Kruggel, Turner, Muftuler, & Alzheimer's Disease Neuroimaging, 2010). This scanner was also kept consistent over all patients to reduce bias caused by using different machines.

It is also necessary to note the limitations of the segmentation program used, most importantly that it is not based on histological landmarks and therefore definition of the distinct subfields may be inaccurate and should be interpreted with caution. The FreeSurfer software is not validated against manual segmentation, with a tendency to over-estimate subfield volumes (Van Leemput et al., 2009; Wenger et al., 2014; Wolf, Fischer, de Flores, Chetelat, & Fellgiebel, 2015), yet this is a well-known problem in hippocampal subfield analyses (Iglesias et al., 2015). There is great need for a standardized segmentation technique that specifies, for example, number of segmented subfields as well as border definitions for segments, as different segmentation techniques in previous studies contribute to the variability in study results. However, FreeSurfer still provides useful information, and by combining information from T1, T2, and Fluid-Attenuated Inversion Recovery (FLAIR) sequences enhances the precise identification of hippocampal subfield boundaries.

Although the study group was predominantly male, we corrected for a possible bias towards larger hippocampal size by including the intracranial volume into our correlations. Previous studies have also found significant correlations between the hippocampus, disease

severity (Apostolova et al., 2012; Bouchard et al., 2008), and age (Apostolova et al., 2010a; Camicioli et al., 2003). As motor severity, assessed using the UPDRS-III, and disease duration were not significant between cognitive groups in our cohort, disease progression and severity as an indicator for differences in hippocampal volume can be excluded. One study found hippocampal volume was correlated with age, but not with disease duration, disease onset, education, global cognition, or UPDRS-III scores (Apostolova et al., 2010a). We did not look at demographic correlations as we were more interested in associations to cognition and CSF markers, and therefore cannot exclude the influence of demographic factors. Nonetheless, as they were not significant between stratified groups, we chose not to include these potential cofounders. Lastly, due to lack of a healthy control group, hippocampal volumes in PD patients could not be compared to normal ageing effects.

Overall, the findings from the third publication add to our understanding of how the hippocampus is affected in PD, and how it is associated with CSF biomarkers, cognition, and ADL dysfunction. Hippocampal subfields showed significant associations with cognitive functions, namely memory, spatial working memory, language, and executive functions, and specifically the HATA was able to differentiate between cognitive groups. No substantial association was found for CSFAβ42 levels, yet tau levels showed significant associations with the subiculum. While further longitudinal studies are urgently needed, structural changes in hippocampal subfields may present early risk markers for cognitive progression and development of PDD.

3.4. General Research Limitations

There are some overarching limitations of this thesis that need to be addressed. It is important to note that the cross-sectional analysis design of all three studies impedes any definitive conclusions as to how the identified risk markers predict cognitive decline and PDD development. The large scale of the ABC-PD study disallowed for all factors to be controlled, such as test administration by the same neuropsychologist and similar time frames of testing for each patient. However, such variables are difficult to control in clinical settings. Moreover, there was no post-mortem verification of PD diagnosis, nevertheless participants were seen by an experienced neurologist to confirm the diagnosis according to the most recent clinical consensus criteria. Patients where a differential diagnosis after study inclusion was given were excluded from the analyses.

Patients with severe depressive symptoms, as indicated by a Beck-Depression-Inventory II (Beck, Steer, & Brown, 1996) score >19 points, were also excluded from analyses in all three papers. The reasoning was that severe depression been shown to negatively affect cognition in PD (Chagas et al., 2014; Ng, Chander, Tan, & Kandiah, 2015). Presence of major depression is also an exclusion factor for the diagnosis of both PD-MCI and PDD (Emre et al., 2007; Litvan et al., 2012), which would have made our PD-MCI sample less clear-cut. It would have therefore been difficult to determine the relationship between the clinical and structural markers, and cognitive function. Moreover, for the second study, a major depressive episode would introduce bias into the DASH score, with depression driving a correlation between higher DASH scores and worse cognitive performance, driven by severe depression. Naismith and Lewis (2011) did not include patients with major depressive disorder defined by the Beck Depression Inventory-II values. As one of the aims was to replicate this score in a larger cohort, we attempted to keep the set-up of the study as similar as possible, leading to the exclusion of patients with major depression. For the third study, it should be noted that hippocampal atrophy in PD may result from other factors apart from PDD or PD-related neuropathology. Major depression has been shown to negatively influence the size of the hippocampus in the general population (van Mierlo, Chung, Foncke, Berendse, & van den Heuvel, 2015). Although our PD patients were not clinically depressed at the time of visit, we cannot rule out that a possible occurrence of minor depressive symptoms during their lifetime may have had an effect on hippocampal volume.

To diagnose PD-MCI, criteria set forth by the Movement Disorder Society, as well as their guidelines for allocating each neuropsychological subtest to a cognitive domain, were used (Litvan et al., 2012). Classification in the first two papers was based on the comprehensive Level-II criteria, which recommends using at least two tests for each of the five cognitive domains. However, the assignment of neuropsychological tests to the specific domains has been debated, as certain tests can be sensitive to more than one domain or even have overlapping features with other tests (e.g. visuospatial tests include components of attention and executive function) (Williams-Gray et al., 2007). Variations between study centers therefore leads to the heterogeneity in diagnosing PD-MCI throughout the literature. While we did not conduct a factor analysis to determine how each neuropsychological test loads on the five cognitive domains, it may be beneficial for future studies, especially within this cohort, to examine this and determine whether the Level-II guidelines used are accurate. For the third paper, we only used Level-I classification based on the MoCA score, but stratification was supported by

between-group differences on both computerized and paper-pencil neuropsychological tests, where PD-MCI patients performed significantly worse on measures of attention and language.

4. Conclusion

The diagnosis of PDD indicates an important milestone of the disease, as it is associated with a higher likelihood of a rapid disease progression, reduced quality of life, and mortality. Therefore, it is of the utmost priority to identify features and valid assessments that detect cognitive impairment in PD at an early stage and can predict development of PDD with high accuracy. Distinctive clinical symptoms (ADL impairment and NMS burden) as well as structural markers (hippocampal volumes and CSF biomarkers) were examined to determine their relationship to cognitive function in non-demented PD patients in the prodromal stage of PDD. A combination of ADL impairments and DASH burden as well as a specific cognitive profile including deficits in attention, visuo-spatial functions, and language, possibly reflect an at-risk group for PDD conversion. Structural changes in hippocampal subfield volumes may also present early risk markers for cognitive decline, and our results suggest that the HATA has the potential to differentiate cognitive status in PD. Hippocampal atrophy may occur very early in the disease course, underlying future cognitive decline and reflecting impaired frontal functions evident in early PD. While Aβ42 deposition did not reflect cognition, CSF total tau levels were associated with hippocampal atrophy, and may present a better progression marker for cognitive impairment in PD.

In conclusion, this thesis emphasizes that examining combinations of dementia risk markers can be beneficial for characterizing sub-groups of PD-MCI patients, which would allow tailored treatments and therapeutic interventions aimed at delaying cognitive decline and maintaining patients' quality of life for as long as possible. Clinical, structural, and CSF risk markers, as well as specific combinations of these factors, showed associations with cognitive function in the prodromal stage of PDD. Longitudinal studies are now needed to determine whether the groups identified are at high risk for developing dementia, and how the individual markers predict cognitive progression.

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6. Appendix

A) Becker, S., Baumer, A., Maetzler, W., Nussbaum, S., Timmers, M., Van Nueten, L., Salvadore, G., Zaunbrecher, D., Roeben, B., Brockmann, K., Streffer, J., Berg, D., & Liepelt-Scarfone, I. (2020). Assessment of cognitive-driven activity of daily living impairment in non-demented Parkinson's patients. *J Neuropsychol*, 14(1), 69-84. doi:10.1111/jnp.12173

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Assessment of cognitive-driven activity of daily living impairment in non-demented Parkinson's patients

Sara Becker[1,2], Alena Bäumer[1,2], Walter Maetzler[1,3], Susanne Nussbaum[1,2], Maarten Timmers[4,5], Luc Van Nueten[4], Giacomo Salvadore[6], Detlev Zaunbrecher[7], Benjamin Roeben[1,2], Kathrin Brockmann[1,2], Johannes Streffer[4,5], Daniela Berg[1,3] and Inga Liepelt-Scarfone[1,2]*

[1]Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Germany
[2]German Center for Neurodegenerative Diseases (DZNE), University of Tübingen, Germany
[3]Department of Neurology, Christian-Albrechts-University, Kiel, Germany
[4]Janssen Research and Development, Janssen – Pharmaceutical Companies of Johnson & Johnson, Beerse, Belgium
[5]Reference Center for Biological Markers of Dementia (BIODEM), Institute Born-Bunge, University of Antwerp, Belgium
[6]Janssen Research and Development LLC, Janssen – Pharmaceutical Companies of Johnson & Johnson, Raritan, New Jersey, USA
[7]Private Practice for Neurology, Psychiatry, and Psychotherapy, Mössingen, Germany

The core criterion for Parkinson's disease dementia (PDD) is the impairment in activities of daily living (ADL) function primarily caused by cognitive, not motor symptoms. There is evidence to assume that mild ADL impairments in mild cognitive impairment (PD-MCI) characterize those patients at high risk for dementia. Data of 216 Parkinson's disease (PD) patients assessed with comprehensive motor and neuropsychological assessments were analysed. Based on linear regression models, subscores of the Functional Activities Questionnaire (FAQ) primarily reflecting patients' global cognitive status (FAQ_C) or PD-related motor severity (FAQ_M) were developed. A quotient (FAQ_Q) of both scores was calculated, with values >1 indicating more cognitive- compared to motor-driven ADL impairment. Both FAQ_C and FAQ_M scores were higher in PD-MCI than cognitively normal (PD-CN) patients, indicating more severe cognitive- and motor-driven ADL impairments in this group. One third (31.6%) of the PD-MCI group had a FAQ_Q score >1, which was significantly different from patients with PD-CN (p = .02). PD-MCI patients with an FAQ_Q score >1 were more impaired on tests assessing attention (p = .019) and language (p = .033) compared to PD-MCI patients with lower FAQ_Q values. The

*Correspondence should be addressed to Inga Liepelt-Scarfone, Department of Neurodegeneration, German Center of Neurodegenerative Diseases and Hertie Institute for Clinical Brain Research, Hoppe-Seyler Str. 3, D-72076 Tuebingen, Germany (email: inga.liepelt@uni-tuebingen.de).

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differentiation between cognitive- and motor-driven ADL is important, as the loss of functional capacity is the defining factor for a diagnosis of PDD. We were able to differentiate the cognitive-driven from the motor-driven ADL impairments for the FAQ. PD-MCI patients with more cognitive- compared to motor-driven ADL impairments may pose a risk group for conversion to PDD and can be targeted for early treatments.

It is becoming increasingly evident that various non-motor symptoms are an integral part of Parkinson's disease (PD; Chaudhuri & Martinez-Martin, 2008). The presence and severity of non-motor symptoms modulate the rate of PD progression with a high impact on patients' quality of life (Fereshtehnejad, Zeighami, Dagher, & Postuma, 2017). One clinical milestone of the disease is the conversion to Parkinson's disease dementia (PDD), increasing the risk for nursing home placement and mortality (Bjornestad, Pedersen, Tysnes, & Alves, 2017).

Parkinson's disease dementia is a frequent non-motor symptom especially in later stages of the disease (Jellinger, 2013). One of the greatest risk factors for PDD is the presence of mild cognitive impairment in PD (PD-MCI; Delgado-Alvarado, Gago, Navalpotro-Gomez, Jimenez-Urbieta, & Rodriguez-Oroz, 2016). However, only 30% of patients with PD-MCI have been reported to convert to dementia within a short time period, while others reach a stable cognitive status or revert to normal cognition (Santangelo *et al.*, 2015). The identification of a high-risk group for PDD among those with PD-MCI is therefore essential.

The core feature for differentiating PDD from PD-MCI is the loss of the ability to perform activities that are necessary for independent living (Svenningsson, Westman, Ballard, & Aarsland, 2012). This decline is typically measured by assessing activities of daily living (ADL), which can be divided into basic (e.g., self-maintenance skills) and instrumental functions (e.g., complex skills). To justify the diagnosis of PDD, ADL disabilities should be primarily caused by cognitive, not motor problems (Marshall *et al.*, 2015). As PD is primarily a movement disorder, the distinction between motor and non-motor contributions to ADL in PD is an obvious challenge (Cheon, Park, & Kim, 2015).

There has been limited attention directed towards understanding the relationship between ADL impairments and cognitive decline in PD (Dubois *et al.*, 2007). Loss of instrumental ADL functions in some patients precedes cognitive decline and PDD (Reginold *et al.*, 2012), yet cognition and ADL function might worsen in parallel (Rosenthal *et al.*, 2010). Little is known about the nature of ADL performance in PD-MCI, although in some patients with PD-MCI, the first signs of ADL disabilities have been reported (Glonnegger *et al.*, 2016; Martin *et al.*, 2013; Pirogovsky *et al.*, 2013). Therefore, mild ADL impairment in PD-MCI may characterize those patients at high risk for PDD.

In a recent paper, Almeida *et al.* (2017) modified the Pfeffer Functional Activities Questionnaire (FAQ), a validated assessment for ADL impairment, to exclude some questions which might pertain to motor skills. Their data confirmed that the FAQ is a valid measure for functional impairment in PD. However, as an external validation criterion, an informant-based questionnaire was used. It is known that caregivers have difficulties rating whether cognitive or motor impairment contributes to ADL impairment in PD (Benge & Balsis, 2016). Therefore, the aim of the present study was to further differentiate between these two potential causes of ADL impairment in PD and to define a subgroup of patients with PD-MCI and cognitive-driven ADL impairment. Through a data-driven approach, we developed new FAQ subscores for the assessment of cognitive- and motor-driven ADL problems. Furthermore, as we believe PD-MCI patients with more cognitive-

driven ADL impairments will progress faster to PDD, we hypothesized that these patients would perform worse on cognitive tests than PD-MCI patients with more motor-driven ADL impairments.

Materials and methods

Study design and participants

Data were analysed within the frame of the ongoing, single-site 'Amyloid-Beta in cerebrospinal spinal fluid as a risk factor for cognitive dysfunction in Parkinson's Disease' (ABC-PD) study. Inclusion criteria for the ABC-PD study were: age between 50 and 85 years, diagnosis of PD according to the United Kingdom PD Brain Bank (UKBB) criteria (Hughes, Daniel, Kilford, & Lees, 1992), ability to communicate with the investigator and understand study requirements (i.e., give informed consent), and no participation in a medication study 4 weeks prior to examination. Exclusion criteria included diagnosis of PDD according to the ICD-10, any disability or other neurodegenerative diseases preventing the participant from giving informed consent, deep brain stimulation, and current or previous alcohol, drug, or medication abuse (except nicotine). Two hundred fifty-seven non-demented PD patients who agreed to provide cerebrospinal fluid were recruited between 31 March 2014 and 31 August 2017. We excluded 41 (16%) patients due to presence of concomitant neurological diseases (13, 5.1%), signs of major depression indicated by the Beck-Depression Inventory-II Score >20 points (24, 9.3%), previous alcohol abuse (2, 0.8%), and incomplete motor data (2, 0.78%). A total of 216 PD patients were included in the final analyses.

The study was approved by the local ethics committee, and all patients gave written informed consent.

Assessments

Demographic variables, including age, sex, age of onset, and disease duration, were assessed for each patient. Medication intake was collected, including the daily dose of all dopamimetics expressed by the levodopa-equivalent daily dose (LEDD; Tomlinson *et al.*, 2010). Motor function was assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) including the modified Hoehn & Yahr scale (Goetz *et al.*, 2008).

Neuropsychological assessment

Global cognitive status was assessed using the Montreal Cognitive Assessment (MoCA; Nasreddine *et al.*, 2005). Additionally, patients underwent a comprehensive neuropsychological battery, including the German version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-PLUS) battery (Fillenbaum *et al.*, 2008); the Similarities, Digit Symbol Test, and Letter-Number-Sequencing subtests of the Wechsler Intelligence Test for Adults (WIE; Aster, Neubauer, & Horn, 2006), and the Recognition of Incomplete Words (subtest 12) from the *Leistungsprüfsystem* (LPS) 50+ (Sturm, Willmes, & Horn, 1993). Raw cognitive test scores were converted to age-corrected (WIE and LPS 50+) and age- and education-corrected (CERAD-PLUS) *z*-scores. For the final analyses, *z*-scores were averaged over each cognitive domain to provide composite domain scores. Each cognitive subtest was assigned to one of the following five cognitive domains: executive functions, attention/working memory, memory, language, and visuo-constructive abilities. Table S1 shows the allocation of each neuropsychological subtest to its cognitive domain, with each

domain including at least two measures. Patients were diagnosed with PD-MCI according to the Level-II recommendations of the Movement Disorder Task Force if impairment was present in at least two tests (1.5 standard deviations below norm population), but was not yet potent enough to interfere severely with ADL function, as verified through a personalized interview with the patients and/or caregivers (Litvan *et al.*, 2012). PD patients who did not meet these criteria were classified as cognitively normal (PD-CN).

ADL assessment

The Pfeffer Functional Activities Questionnaire, a subjective questionnaire consisting of 10 items, was used to assess instrumental ADL (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982). The ability to perform each item is rated from 0 to 3 (0 = *normal or never did but could do now*; 1 = *has difficulty but does by self or never did but would have difficulty now*; 2 = *requires assistance*; 3 = *dependent*), for a total impairment score of 30 points. If a caregiver (a spouse, child, close friend, or other informant that was specified further) was not available, we asked the patients to fill out the FAQ themselves.

The FAQ is one of the most commonly used scales in research on pathological ageing and dementia and has been translated into a number of different languages (Assis Lde, de Paula, Assis, de Moraes, & Malloy-Diniz, 2014; Bezdicek, Stepankova, Martinec Novakova, & Kopecek, 2016; Cruz-Orduna *et al.*, 2012; Sanchez, Correa, & Lourenco, 2011). Although the FAQ is an indirect measure of ADL function (based on self- and informant reports of dysfunctions), the questionnaire shows promising sensitivity and specificity for discriminating between non-impaired and demented subjects (85–98% and 71–91%, respectively; Teng *et al.*, 2010).

Statistical analyses

Study data were collected and managed using REDCap electronic data capture tools hosted at the Hertie Institute for Clinical Brain Research (Harris *et al.*, 2009). Statistical analyses were performed using SPSS version 24 (SPSS Inc, Chicago, IL, USA), and all α-levels were set at 0.05. Assumptions of normality were tested using the Shapiro–Wilk test. Demographic variables were examined using the nonparametric Pearson chi-squared test or Mann–Whitney *U*-test as appropriate, except for the normally distributed UPDRS-III total score, which was analysed using an independent-samples *t*-test. A separate chi-squared test was performed to examine the relation between cognitive group (PD-CN and PD-MCI) and who filled out the FAQ. The FAQ reporter was categorized as either subjective (patient) or objective (spouse, child, close friend, or other informant).

In the first part of the analysis (part 1), the FAQ subscores and the quotient were constructed, by differentiating the cognitive and motor aspects of the FAQ items. Ten linear regressions were conducted, with each FAQ item as the dependent variable, the MoCA and UPDRS-III scores as independent variables, and age, sex, and disease duration as covariates. Based on the items that were primarily associated with the cognitive aspect (FAQ_C, predicted by the MoCA score in the regression model), a subscore of the FAQ scale was built and put in relation to those items that were primarily associated with the motor aspect (FAQ_M, predicted by the UPDRS-III score), as detailed in the results section. The quotient (FAQ_Q) was then calculated from these two subscores, with scores >1 showing more cognitive- compared to motor-driven ADL impairment, and scores <1 describing more motor- compared to cognitive-driven ADL impairment. Additionally, nonparametric correlations between each UPDRS-III item and the FAQ subscores were conducted.

In a second step (part 2), three binary logistic regressions were conducted to compare the performances of PD-MCI and PD-CN, for each of the new FAQ subscores (FAQ_C, FAQ_M, and FAQ_Q), while correcting for group differences in UPDRS-III and LEDD scores.

For the third step (part 3), the group of PD-MCI patients was divided into those patients that had an $FAQ_Q > 1$ ($PD\text{-}MCI_{Q>1}$) indicating more cognitive- compared to motor-related ADL impairment, and those with an $FAQ_Q \leq 1$ ($PD\text{-}MCI_{Q\leq 1}$), showing more motor- compared to cognitive-driven ADL impairment. A binary logistic regression was conducted to identify which clinical parameters independently predict group classification, including all composite domain scores (executive functions, attention/working memory, language, memory, and visuospatial abilities) as predictors, with all numerical clinical and demographical variables as covariates. A *post hoc* Mann–Whitney *U*-test was conducted to determine which specific subtests were statistically significant between the two groups.

Results

Demographics

Of all 216 PD patients, 89 (41.2%) were diagnosed as PD-MCI and 127 (58.8%) as PD-CN. Patients with PD-MCI had more severe motor problems as assessed by the UPDRS-III and Hoehn & Yahr scores, as well as higher LEDD doses, higher FAQ scores, and lower MoCA scores, indicating more severe ADL and global cognitive impairment than the PD-CN group. All other demographic and clinical variables were not statistically different between the two groups (see Table 1 for details). The chi-squared test between cognitive group and FAQ reporter (subjective vs. objective) was not significant X^2 (1, N = 216) = 1.896, p = .213.

Part 1: Construction of FAQ quotient

Table 2 gives an overview of whether each individual FAQ item was more associated with the UPDRS-III or with the MoCA. Item 7 showed a significant relationship to both tests and was included in both the FAQ_C and FAQ_M. In contrast, item 8 was not found to be associated with either the MoCA or the UPDRS-III and was therefore included as a constant in both subscores. For item 5, the linear regression model was not stable when including all three covariates, so the model was recalculated after excluding disease duration and sex, to create a more stable model.

Based on the regressions conducted, the set of items for the cognitive aspect was defined as $S_{cog} = 1, 2, 7, 8, 9$, while the set of items for the motoric aspect was defined as $S_{mot} = 3, 4, 5, 6, 7, 8, 10$. If s_i denotes the score obtained in item i for a patient and $s_{i,\max}$ denotes the maximum score possible for item i, then the FAQ_C for each patient is defined as

$$FAQ_C = \sum_{i \epsilon S_{cog}} \frac{s_i}{s_{i,\max}}$$

and the FAQ_M for each patient is defined as

$$FAQ_M = \sum_{i \epsilon S_{mot}} \frac{s_i}{s_{i,\max}}$$

Table 1. Demographic and clinical characteristics of the population

	Total sample $N = 216$	PD-CN $n = 127$	PD-MCI $n = 89$	*p*-value
Male gender: *n* (%)	140 (64.8)	83 (65.4)	57 (64)	.89
Age (years)	66.2 (48.1–83.7)	66.0 (48.1–79.9)	67.6 (50.6–83.7)	.06
Education years	13 (8–21)	13 (8–21)	12 (8–21)	.19
Age at onset (years)	60.7 (36.4–79.5)	60.3 (36.4–77.6)	61.2 (45.5–79.5)	.25
Disease duration years	3.9 (0–18.4)	3.7 (0.1–18.4)	4.9 (0–15.4)	.11
LEDD	494.3 (0–1,574)	422.5 (0–1,574)	560 (0–1,380)	.006*
UPDRS-III (0–108)	25 (1–56)	22 (1–56)	29 (3–52)	.002*
Hoehn &Yahr: *n* (%)				.004*
1	29 (13.4)	21 (16.5)	8 (9)	
2	122 (56.5)	79 (62.2)	43 (48.3)	
3	64 (29.2)	26 (20.5)	37 (41.6)	
4	2 (0.9)	1 (0.8)	1 (1.1)	
BDI-II score (0–20)	7 (0–19)	6 (0–19)	7 (0–19)	.15
MoCA (0–30)	26 (16–30)	27 (18–30)	25 (16–30)	<.001*
FAQ score (0–30)	0 (0–21)	0 (0–14)	2 (0–21)	<.001*

Notes. Results are expressed as *Median (Range)*, except where noted; asterisks denote statistically significant differences ($p < .05$).
BDI-II, Beck-Depression Inventory-II; FAQ, Functional Activities Questionnaire; LEDD, levodopa-equivalent daily dose; MoCA, Montreal Cognitive Assessment; PD-CN, Parkinson's disease with no cognitive impairment; PD-MCI, Parkinson's disease with mild cognitive impairment; UPDRS-III, Unified Parkinson's Disease Rating Scale-III.

FAQ_Q: The quotient was formed by dividing the cognitive aspect by the motoric aspect (after adding the constant of 1 to avoid divisions by zero).

$$FAQ_Q = \frac{FAQ_C + 1}{FAQ_M + 1}$$

The FAQ_C was significantly correlated to the speech, facial expression, rigidity of the neck, arising from chair, gait, freezing of gait, postural stability, posture, and body bradykinesia UPDRS-III items ($p < .042$). The FAQ_M was significantly correlated to all individual UPDRS-III items, except for the tremor items ($p < .030$ for all significant correlations). The FAQ_Q was significantly correlated to the following UPDRS-III items: left finger tapping, right and left hand movements, right and left rapid alternating movements, right and left leg agility, arising from chair, gait, freezing of gait, and body bradykinesia ($p < .046$). For more details, please see Table S2.

Part 2: Comparison of the clinical profile of PD-CN and PD-MCI

Using the formulas mentioned above, the FAQ_C and FAQ_M subscores, as well as the FAQ_Q, were calculated. PD-MCI patients had higher values on both the FAQ_C (PD-CN: Median = 0.0, 0–0.40; PD-MCI: Median 0.0, 0–0.67; $p = .022$) and the FAQ_M (PD-CN: Median = 0.0, 0–0.52; PD-MCI: Median = 0.05, 0–0.71; $p = .005$) scores, indicating more impaired ADL functions compared to PD-CN patients. The FAQ_Q also differentiated significantly between the two groups (PD-CN: Median = 1.00, 0.84–1.22; PD-MCI: Median = 1.00, 0.75–1.28; $p = .032$). In total, 32.6% of PD-MCI compared to 17.3% of PD-CN patients showed an FAQ_Q score >1 ($p = .02$).

Table 2. Association of each FAQ item with cognitive and motor status

		MoCA		UPDRS-III	
FAQ item	Median (Range)	β-weight	*p*-value	β-weight	*p*-value
1: Accounting and finances	0.00 (0–3)	−0.21	.007*	0.04	.56
2: Tax and business records	0.00 (0–3)	−0.26	<.001*	0.04	.60
3: Shopping alone	0.00 (0–3)	0.01	.91	0.30	<.001*
4: Skills and hobbies	0.00 (0–3)	−0.02	.79	0.30	<.001*
5: Using appliances	0.00 (0–2)	−0.02	.76	0.18	.01*
6: Meal preparation	0.00 (0–3)	−0.07	.35	0.19	.008*
7: Tracking current events	0.00 (0–2)	−0.20	.007*	0.24	.001*
8: Information uptake	0.00 (0–3)	−0.14	.07	0.13	.07
9: Remembering important events	0.00 (0–3)	−0.17	.02*	0.09	.23
10: Travelling out of house	0.00 (0–3)	−0.12	.11	0.15	.04*

Notes. Asterisks denote statistically significant differences ($p < .05$).
FAQ, Functional Activities Questionnaire; MoCA, Montreal Cognitive Assessment; UPDRS-III, Unified Parkinson's Disease Rating Scale-III.

Part 3: Cognitive profile of PD-MCI patients with and without cognitive-driven ADL impairment

Of all 89 PD-MCI patients, 29 (32.6%) had FAQ_Q values >1, and 60 (67.4%, PD-$MCI_{Q\leq1}$ scored below this cut-off. The frequency of males was comparable between both PD-MCI subgroups (PD-$MCI_{Q\leq1}$ 63.3%, PD-$MCI_{Q>1}$ 65.5%; $p = 1.0$). Among the PD-$MCI_{Q\leq1}$ group, 6 (10.0%) patients had a Hoehn & Yahr Stage of 1, 29 (48.3%) of 2, 24 (40.0%) of 3 and 1 (1.7%) of 4, compared to 2 (6.9%); 14 (48.3), 13 (44.8), and no patients of the PD-$MCI_{Q>1}$ group, respectively. Logistic regression analyses showed that PD-$MCI_{Q>1}$ was more impaired in tests assessing attention/working memory ($p = .033$) and language performance ($p = .019$) than the PD-$MCI_{Q\leq1}$ group (see Table 3 and Figure 1), while motor symptom severity was not statistically different between groups ($p = .095$). The *post hoc* Mann–Whitney *U*-test revealed the *z*-scores of the Digit Symbol Test ($p = .025$) and the Boston Naming Test ($p = .019$) from the attention/working memory and language domains, respectively, were significantly different between both PD-MCI groups.

Discussion

In PD, cognitive decline and dementia are often experienced as more disabling than the motor symptoms, and further contribute to caregiver distress and nursing home placement (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999). There is a need for the identification of prodromal markers to diagnose PDD at an early stage and start appropriate treatment as soon as possible, to maintain patients' quality of life and their independence from caretakers. We show that even PD-MCI patients can already exhibit mild impairments in ADL and that these patients exhibited stronger deficits in the cognitive domains attention and language than PD-MCI patients without any ADL impairment. This combination may identify a subgroup of PD patients at particularly high risk for subsequent conversion to PDD. However, as this was an exploratory analysis using cross-sectional data and non-demented PD patients, further longitudinal studies are needed to examine whether this particular group will indeed progress to dementia faster.

Table 3. Demographic characteristics and results of the prediction model for cognitive-driven ADL impairment (PD-MCI$_{Q>I}$) among all patients with PD-MCI

	PD-MCI$_{Q\leq I}$ $n = 60$	PD-MCI$_{Q>I}$ $n = 29$	Exp(B)	95% CI for Exp(B)	*p*–value
Age (years)	66.7 (50.6–82.2)	68.9 (55.8–83.7)	0	$0–1.9•10^{40}$	.59
Education years	12.5 (8–21)	12 (8–19)	1.2	1–1.5	.11
Age at onset (years)	61 (46.1–79.5)	61.4 (45.5–78.1)	$2.1•10^{15}$	$0–8.1•10^{70}$	.59
Disease duration years	5.5 (0–15.37)	3.7 (0.6–14.4)	$2.1•10^{15}$	$0–8.3•10^{70}$	.59
LEDD	550 (100–1,330)	560 (0–1,380)	1	1–1	.52
UPDRS-III (0–108)	29 (3–52)	28 (4–46)	1	0.9–1	.10
BDI-II score (0–19)	7 (0–19)	8 (0–18)	1.1	0.95–1.2	.34
Executive functions	−0.6 (−2.5 to 0.8)	−0.9 (−2.2 to 0.4)	1.6	0.6–4.2	.33
Attention/Working memory	−0.4 (−2.0 to 0.9)	−0.8 (−1.8 to 1.3)	0.3	0.1–0.8	.019*
Language	−0.2 (−2.0 to 1.6)	−0.6 (−2.1 to 0.6)	0.4	0.2–0.9	.033*
Memory	−0.9 (−2.3 to 0.7)	−1.0 (−2.3 to 1.1)	1.4	0.7–2.9	.36
Visuo-constructive functions	−0.9 (−2.8 to 0.6)	−0.9 (−2.4 to 0.7)	1	0.5–2	.97

Notes. Results are expressed as *Median* (*Range*); Asterisks denote statistically significant differences ($p < .05$).
BDI-II, Beck-Depression Inventory-II; CI, confidence interval, LEDD, levodopa-equivalent daily dose; PD-MCI$_{Q>I}$, Parkinson's disease patients with mild cognitive impairment and more cognitive- compared to motor-related activities of daily living impairment; PD-MCI$_{Q\leq I}$, Parkinson's disease patients with mild cognitive impairment and more motor- compared to cognitive-driven ADL impairment; UPDRS-III, Unified Parkinson's Disease Rating Scale-III.

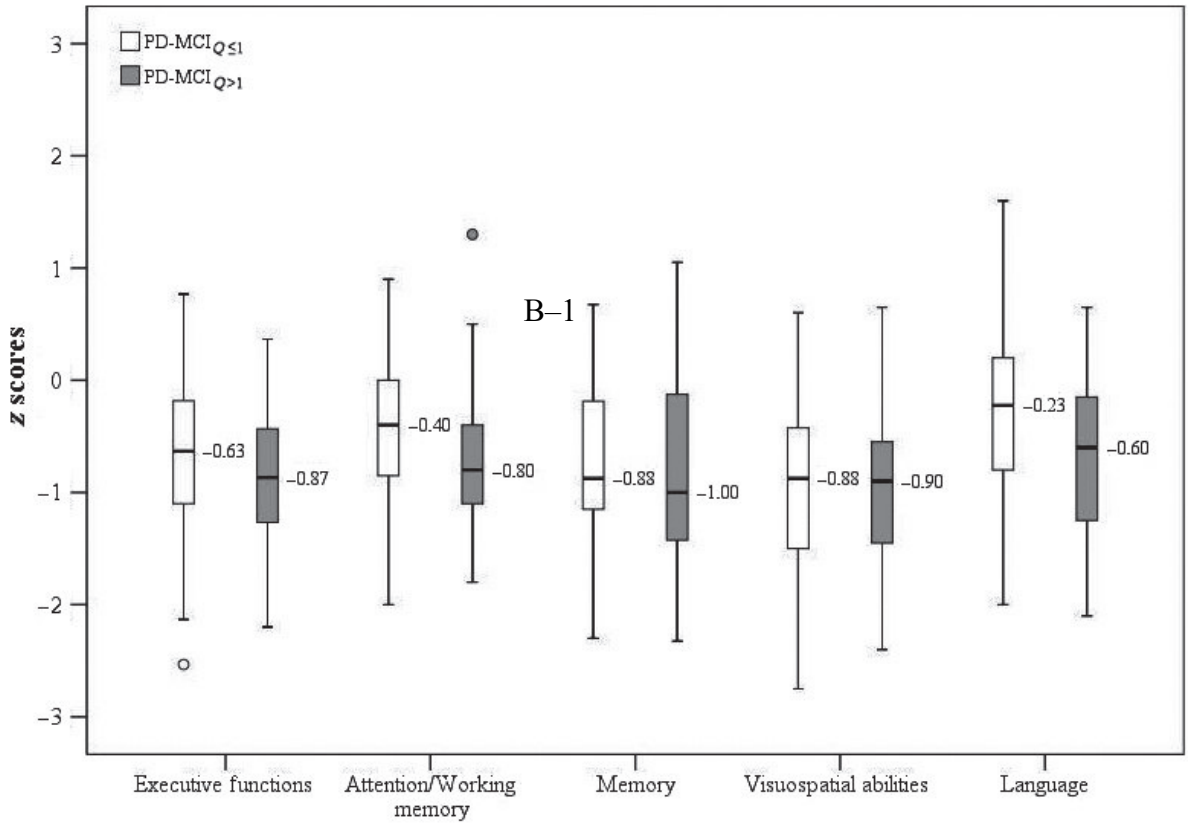

Figure 1. Clustered box-and-whisker plots for each cognitive domain representing the cognitive-driven (PD-MCI$_{Q>1}$) and motor-driven (PD-MCI$_{Q\leq1}$) ADL subgroups of all PD-MCI patients; boxes represent the interquartile range and whiskers denote the minimum and maximum.

For this approach, we used the FAQ, which was divided into two subscores, the FAQ_C and the FAQ_M, to differentiate cognitive- and motor-driven aspects of ADL function. Contrary to the approach by Almeida *et al.* (2017), we chose to include all FAQ items in our analyses and separate the cognitive and motor contributions using a data-driven analysis. Their approach was theory-driven by validating their modified FAQ and its cut-off using a separate, informant-based questionnaire assessing ADL impairment changes over 2 years, instead of using motor and cognitive scales as validation. Our results suggest that separating the FAQ items more correlated to cognitive aspects from those more correlated to motoric aspects can help to identify patients that present with cognitive-driven ADL dysfunctions. Furthermore, our approach was data-driven, as we derived the individual subscores from our patient data, as well as validated using a variety of motor assessments and cognitive tests.

We took into account the associations between the UPDRS-III items and each of the FAQ subscores by examining the correlations between all variables. There were strong associations between the FAQ_M and all UPDRS-III items except tremor, which were to be expected as the FAQ_M measures motor-related ADL impairment. Correlations between the FAQ_C and the UPDRS-III scores show the following pattern: strong positive correlations to the items arising from chair, gait, freezing of gait, postural stability, posture, and body bradykinesia. Studies have confirmed that cognition is associated with the postural instability/gait disturbance (PIGD) phenotype; in particular, that poorer cognitive performance and a higher risk for conversion to PDD are associated to gait impairments, freezing of gait, and postural instability (Kelly *et al.*, 2015; Williams-Gray, Foltynie,

Brayne, Robbins, & Barker, 2007). In our sample, the FAQ_C was positively correlated to these PIGD items so that higher cognitive ADL impairment denoted a higher PIGD-related motor impairment. The FAQ_Q showed significant negative associations to some of the PIGD items, as well as agility of both the hands and the legs. We would expect this direction, as a higher FAQ_M denotes a smaller motor component. Further longitudinal studies are needed to investigate the predictive value of the FAQ scores for motor and cognitive worsening and PDD.

Examining the subscores FAQ_C and the FAQ_M, we found that both were more severely impaired in patients with PD-MCI than PD-CN. In our sample, around 30% of PD-MCI patients had more problems with ADLs associated to cognitive, rather than to motor problems. Previous longitudinal studies have indicated similar percentages of PD-MCI patients who converted to PDD: Broeders *et al.* (2013) found that 26% of PD-MCI patients converted after a 5-year follow-up, while Pedersen, Larsen, Tysnes, and Alves (2017) found that 39.1% of patients with baseline or incident PD-MCI progressed to dementia within 5 years. In a newly diagnosed PD cohort, around 33% showed cognitive decline within 3 years from the baseline visit (Lawson *et al.*, 2017). PD-MCI patients with mild ADL deficits may correspond to a group at risk for PDD conversion.

To date, very little attention has been directed towards understanding ADL performance in PD-MCI patients, with most studies focusing solely on patterns of cognitive loss, rather than functional changes, in this group. We showed that PD-MCI patients with more cognitive-driven ADL impairments had greater deficits in attention/working memory domains, as well as in the language domain. Bronnick *et al.* (2006) showed that for PDD patients, attentional dysfunction is a primary factor associated with functional impairment. Attention contributed to ADL skills even when controlling for age, sex, educational level, and motoric functions. A study by Bezdicek *et al.* (2016) found that, in healthy older adults, the FAQ was dependent on both age and education, but not on gender. In our sample, attention contributed to ADL skills even when controlling for age, sex, educational level, and motoric functions. Recent studies have also shown attention deficits in PDD, highlighting attention deficits as a possible marker for conversion to PDD in PD-MCI (Biundo *et al.*, 2014; Miura, Matsui, Takashima, & Tanaka, 2015; Pedersen, Larsen, Tysnes, & Alves, 2013). Other studies have demonstrated that language problems arise in the transition to dementia, with patients presenting problems understanding and producing language, together with impaired sentience comprehension (Bastiaanse & Leenders, 2009). These findings are reflected in our cohort of PD-MCI patients with cognitive-driven ADL dysfunctions.

It is possible that a specific profile of cognitive impairment combined with mild impairments in ADL function could contribute to faster cognitive decline resulting in PDD. Research shows that patients experience limitations in functional capacity early in the disease course, and report having difficulty with instrumental ADL (Foster & Hershey, 2011). They specifically show deficits in the performance of cognitive-loaded instrumental ADLs, and later cognitive decline more predominantly affects their ability to perform these functions (Brennan *et al.*, 2016). Mild cognitive impairment coupled with mild cognitive-driven ADL dysfunctions may pose as a risk factor for faster conversion to PDD, an association which further longitudinal studies should examine.

When specifically examining PD-MCI patients, it becomes evident that they not only have higher scores on the FAQ_C, but also on the FAQ_M, compared to PD-CN patients. Previous literature has shown an association between cognitive dysfunction and higher motor symptoms, with patients who developed PDD declining more in motor functions than patients who did not develop dementia (Domellof, Ekman, Forsgren, & Elgh, 2015).

Motor symptom worsening does not imply cognitive decline in PD, however increasing cognitive impairment is associated with higher PD severity (Lawson *et al.*, 2014). Higher scores on the FAQ_M can therefore be explained by the progressive nature of the disease and by the severity of motor symptoms as a risk factor for PDD development. As PD-MCI patients did not have a longer duration of illness, it can be stated that their symptoms, both motor and cognitive, are more severe than PD-CN patients.

Limitations

There are a few limitations to this study that need to be mentioned. The first is the cross-sectional design of the study, which does not allow us to follow patients over time to track cognition and gain information about possible cognitive decline. However, as this was intended as an exploratory analysis to identify a possible risk group for PDD, the cross-sectional nature of the data is justified. As already stated, additional longitudinal studies are still needed to confirm whether this specific group is at risk for subsequent PDD development. The second limitation is that only patients who agreed to a lumbar puncture were included in the ongoing study, which potentially biases the study group. A further limitation is the small sample size for the PD-$MCI_{Q>1}$ group, despite the large sample size for the total PD-MCI group. However, as we expect these patients to progress faster to PDD, we assumed from the start that this would be a small sample group, the size of which is comparable to previous literature. It is also important to note that the existing assessments used to measure ADLs were all developed for Alzheimer's disease and not for PD; however, our aim was to validate one of these questionnaires for use in PD. In recent years, specific questionnaires have been developed to assess ADL function in PD patients, such as the Parkinson's Disease Activities of Daily Living Scale (Hobson, Edwards, & Meara, 2001), the Parkinson Disease Cognitive Functional Rating Scale (Kulisevsky *et al.*, 2013), and the Penn Daily Assessment Questionnaire (Brennan *et al.*, 2016). To the author's knowledge, these specific scales have not been translated into many different languages, which is an important aim for future research. As the FAQ is one of the few ADL scales that has been translated into multiple languages for use in other countries, we believe that by using the FAQ, our results can be applicable to various cohorts. However, the FAQ itself is, as already stated, an indirect measure of ADL function and has been shown to be dependent on age and education level in healthy adults (Bezdicek *et al.*, 2016). In healthy adults, more deficits were found in ADL function with increasing age, possibly reflecting an age-related decline in speed of processing. However, our binary logistic regression analysing the PD-MCI groups with and without ADL impairments included age and education as covariates, to control for their potential influence. We can therefore assume that our results are independent of these two factors and greater impairment, especially in the attention domain, is not mediated by age-related ADL worsening or reduced speed of processing. Another limitation is that we constructed the FAQ subscores and Quotient in one cohort and have not validated it in a separate, independent cohort. Future cross-sectional and longitudinal studies could validate these scores. Lastly, an important limitation is that instead of a performance-based measure, a self-/informant-based report was used, which can have various forms of bias including lack of insight or emotional factors, leading to over- as well as underestimation of actual abilities (Shulman *et al.*, 2006). It is furthermore possible that ADL impairments were over-reported in this study, as patients or informants could have given the highest score for some items based on motor abilities, and not cognition. However, as we were aiming to

disentangle these two factors (cognitive and motor aspects of ADL), we did not take this further into account.

Conclusion

The differentiation between cognitive- and motor-driven ADL is important, as the loss of functional capacity is the defining factor for a diagnosis of PDD. PD-MCI has been shown to be a risk factor for subsequent PDD; however, there are no clear progression markers to identify patients who will develop dementia. Using a validated ADL assessment questionnaire, the FAQ, we were able to differentiate the cognitive-driven from the motor-driven ADL impairments in a cohort of non-demented PD patients. PD-MCI patients with more cognitive- compared to motor-driven ADL impairments may pose a risk group for conversion to PDD and can be targeted for early treatments. Future longitudinal studies are still needed to confirm that this particular group is at a higher risk for developing subsequent PDD than those patients without mild impairments in ADL function.

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Conflict of interest declaration

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

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Supporting Information

The following supporting information may be found in the online edition of the article:

Table S1. List of neuropsychological tests and corresponding cognitive domains for the diagnosis of Parkinson's disease patients with mild cognitive impairment (PD-MCI) versus cognitively normal (PD-CN).

Table S2. Correlations between individual UPDRS-III items and FAQ sub-scores.

Supplementary Table 1: List of neuropsychological tests and corresponding cognitive domains for the diagnosis of Parkinson's disease patients with mild cognitive impairment (PD-MCI) versus cognitively normal (PD-CN)

Cognitive Domain	Neuropsychological Test	PD-CN	PD-MCI	p-value
Executive Functions	Semantic Fluency [a]	-0.10 (-2.4-2.7)	-0.70 (-3.0-3.0)	<0.001*
	Phonemic Fluency [a]	0.30 (-1.9-2.9)	-0.30 (-3.7-1.9)	<0.001*
	Trail Making Test Part B [a]	0.30 (-2.3-4.0)	-1.40 (-3.0-1.6)	<0.001*
Attention/Working Memory	Digit-Symbol Test [b]	-0.20 (-1.6-1.8)	-0.60 (-2.2-1.4)	<0.001*
	Letter-Number-Sequencing [b]	0.40 (-1.6-2.4)	-0.60 (-2.4-1.8)	<0.001*
Language	Boston Naming test [a]	0.60 (-1.7-1.7)	-0.25 (-2.7-1.8)	<0.001*
	Similarities [b]	0.00 (-2.6-2.4)	-0.60 (-2.6-2.4)	<0.001*
Memory	Word List Learning [a]	0.30 (-2.5-3.1)	-0.90 (-3.0-2.7)	<0.001*
	Word List Recall [a]	0.20 (-1.3-2.7)	-0.70 (-2.5-2.0)	<0.001*
	Constructional Praxis Recall [a]	0.00 (-3.1-1.9)	-1.35 (-3.7-1.6)	<0.001*
	Word List Discriminability [a]	0.40 (-2.5-1.1)	-0.90 (-2.8-1.2)	<0.001*
Visuo-constructive functions	Constructional Praxis [a]	0.50 (-2.5-1.6)	-1.10 (-3.1-1.3)	<0.001*
	Fragmented Words [c]	0.00 (-2.3-3.0)	-1.10 (-2.8-0.7)	<0.001*

Note. Results are expressed as *Median (Range)*; Asterisks denote statistically significant differences ($p<0.05$); PD-CN, Parkinson's Disease with no cognitive impairment; PD-MCI, Parkinson's Disease with mild cognitive impairment

[a] Subtest of the CERAD-PLUS: Consortium to Establish a Registry for Alzheimer's Disease – PLUS Battery

[b] Subtest of the WIE: Wechsler Adult Intelligence Scale

[c] Subtest of the LPS 50+: Leistungsprüfsystem 50+

Supplementary Table 2: Correlations between individual UPDRS-III items and FAQ sub-scores

UPDRS-III Item	FAQ_C		FAQ_M		FAQ_Q	
	r_s	*p*-value	r_s	*p*-value	r_s	*p*-value
1. Speech	0.16	0.016*	0.22	0.001*	-0.08	0.25
2. Facial Expression	0.15	0.029*	0.19	0.0046*	-0.02	0.81
3. Rigidity Neck	0.14	0.042*	0.22	<0.001*	-0.06	0.36
3. Rigidity RUE	0.07	0.33	0.15	0.030*	-0.04	0.57
3. Rigidity LUE	0.07	0.32	0.16	0.021*	-0.06	0.41
3. Rigidity RLE	0.11	0.099	0.25	<0.001*	-0.06	0.39
3. Rigidity LLE	0.13	0.053	0.26	<0.001*	-0.10	0.14
4. Finger Tapping R	0.06	0.40	0.17	0.013*	-0.12	0.08
4. Finger Tapping L	0.02	0.74	0.20	0.003*	-0.22	<0.001*
5. Hand Movements R	0.03	0.64	0.16	0.017*	-0.14	0.034*
5. Hand Movements L	0.004	0.95	0.20	0.003*	-0.25	<0.001*
6. Rapid Alternating Movements R	0.03	0.70	0.17	0.013*	-0.14	0.039*
6. Rapid Alternating Movements L	0.02	0.79	0.23	<0.001*	-0.22	<0.001*
7. Foot Tapping R	0.08	0.27	0.14	0.037*	-0.04	0.52
7. Foot Tapping L	0.07	0.34	0.17	0.012*	-0.10	0.13
8. Leg Agility R	0.10	0.15	0.27	<0.001*	-0.14	0.046*
8. Leg Agility L	0.09	0.19	0.23	<0.001*	-0.16	0.022*
9. Arising from Chair	0.28	<0.001*	0.43	<0.001*	-0.15	0.028*
10. Gait	0.15	0.029*	0.29	<0.001*	-0.15	0.03*
11. Freezing of Gait	0.22	0.001*	0.35	<0.001*	-0.17	0.014*
12. Postural Stability	0.22	0.001*	0.28	<0.001*	-0.07	0.33
13. Posture	0.19	0.006*	0.24	<0.001*	-0.04	0.56
14. Body Bradykinesia	0.18	0.01*	0.32	<0.001*	-0.15	0.028*
15. Postural Tremor RUE	-0.03	0.72	-0.04	0.52	0.057	0.41
15. Postural Tremor LUE	0.11	0.11	0.30	0.66	0.11	0.12
16. Kinetic Tremor RUE	0.06	0.37	0.05	0.47	-0.02	0.75
16. Kinetic Tremor LUE	0.11	0.11	0.05	0.43	0.10	0.15
17. Rest Tremor RUE	-0.07	0.32	-0.09	0.17	0.007	0.92
17. Rest Tremor LUE	0.04	0.53	0.10	0.88	0.073	0.29
17. Rest Tremor RLE	-0.03	0.63	-0.05	0.47	0.033	0.62
17. Rest Tremor LLE	-0.04	0.54	0.001	0.99	-0.10	0.89
17. Rest Tremor Lip/Jaw	-0.03	0.65	0.04	0.58	-0.01	0.88
18. Constant of Rest Tremor	-0.09	0.17	-0.10	0.13	0.032	0.66

Note. Asterisks denote statistically significant differences ($p<0.05$); FAQ, Functional Activities Questionnaire; FAQ_C, cognitive sub-score of the Functional Activities Questionnaire; FAQ_M, motor sub-score of the Functional Activities Questionnaire; FAQ_Q, quotient of the cognitive and motor sub-scores of the Functional Activities Questionnaire; L, left; LLE, left lower extremity; LUE, left upper extremity; R, right; RLE, right lower extremity; r_s, Spearman's rho; RUE, right upper extremity; UPDRS-III, Unified Parkinson's Disease Rating Scale-III

Association of Cognitive Activities of Daily Living (ADL) Function and Nonmotor Burden in Nondemented Parkinson's Disease Patients

Sara Becker[a,b], Alena Bäumer[a,b], Walter Maetzler[a,c], Susanne Nussbaum[a,b], Zuzanna Tkaczynska[a,b], Patricia Sulzer[a,b], Maarten Timmers[d,e], Luc Van Nueten[d], Giacomo Salvadore[f], Kathrin Brockmann[a,b], Johannes Streffer[d,e,g], Daniela Berg[a,c], Inga Liepelt-Scarfone[a,b]

[a]Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, Tübingen, Germany

[b]German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany

[c]Department of Neurology, Christian-Albrechts-University, Kiel, Germany

[d]Janssen Research and Development, a division of Janssen Pharmaceutica N.V., Beerse, Belgium

[e]Reference Center for Biological Markers of Dementia (BIODEM), Institute Born-Bunge, University of Antwerp, Antwerp, Belgium

[f]Janssen Research and Development LLC, Titusville, NJ, USA

[g]Translational Medicine Neuroscience, UCB Biopharma SPRL, Braine-l'Alleud, Belgium

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Correspondence concerning this article should be addressed to Sara Becker, Hertie Institute for Clinical Brain Research, Department of Neurodegeneration, Hoppe-Seyler Str. 3, 72076 Tübingen, Germany. E-Mail: sara.becker@med.uni-tuebingen.de

Abstract

Objective

In Parkinson's disease (PD), non-motor symptoms (NMS) considerably influence disease progression and cognitive decline. Depression, anxiety, sleep disturbances and hallucinations (DASH), may indicate a risk for dementia (PDD). Mild impairments in activities of daily living (ADL) caused by cognitive dysfunction are also present in the prodromal stage of PDD. The association of both factors has been sparsely investigated. Aim was to evaluate these specific NMS in a large non-demented PD cohort and their co-occurrence with cognitive dysfunction and ADL impairments.

Methods

Data of 226 PD patients was analyzed. Using corresponding items, two DASH scores were constructed from the NMS-Scale and Parkinson's Disease Questionnaire (PDQ-39). Correlations between DASH scores and PDD risk factors were examined. PD patients with mild cognitive impairment (PD-MCI) were additionally split into patients with low and high DASH burden, the latter group additionally stratified by presence of cognitive-driven ADL impairment.

Results

DASH-NMS scores differed significantly between PD-MCI and cognitively normal (PD-CN) patients (p=0.04), while the DASH-PDQ did not (p=0.73). The only significant predictor of the DASH-NMS score was cognitive-driven ADL (p=0.01). PD-MCI patients with a high DASH burden and more cognitive ADL impairment presented with worse global cognition than patients with a low burden (p=0.045).

Conclusion

Our results show that the DASH-NMS is superior to the DASH-PDQ score, related to the severity of cognitive impairment, and strongly influenced by cognitive-driven ADL

impairment. Presence of DASH symptoms and cognitive-ADL in PD-MCI patients may define a risk group for PDD conversion.

Keywords: Activities of daily living; Cognitive Dysfunction; Neuropsychological Tests; Non-motor symptoms; Parkinson's disease

Key Points

Question: A key research priority in Parkinson's disease is the identification of risk factors that can predict cognitive decline and conversion to dementia.

Findings: The present study suggests that a specific burden of nonmotor symptoms in combination with cognitive-driven activity of daily living impairment is related to more severe cognitive impairment in Parkinson's Disease.

Importance: This association may be able to characterize a group at risk of developing Parkinson's Disease dementia within a short time period.

Next Steps: Longitudinal studies are now needed to determine progression of these factors and their suitability for assessing conversion to dementia in Parkinson's disease.

Association of cognitive ADL function and non-motor burden in non-demented Parkinson's Disease patients

Non-motor symptoms (NMS) in Parkinson's disease (PD) considerably influence patients' quality of life (Bonnet, Jutras, Czernecki, Corvol, & Vidailhet, 2012) and are often reported as more disabling than motor symptoms (Chaudhuri & Martinez-Martin, 2008). Almost all patients present with at least one NMS during the disease course (Barone et al., 2009), with some of the most common symptoms including: depression, sleep problems, apathy, anxiety, fatigue, visual disturbances, and cognitive symptoms (McKinlay et al., 2008). As NMS tend to increase in terms of occurrence and severity in PD and can manifest several years before motor disability (Berg et al., 2015), it is important to monitor their severity during the disease course.

Cognitive impairments are some of the most commonly reported NMS (Munhoz, Moro, Silveira-Moriyama, & Teive, 2015), with 80% of PD patients progressing from normal cognition (PD-CN), to mild cognitive impairment (PD-MCI) and Parkinson's disease dementia (PDD) (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003). Recognition and diagnosis of PDD is essential, as it is associated with shorter life expectancy, and contributes to significant caregiver distress and nursing home placement (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999; Marder et al., 1991). The defining feature of dementia is the loss of the ability to perform activities that are necessary for independent living (activities of daily living, ADL) (Desai, Grossberg, & Sheth, 2004). It has been proposed that mild cognitive ADL dysfunction already occurs in a subgroup of PD-MCI patients, potentially characterizing those at high risk for PDD (Becker et al., 2018; Beyle et al., 2018).

Presence of PD-MCI and older age are the most established risk factors for PDD, others include disease duration and severity of motor symptoms (Anang et al., 2014). Recently, NMS associated with cognitive impairment have been further explored. Two studies found the NMS depression, apathy, anxiety, and hallucinations are most commonly associated with PD-MCI

(Aarsland et al., 2007; Delgado-Alvarado, Gago, Navalpotro-Gomez, Jimenez-Urbieta, & Rodriguez-Oroz, 2016) while another described the symptoms of depression, sleep disorders, apathy and anxiety as associated with the presence of mild cognitive impairment (Monastero, Di Fiore, Ventimiglia, Camarda, & Camarda, 2013). Naismith and Lewis (2011) examined a specific constellation of NMS and their relation to cognitive impairment: depression, anxiety, sleep disturbances, and hallucinations, summed into a "DASH" score. In their study with 53 non-demented patients, greater severity of DASH symptoms was strongly associated with poorer executive function. They therefore suggested that increased severity of these symptoms have the potential to detect cognitive decline in PD.

It is important to note that PD-MCI is a heterogeneous concept. Some patients progress to PDD, others remain cognitively stable, and some even revert back to PD-CN (Lawson et al., 2017). This highlights the importance of identifying markers that characterize a group at risk for progression to PDD. Possible and probable prodromal PD is defined as an accumulation of risk and prodromal markers associated with a higher likelihood of disease onset (Berg et al., 2015). Analogous to this concept, we evaluated whether combinations of PDD risk markers are more common in PD-MCI and associated with lower cognitive function. Impairments in cognition and ADL function, and presence of behavioral features are independently necessary for the diagnosis of dementia (Emre et al., 2007); therefore examining their interaction may propose a potential risk group for PDD development.

The overall purpose of this study was to evaluate specific NMS (the DASH score) and their co-occurrence with cognitive impairment and cognitive ADL dysfunction. The first aim was to evaluate the DASH score devised by Naismith and Lewis (2011) and replicate their results in a large cohort of non-demented PD patients. To examine the efficacy and generalizability of their score, we constructed a second DASH score using NMS-Scale items, as detailed below. A second aim was, on a cross-sectional level, to examine the association of both DASH scores to other known risk factors for PDD, specifically presence of PD-MCI and

mild cognitive-driven ADL impairment. Additionally, the association of DASH scores and ADL impairment was examined only in the PD-MCI group, to determine whether a specific accumulation of prodromal symptoms is associated with lower cognitive function.

Methods

Study design and participants

Data were analyzed 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 were included in the study if they: had a definite diagnosis of PD according to the United Kingdom PD Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992), were between 50-85 years, were able to give informed consent, agreed to a lumbar puncture, did not have a diagnosis of PDD or concomitant diseases affecting cognition, deep brain stimulation or previous alcohol or drug abuse. The study was approved by the local Ethics Committee; all patients gave written informed consent.

Between April 2014 and April 2018, 255 non-demented patients were recruited. Twenty-nine patients were excluded [major depression indicated by the Beck-Depression Inventory-II Score ≥20 points (25, 9.8%) and incomplete data (4, 1.6%)] for a total of 226 PD patients in the final analyses.

Assessments

Demographics (age, sex, education years, age of onset, and disease duration) were assessed for each patient, daily dose of all antiparkinsonian medication was expressed using the levodopa equivalent daily dose (LEDD) (Tomlinson et al., 2010). The Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) and Hoehn & Yahr staging were used to assess motor severity. All motor and cognitive assessments were performed in the "On" medication state.

Global cognitive functioning was assessed using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). All patients underwent a comprehensive neuropsychological battery assessing five cognitive domains. *Executive functions*: semantic and phonemic fluency

and Trail Making Test Part B subtests of the Consortium to Establish a Registry for Alzheimer's Disease–Plus Battery (CERAD-PLUS) (Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1988). *Attention/working memory*: Digit-Symbol and Letter-Number-Sequencing subtests of the "Wechsler Intelligenztest für Erwachsene" (WIE, intelligence test for adults) (Aster, Neubauer, & Horn, 2006; Petermann, 2012). *Language*: Boston Naming Test from the CERAD-PLUS and Similarities subtest of the WIE. *Memory*: word list learning, recall, and discriminability as well as recall of constructional praxis subtests of the CERAD-PLUS. *Visuospatial functions*: constructional praxis subtest from the CERAD-PLUS and fragmented words subtest of the "Leistungsprüfsystem 50+" (LPS50+; cognitive test battery for adults aged 50 and above) (Sturm, Willmes, & Horn, 1993). CERAD-PLUS raw scores were converted to age- and education-corrected z-scores, while raw scores for the WIE and LPS50+ subtests were converted to age-corrected z-scores. All reference values, determined in a healthy population, were taken from the respective test manual; z-scores were averaged over each cognitive domain to provide domain scores. Only z-scores and composite domain scores were used in the final analyses. Level-II recommendations of the Movement Disorder Task Force were used to classify patients as PD-MCI: impairment (1.5 standard deviation below population norms) needed to be present in at least two tests, while ADL function needed to be substantially preserved (Litvan et al., 2012). Patients who did not meet these criteria were classified as PD-CN.

Instrumental ADL impairment was measured using the Functional Activities Questionnaire (FAQ) (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982). Cognitive, motor and quotient subscores of the FAQ (FAQ_C, FAQ_M, and FAQ_Q, respectively) were calculated for each patient, their construction has been described elsewhere (Becker et al., 2018). The FAQ_C was calculated based on FAQ item association to the MoCA (e.g. handling finances and tax records, tracking current events, and remembering current events), and the FAQ_M was based on item association to the UPDRS-III (e.g. shopping, playing a game of skill/working on a hobby,

traveling out of the neighborhood). The FAQ_Q divides the cognitive by the motor part with a cut-off of 1 distinguishing more cognitive- (>1) from motor-driven (≤1) ADL impairments.

DASH Score

For each of the scales described below, a DASH score was built-up using the items assessing depression, anxiety, sleep disturbances, and hallucinations (see Table 1), resulting in two separate scores based on separate instruments both evaluating the same symptom combination.

The Parkinson's Disease Questionnaire-39 (PDQ-39) was developed to evaluate the impact of PD on the quality of life of patients (Peto, Jenkinson, & Fitzpatrick, 1998). The questionnaire is self-reported and consists of 39 items, answered on a scale from 0 (never) to 4 (always).

The NMS-Scale is an interview-based tool quantifying a wide range of NMS, with 30 questions distributed over nine NMS domains (Chaudhuri et al., 2007). Each item can be classified with regard to severity (0-3) and frequency (1-4), multiplied to obtain a total score.

Naismith and Lewis (2011) used PDQ-39 items to construct their DASH score. However, as quality of life is not the central issue addressed by the DASH, we chose to construct a second DASH score based on the NMS-Scale, which has been developed specifically for the assessment of NMS in PD. Items from the NMS-Scale were chosen by the authors based on similarity (wording, specific construct measured, number of questions chosen) to the original PDQ-39 questions. In the following paper we refer to the scores as the DASH-PDQ and the DASH-NMS. As Naismith and Lewis (2011) showed a greater severity of DASH symptoms was associated with cognition, we examined severity of symptoms using the DASH burden (defined using a median-split).

Statistical Analyses

Study data was collected and subsequently managed using REDCap electronic data capture tools (Harris et al., 2009). Data analyses were carried out using IBM SPSS version 25

(SPSS Inc., Chicago, IL, USA). Assumptions of normality were tested with Shapiro-Wilk tests. Data that was not normally distributed was described descriptively by median and minimum/maximum, with frequencies shown as percentages. Cross-tables and chi-squared tests were calculated for categorical variables while non-parametric Mann-Whitney U tests were used for interval variables. Significant demographic variables were included in further analyses as covariates. All α levels were set at 0.05.

Analyses were split into two parts. First, both DASH scores were compared using Spearman's correlation coefficient. Two binary logistic regressions examined the relation between cognitive group (PD-CN vs. PD-MCI) and each DASH score, with age, LEDD, and UPDRS-III score as cofounders. Spearman's correlation coefficients were calculated for each DASH score, with the MoCA, the five cognitive domain scores, age, LEDD, disease duration, and age at onset as covariates. As only the DASH-NMS score was able to differentiate between cognitive groups, a post-hoc linear regression was performed with all significant variables from the Spearman's correlation as predictors.

In the second part, only the PD-MCI subgroup was analyzed. Patients were split according to the 50^{th} percentile of the DASH-NMS. A Mann-Whitney-U test was performed between these two groups, the MoCA, and all cognitive domains. Only patients with a high DASH burden (DASH-NMS_H) were additionally stratified according to the FAQ_Q cutoff of 1, as these patients were defined as the risk group. An independent samples Kruskal-Wallis test (significance level adjusted by Bonferroni correction for multiple tests) and post hoc Dunn's pairwise tests were performed between all three resulting DASH-NMS groups, the MoCA, and all five cognitive domain scores.

Results

Demographics

Of all patients, 131 (58%) were diagnosed as PD-CN and 95 (42%) as PD-MCI. Nine (9.5%) PD-MCI patients were classified as single-domain, and 86 (90.5%) were classified as

multi-domain PD-MCI, with impairment in two (45.3%), three (27.4%), four (11.6%) and five (6.3%) domains. Compared to PD-CN patients, PD-MCI patients were significantly older, took more antiparkinsonian medications, had greater motor severity, and a lower global cognitive status (see Table 2). All other demographic comparisons were not statistically significant.

Characteristics of the DASH scores and correlations cognition

The DASH-PDQ (*Mdn*=1, *Range* 0-15) and the DASH-NMS (*Mdn*=1, *Range* 0-27) were moderately but significantly correlated to one another (r_s=0.55, p<0.001). Relation between cognitive group and the DASH scores was examined using binary logistic regression. The DASH-NMS model was statistically significant $\chi^2(4)=25.67$, p<0.001, explaining 14.5% (Nagelkerke R^2) of the variance. The DASH-NMS significantly differentiated between cognitive groups (p=0.04), as did the UPDRS-III (p=0.007). The model using the DASH-PDQ was also statistically significant $\chi^2(4)=21.20$, p<0.001, explaining 12.0% (Nagelkerke R^2) of the variance. In this model, only the UPDRS-III significantly differed between groups (p=0.006), while the DASH-PDQ score did not (p=0.73).

Results of the Spearman's correlation (see Table 3) showed the DASH-PDQ was correlated with LEDD, disease duration, MoCA score, as well as both subscores of the FAQ. In contrast, the DASH-NMS was significantly correlated with MoCA score, attention/working memory, visuospatial functions, and language domains, as well as both FAQ subscores. A post-hoc multivariate linear regression model examining the relation between the DASH-NMS and all significant variables identified in the previous correlation analysis was stable: $F(6,219)=5.91$, p<0.001 with an R^2 of 0.14. In this model, the FAQ_C was the only statistically significant predictor of the DASH-NMS (p=0.01) (see Supplementary Table 1).

PD-MCI subgroup analysis

The 50th percentile of the DASH-NMS was identified (score=1) and used to divide the PD-MCI into patients with high ($DASH\text{-}NMS_H$, >50th percentile) and low ($DASH\text{-}NMS_L$, ≤50th percentile) NMS burden. Demographic and clinical variables were comparable between groups

(see Supplementary Table 2). MoCA scores were lower in DASH-NMS_H compared to DASH-NMS_L patients (U=809.5, p=0.017), the visuo-spatial domain showed a trend for more impairment in DASH-NMS_H patients (U=879, p=0.065).

The DASH-NMS_H group was additionally stratified according to the FAQ_Q cutoff into DASH-NMS_{H+} (more cognitive ADL dysfunction) and DASH-NMS_{H-} (more motor ADL dysfunction) groups. A Kruskal-Wallis test showed the MoCA was lowest in patients with high DASH burden and cognitive-driven ADL impairment (p=0.036, see Figure 1). Post-hoc Dunn's pairwise comparison indicated that MoCA performance differed significantly only between the DASH-NMS_L and DASH-NMS_{H+} groups (adjusted p=0.045).

Discussion

The disease course of PD is associated with an increased likelihood of developing cognitive deficits including PDD (Goldman & Litvan, 2011). The aim of the present study was to examine the association of the DASH score with cognitive function and other potential PDD prodromal markers in a large non-demented PD cohort. Of all patients, 58% were classified as PD-CN, and 42% as PD-MCI. Our results reflect previous studies showing that PD-MCI is associated with increasing age and greater motor severity, indicated by higher UPDRS-III scores and increased daily intake of levodopa in our cohort (Aarsland et al., 2010; Biundo et al., 2014; Caviness et al., 2007).

Results show that the DASH-NMS score was able to differentiate between PD-CN and PD-MCI while the DASH-PDQ score did not. This is likely due to the different purposes for which the two assessments (PDQ-39 and NMS-Scale) were developed. As described earlier, it is questionable whether the PDQ-39 is suitable as the basis for the DASH score. The NMS-Scale has been explicitly developed to assess NMS in PD (Chaudhuri et al., 2007) and seems a more promising scale for assessing DASH symptoms. As the DASH-NMS score was more closely associated with cognitive impairment, it can be assumed that an assessment validated for NMS is essential to the formation of the DASH score. Results also show that the DASH-

PDQ, in contrast to the DASH-NMS, was associated with demographic variables primarily reflecting certain motor parts of the disease, even showing a stronger association to motor-driven ADL impairment (FAQ_M). While the goal of Naismith and Lewis (2011) was to use the original DASH score to develop an instrument that is primarily associated to cognitive functions, using PDQ-39 items does not seem optimal. We show that the NMS-Scale is a viable alternative and may have more predictive value, with further studies needed to confirm this.

Our results show a high correlation of the DASH NMS score with specific cognitive domains, namely attention/working memory, visuospatial functions, and language. These domains have been shown in the literature to be associated with PDD. Stronger deficits in attention have been shown to be present in PD-MCI patients that convert to PDD (Biundo et al., 2014; Bronnick et al., 2006; Miura, Matsui, Takashima, & Tanaka, 2015). Language problems have also been shown to arise in transition from PD-MCI to dementia (Bastiaanse & Leenders, 2009), as have problems in the visuospatial domain (Kehagia, Barker, & Robbins, 2010). Interestingly, the DASH-NMS did not show a significant relationship with executive functions, which are often described as particularly impaired in PD (McKinlay, Grace, Dalrymple-Alford, & Roger, 2010). However, there are studies that point to the heterogeneity of impaired cognitive domains, with executive functions not necessarily showing in all PD patients (Kehagia et al., 2010). In addition, there are studies that describe that other (especially posterior) functions are more important for the prediction of PDD, suggesting deficits in executive tasks may occur early in PD, but may not be the dominating area for predicting dementia development at later stages (Williams-Gray et al., 2009).

The DASH-PDQ was not significantly correlated with any cognitive domains, differing from the original study results where correlations with poorer working memory and set-shifting performance were found. This may be due to the sample size difference: the original DASH was developed in a small sample of 53 patients while our dataset consisting of 226 patients could be considered more representative of the population of interest. As discussed above,

studies have shown that executive functions in PD patients are affected very early on, especially using task change tests which Naismith and Lewis (2011) found correlated with the DASH-PDQ. Further studies are needed to examine the relationship between the DASH-PDQ and cognitive impairment, especially executive functions.

It is interesting to note the different associations with cognition of both DASH scores. The DASH-PDQ measures only the frequency of NMS, and could neither distinguish between cognitive groups, nor was it correlated with any of the cognitive domains measures. However, the DASH-NMS, which assesses both frequency and severity of NMS, was able to classify PD-MCI patients and showed a high correlation to cognitive domains that have been reported to be associated with a higher PDD risk (Becker et al., 2018; Bronnick et al., 2006; Kehagia et al., 2010). While the number of NMS that a patient presents can determine their quality of life (Titova & Chaudhuri, 2018), our results show that the severity of the NMS may determine their risk for cognitive decline and ADL impairment. NMS have been shown to increase in terms of occurrence and severity throughout the disease course, reflecting the spread of pathology in the peripheral and central nervous systems (Erro et al., 2016; Mou, Ding, & Fernandez-Funez, 2019). One study found that PD patients who were older, had more severe motor symptoms, a higher NMS burden, and a lowered ability to carry out ADL were at a higher risk of death in the short term (Santos-Garcia et al., 2018). It is possible that targeted treatment of the separate DASH components would be beneficial, as both pharmacological (Schapira, Chaudhuri, & Jenner, 2017; Titova & Chaudhuri, 2018) and non-pharmacological (Cusso, Donald, & Khoo, 2016) treatments exist to ameliorate these symptoms. As previous studies examining NMS have focused mainly on their frequency and prevalence in PD patients, it is important for future studies to examine how the severity of NMS affect cognitive decline and changes in ADL function.

The additional study of ADL impairments in relation to cognitive dysfunction is important, as it is crucial for the diagnosis of PDD. Both FAQ subscores had a clear correlation

to both DASH scores, showing an association between the amount of DASH symptoms and ADL functioning in both cognitive (FAQ_C) and motor (FAQ_M) areas. Moreover, cognitive-driven ADL impairment was the most significant predictor of the DASH-NMS score. Previous work has shown the FAQ_C subscore differentiates between the cognitive groups PD-CN and PD-MCI (Becker et al., 2018), while the current study shows the DASH-NMS also differentiated between the cognitive groups and was highly associated to the FAQ_C. It is possible that higher burden of DASH symptoms and mild cognitive-related ADL impairment are possible prodromal markers for subsequent PDD development. Splitting the PD-MCI group, known to be of higher risk for PDD (Anang et al., 2014), using the 50^{th} percentile showed that a higher burden of DASH symptoms results in lowered global cognitive status, assessed by the MoCA. This effect remained when stratifying the groups according to both non-motor burden and the FAQ_Q, specifically between patients with increased DASH burden and more cognitive-driven ADL impairment compared to those without both characteristics. Given that the cross-sectional study design impedes any definitive conclusions, we can only speculate that the combination of these two prodromal markers may present a risk group within PD-MCI patients that are at risk for conversion to PDD within a short time period. Long-term studies are therefore urgently needed to evaluate the predictive value of the DASH-NMS score and the FAQ subscores for PDD development.

Some limitations of this study need to be mentioned. The cross-sectional design of the study and the exclusion of PDD patients does not allow the determination of the predictive value of both DASH scores in relation to the development of cognitive disorders or PDD, despite the high association of the DASH-NMS score with cognitive domains. The DASH-NMS score was constructed based on the similarity to the DASH-PDQ questions; as no procedure was used to remove subjectivity, further studies should compare whether full versions of the NMS-Scale are more suitable than using only the DASH-NMS items. Comparisons between the DASH scores and the full questionnaires (PDQ-39 and NMS-Scale)

should be examined in future studies, to determine whether the DASH scores have a better predictive value than simply using the full questionnaires. Moreover, as the results of the DASH scores were dependent on the underlying survey instruments, the creation and validation of a uniform scale explicitly for the collection of the DASH symptoms should be considered. Exclusion of patients with major depressive disorder, characterized by a BDI-II score ≥20, is an important limitation of this study, as depression is one of the factors contributing to the DASH score. It has been shown that severe depression negatively affects cognition (Chagas et al., 2014; Ng, Chander, Tan, & Kandiah, 2015), which could have biased the relationship between the DASH and cognitive domain scores. Naismith and Lewis (2011) did not include patients with major depression in their original study, and as the aim was to replicate their study in a larger cohort, these patients were also excluded. Lastly, it should be noted that the assignment of neuropsychological tests to specific cognitive domains has been debated, as certain tests can be sensitive to more than one domain or even have overlapping features with other tests (e.g. visuospatial tests include components of attention and executive function) (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). In this paper, we adhered to the PD-MCI guidelines set forth by (Litvan et al., 2012) to determine the appropriate cognitive domain for each test.

In conclusion, we developed a novel DASH-NMS score that was able to differentiate between cognitive groups with significant associations to cognitive domains associated with PDD development and cognitive-driven ADL impairment. PD-MCI patients with a high burden of DASH symptoms and more cognitive-driven ADL impairment performed worse on the MoCA than patients with low DASH burden. The combination of DASH burden and cognitive ADL impairment shows promise in characterizing a risk group for PDD among PD-MCI; longitudinal studies are now needed to determine progression of these factors and their suitability for assessing conversion to PDD.

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Table 1. *Construction of the DASH-PDQ-39 and DASH-NMS Scores*

Item	**DASH-PDQ-39** Symptoms based on scale from 0 (never) to 4 (always)	**DASH-NMS** Symptoms assessed over last month, scored with respect to severity (0, none – 3, severe) and frequency (1, rarely – 4, very frequently)
	Due to having Parkinson/s Disease, how often during the last month have you….	
Depression	17. …felt depressed?	3.10. Does the patient seem sad or depressed or has he/she reported such feelings?
Anxiety	21. …felt anxious?	3.9. Does the patient feel nervous, worried or frightened for no apparent reason?
Sleep Disturbances	30. …unexpectedly fallen asleep during the day?	2.3. Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversations, during mealtimes, or while watching television or reading).
Hallucinations	33. …had distressing dreams or hallucinations?	4.13. Does the patient indicate that he/she sees things that are not there?
Maximum Points	16	48

DASH-NMS, Depression-Anxiety-Sleep Disturbances-Hallucinations Score from the Non-Motor Symptoms-Scale; DASH-PDQ-39, Depression-Anxiety-Sleep Disturbances-Hallucinations Score from the Parkinson's Disease Questionnaire-39

Table 2. *Demographic and clinical characteristics of the population*

Characteristic		Total Sample *N=226*	PD–CN *n=131*	PD–MCI *n=95*	*p*–value
Male Gender: *n* (%)		145 (64.2)	84 (64.1)	61 (64.2)	1.00
Age (years)		66.19 (48.07-83.67)	65.15 (48.07-79.93)	67.95 (50.01-83.67)	0.03*
Education Years		13 (8-21)	13 (8-21)	12 (8-21)	0.07
Age at Onset (years)		60.58 (36.43-79.49)	59.78 (36.43-77.63)	61.36 (41.02-79.49)	0.16
Disease Duration (years)		3.88 (0-18.40)	3.67 (0.11-18.40)	4.85 (0-15.37)	0.09
LEDD		480 (0-1574)	417.5 (0-1574)	560 (0-1380)	0.003*
UPDRS-III		25 (1-56)	22 (1-56)	28 (3-52)	<0.001*
Hoehn & Yahr: *n* (%)					0.002*
	1	30 (13.3)	22 (16.8)	8 (8.4)	
	2	129 (57.1)	82 (62.6)	47 (49.5)	
	3	65 (28.8)	26 (19.8)	39 (41.1)	
	4	2 (0.9)	1 (0.8)	1 (1.1)	
MoCA		26 (16-30)	27 (18-30)	25 (16-30)	<0.001*
BDI-II Total Score		6 (0-19)	6 (0-19)	7 (0-19)	0.18

Results are expressed as *Median (Range)* except where noted; Asterisks denote statistically significant differences

BDI-II, Beck Depression Inventory-II; LEDD, Levodopa-Equivalent Daily Dose; MoCA, Montreal Cognitive Assessment; PD-CN, Parkinson's Disease with no cognitive impairment; PD-MCI, Parkinson's Disease with mild cognitive impairment; UPDRS-III, Unified Parkinson's Disease Rating Scale-III

Table 3. *Correlations between the DASH scores, demographic variables, cognitive domain scores, and FAQ subscores*

Measure	DASH-NMS		DASH-PDQ	
	r_s	*p*-value	r_s	*p*-value
Age	0.10	0.13	0.13	0.05
LEDD	0.06	0.37	0.20	0.002*
Age at Onset	0.05	0.51	0.05	0.49
Disease Duration	0.11	0.10	0.20	0.002*
UPDRS-III Total Score	0.11	0.09	0.12	0.06
MoCA Total Score	-0.24	<0.001*	-0.20	0.003*
Executive Functions	-0.07	0.28	0.007	0.92
Attention/Working Memory	-0.18	0.007*	-0.11	0.10
Memory	-0.11	0.11	-0.10	0.15
Visuospatial Functions	-0.20	0.003*	-0.11	0.09
Language	-0.13	0.04*	-0.06	0.40
FAQ_C	0.28	<0.001*	0.33	<0.001*
FAQ_M	0.21	0.002*	0.27	<0.001*
FAQ_Q	0.05	0.44	0.03	0.69

Asterisks denote statistically significant differences

DASH-NMS, Depression-Anxiety-Sleep Disturbances-Hallucinations Score from the Non-Motor Symptoms Scale; DASH-PDQ, Depression-Anxiety-Sleep Disturbances-Hallucinations Score from the Parkinson's Disease Questionnaire-39; FAQ_C, Functional Activities Questionnaire Cognitive subscore; FAQ_M, Functional Activities Questionnaire Motor subscore; FAQ_Q, Functional Activities Questionnaire Quotient; LEDD, Levodopa-Equivalent Daily Dose; MoCA, Montreal Cognitive Assessment; UPDRS-III, Unified Parkinson's Disease Rating Scale-III

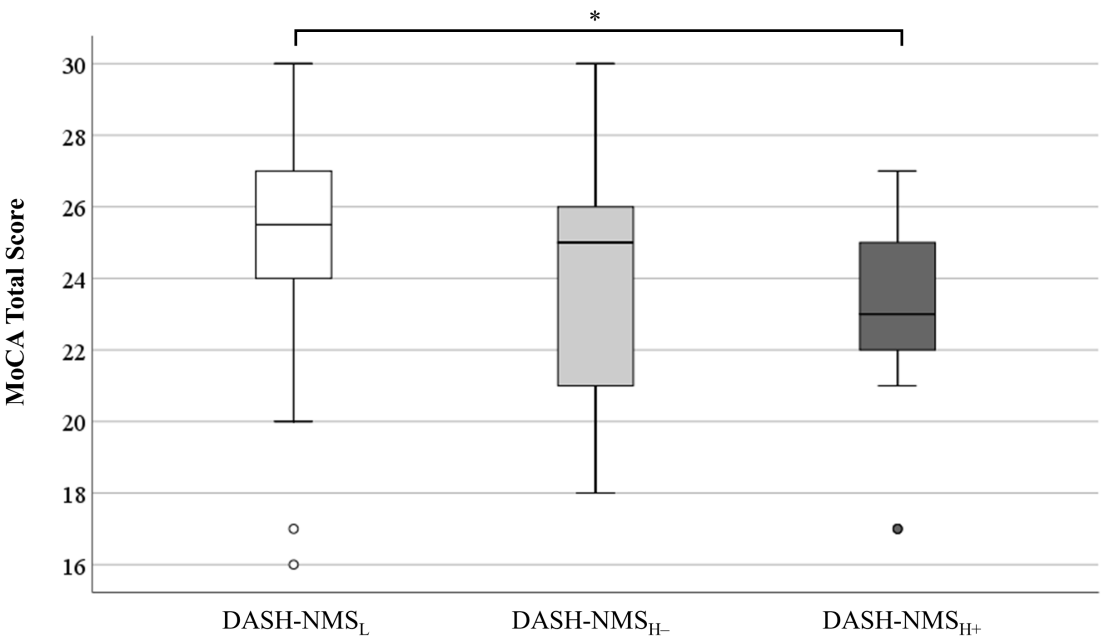

Figure 1. Box-and-whisker plot of MoCA Scores across the three PD-MCI groups; asterisks denote statistically significant differences

Supplementary Table 1. *Results of the linear regression between the DASH-NMS score and significant predictors*

Factor	Unstandardized Coefficients		Standardized Coefficients			95% Confidence Interval for B	
	B	Std. Error	Beta	*t*	*p*-value	Lower Bound	Upper Bound
MoCA	-0.082	0.105	-0.060	-0.780	0.436	-0.290	0.125
Attention/Working Memory	-0.169	0.456	-0.029	-0.371	0.711	-1.067	0.729
Visuospatial Functions	-0.609	0.366	-0.120	-1.661	0.098	-1.330	0.113
Language	0.376	0.435	0.066	0.864	0.388	-0.482	1.234
FAQ_C	10.346	3.976	0.253	2.602	0.010*	2.510	18.182
FAQ_M	3.144	3.821	0.076	0.823	0.411	-4.386	10.674

Asterisks denote statistically significant differences

FAQ_C, Functional Activities Questionnaire Cognitive subscore; FAQ_M, Functional Activities Questionnaire Motor subscore; MoCA, Montreal Cognitive Assessment

Supplementary Table 2. *Demographic and clinical characteristics of the PD-MCI subgroup*

Measure		DASH-NMS$_L$ *n=48*	DASH-NMS$_H$ *n=47*	*p*–value
Male Gender: *n* (%)		31 (64.6)	30 (63.8)	1.00
Age (years)		67.78 (50.01-82.20)	68.71 (50.54-83.67)	0.90
Education Years		12.5 (8-21)	12 (8-21)	0.25
Age at Onset (years)		62.48 (41.02-79.49)	60.77 (46.05-78.05)	0.71
Disease Duration Years		3.76 (0-14.31)	5.88 (0.02-15.37)	0.30
LEDD		502.5 (100-1120)	627 (0-1380)	0.12
UPDRS-III		27.5 (4-49)	29 (3-52)	0.40
Hoehn & Yahr: *n* (%)				0.22
	1	2 (4.2)	6 (12.8)	
	2	27 (56.3)	20 (42.6)	
	3	19 (39.6)	20 (42.6)	
	4	0 (0)	1 (2.1)	

Results are expressed as *Median (Range)* except where noted
LEDD, Levodopa-Equivalent Daily Dose; UPDRS-III, Unified Parkinson's Disease Rating Scale-III

HIPPOCAMPAL SUBFIELDS, COGNITION AND CSF BIOMARKERS IN NON-DEMENTED PARKINSON'S DISEASE PATIENTS

Authors: Sara Becker, M.Sc.; Oliver Granert, Dipl.-Inf.; Maarten Timmers, PhD; Andrea Pilotto, MD; Luc Van Nueten, MD; Benjamin Roeben, MD; Giacomo Salvadore , MD; Wendy R. Galpern, MD, PhD; Johannes Streffer, MD; Klaus Scheffler, PhD, Prof.; Walter Maetzler, MD; Daniela Berg, MD, Prof.; Inga-Liepelt Scarfone, PhD, PD

Sara Becker, Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, Tübingen, Germany, and German Center for Neurodegenerative Diseases, Tübingen, Germany

Oliver Granert, Department of Neurology, Christian-Albrechts-University, Kiel, Germany

Maarten Timmers, Janssen Research and Development, a Division of Janssen Pharmaceutica N.V., Beerse, Belgium, and Reference Center for Biological Markers of Dementia, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium

Andrea Pilotto, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, and Parkinson's disease Rehabilitation Centre, FERB ONLUS Sant'Isidoro Hospital, Trescore Balneario, Bergamo, Italy

Luc Van Nueten, Janssen Research and Development, a Division of Janssen Pharmaceutica N.V., Beerse, Belgium

Benjamin Roeben, Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, Tübingen, Germany, and German Center for Neurodegenerative Diseases, Tübingen, Germany

Giacomo Salvadore, Janssen Research and Development LLC, Titusville, NJ, USA

Wendy R. Galpern, Janssen Research and Development LLC, Titusville, NJ, USA

Johannes Streffer, Janssen Research and Development, a Division of Janssen Pharmaceutica N.V., Beerse, Belgium, and Translational Medicine Neuroscience, UCB Biopharma SPRK, Braine-l'Alleud, Belgium

Klaus Scheffler, Magnetic Resonance Center, Max Planck Institute for Biological Cybernetics, Tübingen, Germany, and Department of Biomedical Magnetic Resonance, University Hospital Tübingen, Tübingen, Germany

Walter Maetzler, Department of Neurology, Christian-Albrechts-University, Kiel, Germany

Daniela Berg, Department of Neurology, Christian-Albrechts-University, Kiel, Germany

Inga Liepelt-Scarfone, Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, Tübingen, Germany, and German Center for Neurodegenerative Diseases, Tübingen, Germany

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Corresponding Author:
Sara Becker
Hertie Institute for Clinical Brain Research
Department of Neurodegeneration
Hoppe-Seyler-Str. 3
D-72076 Tübingen, Germany
Tel.: +4970712985790
Fax: +497071294990
Email: sara.becker@med.uni-tuebingen.de

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Statistical Analysis conduced by Sara Becker, M.Sc., Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases

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Abstract

Objectives

The mechanisms underlying cognitive impairment in Parkinson's disease (PD) are not well understood. Co-existing Alzheimer's pathology, namely hippocampal atrophy and amyloid deposition, may play a role in the cognitive decline observed in PD. It is currently unclear whether hippocampal volume loss is primarily associated with cognitive impairment or Amyloid-β 1-42 burden. This study investigated hippocampal subfield volumes between both PD patients with (PD-MCI) and without (PD-CN) cognitive impairment and between patients with low and high Aβ42 levels. Additionally, we examined the relationship between hippocampal subfield volumes, cerebrospinal fluid (CSF) biomarkers (Aβ42, phosphorylated and total tau), neuropsychological tests, and activities of daily living.

Methods

Forty-five non-demented PD patients underwent CSF analyses and magnetic resonance imaging as well as comprehensive motor and neuropsychological examinations. Hippocampal segmentation was conducted using FreeSurfer image analysis suite 6.0. Regression models were used to compare hippocampal subfield volumes between groups, and partial correlations defined the association between variables while controlling for intracranial volume.

Results

The hippocampal-amygdaloid transition area was significantly smaller in PD-MCI than PD-CN. In contrast, no significant differences were found for hippocampal subfield volumes and cognition after group stratification according to CSF Aβ42 levels. Smaller hippocampal subfield volume was associated with worse memory, language, spatial working memory and executive functioning as well as higher CSF tau levels.

Conclusion

Hippocampal subfield volume showed associations to memory, visuospatial working memory and executive dysfunction, as well as to tau pathology, but not to CSF Aβ42 levels.

Introduction

Over time, up to 80% of Parkinson's disease (PD) patients progress from normal cognition (PD-CN), to mild cognitive impairment (PD-MCI) and PD dementia (PDD)[1]. The most prominent cognitive deficits occur in executive function, working memory, visuospatial, attention, and language domains[2,3]. However, mechanisms underlying cognitive impairment in PD are not well understood, making the identification of risk factors and prodromal markers for progression to PD-MCI and PDD key research priorities in the field.

It is becoming increasingly evident that co-existing Alzheimer's disease (AD) pathology plays a role in PD as well, especially in relation to cognitive decline. Hippocampal atrophy is an established early biomarker for AD, but is also common to other dementias[4]. In PD, pathological studies report atrophy in the medial temporal lobe, and hippocampal atrophy has been suggested as a biomarker of initial cognitive decline[5]. However, unlike in AD, presence of hippocampal atrophy in PD is more variable, and its association to specific cognitive domains is still unclear. Greater hippocampal atrophy has been found in PDD compared to non-demented PD patients[6], and in both non-demented PD[7] and PDD[8] patients compared to controls. Density of Lewy bodies and Lewy neurites in the Cornu Ammonis (CA) 2-3 region of the hippocampus was shown to be higher in PDD than in non-demented PD patients[9]. This region along with the CA4 and dentate gyrus regions showed significantly smaller volumes in PD patients compared to controls[10]. Newly-diagnosed, untreated PD patients showed less hippocampal volume than controls in one study[11], whereas other studies found no difference in hippocampal size between PD-MCI and PD-CN patients[12] or between PD patients and controls[13]. These conflicting results may arise from studies considering the hippocampus as a whole structure, instead of a composite of sub-structures, which are differently affected by Lewy body pathology[14]. Moreover, the relationship between hippocampal atrophy and activity of daily living (ADL) function, the core criteria for diagnosing PDD, has rarely been examined. The few studies examining this interaction AD patients have identified hippocampal atrophy as a correlate of ADL function[15], yet it is unclear if this association is also observed in PD patients. Understanding how both of these aspects are related can provide a better explanation for cognitive decline in PD.

Hippocampal atrophy has also been linked to cerebrospinal fluid (CSF) Amyloid-β 1-42 (Aβ42) levels, an established biomarker for AD that reflects brain Amyloid-β burden[12]. Lowered CSF Aβ42 values have been shown in PD patients compared to controls[16]. Moreover, longitudinal studies indicate that low CSF Aβ42 levels at baseline are associated with a more rapid cognitive decline in PD[17,18]. Therefore, CSF Aβ42 has been proposed as a

risk factor for PDD development[19]. These low CSF Aβ42 levels in PD seem to be related specifically to deficits in verbal fluency, memory loss, and slowed processing speed[20]. However, to date, the association between Aβ42, hippocampal volume, and cognition using a comprehensive battery in PD has only been sparsely investigated[21].

Aim

As it is currently unclear whether hippocampal volume loss is primarily associated with cognitive impairment or pathological Aβ42 (as defined by low CSF Aβ42 levels), the aims of this study were two-fold. We compared hippocampal subfield volumes between both PD-CN and PD-MCI patients and between patients with low and high Aβ42. We hypothesized that patients with PD-MCI and those with low CSF Aβ42 levels have smaller hippocampal volumes especially in the CA2-3 and CA4 regions. Second, we investigated the relationship between hippocampal atrophy, cognitive performance, CSF biomarker profiles, and activity of daily living (ADL) impairment.

Methods

Study design and participants

Data was analyzed as part of the longitudinal study "Non-demented patients with Parkinson's disease with and without low Amyloid-beta 1-42 in cerebrospinal fluid." Study inclusion criteria were: age 50-85 years, diagnosis of PD according to the United Kingdom PD Brain Bank criteria[22] confirmed after at least one year of follow up, German as mother tongue, and ability to give informed consent and communicate with investigator. Exclusion criteria were: i) diagnosis of PDD, ii) cerebrovascular infarcts or hemorrhages on MRI, iii) concomitant diseases potentially affecting cognition (i.e., hepatic or renal failure, stroke, or traumatic brain injury), iv) deep brain stimulation, v) history of drug or alcohol abuse, vi) current major depressive episode defined by a Beck-Depression-Inventory II score >19 at time of visit, or vii) participation in medication study 4 weeks prior to baseline visit. The study was approved by the local Ethics Committee (Ethics-Nr: 686/2013BO1), and all patients gave written informed consent.

Between April 2015 and September 2018, 100 non-demented PD patients completed the baseline visit of the study. All patients underwent a neurological and neuropsychological examination as well as lumbar puncture at screening conducted at least six weeks before imaging. CSF Aβ42, total tau and phosphorylated-tau levels were determined using commercially available ELISA kits (Fujirebio Europe, Gent, Belgium). A cut-off of 600

pg/mL[23] was used to divide the sample into two groups: Aβ42+ (<600 pg/mL, *n*=50) and Aβ42– (≥600 pg/mL, *n*=50). As the sample was collected prospectively, groups could be matched according to gender, age, educational level, and disease duration. In total, 48 patients were eligible for Magnetic Resonance Imaging (MRI) scans. Scans of three patients were excluded due to an incomplete scan (*n*=1), and diagnosis of multiple system atrophy-parkinsonian subtype established after the baseline visit (*n*=2). Therefore, clinical and imaging data of 45 patients were analyzed.

Diagnosis of PD-MCI was made according to Level I criteria recommended by the Movement Disorder Society[24], using the Montreal Cognitive Assessment (MoCA)[25], a measure of global cognitive functioning. MoCA scores below 26 points classified PD-MCI, and higher values PD-NC. None of the patients had ADL impairment indicative of PDD, determined using the Functional Activities Questionnaire (FAQ) and a MoCA score below 18 points.

Assessments

Demographic data were collected for each patient, including age, sex, education years, age of PD onset, and disease duration. Medication intake was collected, and anti-parkinsonian medication was expressed using the levodopa equivalent daily dose (LEDD)[26]. To assess disease severity, the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) and Hoehn & Yahr scores were used.

Comprehensive neuropsychological assessment included the Cambridge Neurological Test Automated Battery (CANTAB) and the Repeated Battery for the Assessment of Neuropsychological Status (RBANS). The CANTAB is a language-independent computerized assessment validated for elderly patients with neurodegenerative diseases[27]. Six subtests were chosen to measure: memory (Paired Associates Learning, PAL; Pattern Recognition Memory, PRM; Spatial Working Memory, SWM), attention/psychomotor speed (Match to Sample Visual Search, MTS), executive functions (Stockings of Cambridge, SOC), and information sampling (Information Sampling Task, IST). Table 1 provides an in-depth explanation of the CANTAB subtests and functions measured. The RBANS is a brief neurocognitive assessment battery for detecting and describing dementia in the elderly[28]. Twelve subtests measure: immediate memory (list learning and story memory), visuospatial/ constructional (figure copy and line orientation), language (picture naming and semantic fluency), attention (digit span and coding), and delayed memory (list recall, list recognition,

story memory, and figure recall). All RBANS subtests were administered and subsequently scored as described in the manual, providing age-group corrected z-scores for each subtest.

For each patient, cognitive and motor subscores of the Functional Activities Questionnaire (FAQ_C and FAQ_M, respectively) were calculated in order to evaluate ADL dysfunction. Based on previous work[29], these novel subscores were calculated based on the FAQ item association to the MoCA (FAQ_C) and the UPDRS-III (FAQ_M).

MRI acquisition and hippocampal segmentation

All MRI data were collected using a 3 Tesla Siemens Magnetom Prisma (software versions Syngo MR D13D and E11C). The following protocols were used: MPRAGE (T1): 3D GE, repetition time (TR)/inversion time (TI)/echo time(TE) 2300/900/2.93 ms, flip angle 9°, 176 slices with no gap, matrix 256x256, voxel size 1.0×1.0×1.0 mm^3; SPACE (T2): 3D TSE, repetition time (TR)/echo time(TE) 3500/352.0 ms, variable flip angle, 64 slices with no gap, matrix 384x384, voxel size 0.5×0.5×1.5 mm^3; FLAIR: 3D TSE, repetition time (TR)/inversion time (TI)/echo time(TE) 5000/1800/394 ms, variable flip angle, 192 slices with no gap, matrix 256x256, voxel size 1.0×1.0×1.0 mm^3.

Hippocampal subfield segmentation and grey/white matter volumetric segmentation was performed using Freesurfer image analysis suite 6.0 (stable6-20170118) and the integrated hippocampal subfield segmentation module[30], which is documented and freely available for download at http://surfer.nmr.mgh.harvard.edu. All T1-weighted images were preprocessed with the standard Freesurfer processing pipeline using the "recon-all" script. In addition to the default processing pipeline, the high-resolution T2-weighted images of each subject were submitted using the "hippocampal-subfield-T1T2" parameter. These T2 images were used simultaneously with the T1-weighted image to improve the results of the automatic hippocampus subfield segmentation algorithm[30]. The Freesurfer algorithms segments 12 hippocampal subfields: hippocampal tail, subiculum, CA1, hippocampal-fissure, presubiculum, parasubiculum, molecular layer, granule cell layer of the dentate gyrus (GC-DG), CA2-3, CA4, fimbria, and the hippocampal-amygdaloid transition area (HATA). The volume estimates of these subfields (combined for right and left hemispheres of each subfield) were then used in the final analysis.

Statistical Analyses

All data were collected and managed using REDCap electronic data capture tools hosted at the Hertie Institute for Clinical Brain Research[31]. Data analyses were carried out

using IBM SPSS version 25 (SPSS Inc., Chicago, IL, USA), with all α levels set at 0.05. Between-group analyses for demographic, cognitive and clinical variables were conducted by using chi-squared tests and Mann-Whitney-*U* tests for dichotomous and continuous variables, respectively. Linear regressions were calculated for each hippocampal subfield, with either diagnosis (PD-MCI, PD-CN) or CSF Aβ42 levels (Aβ42+ and Aβ42–) as independent variables, correcting for estimated intracranial volume (ICV). Partial correlations assessed the association between neuropsychological tests, CSF biomarkers, FAQ subscores and hippocampal subfields, while controlling for ICV.

Data Availability

Due to ethical restrictions imposed by the Ethics Committee of the Medical Faculty of the University of Tübingen relating to approved patient consent procedure and protection of patient privacy, requests for all relevant data should be sent to Dr. Inga Liepelt-Scarfone via inga.liepelt@uni-tuebingen.de or in case of unavailability, to Prof. Dr. Thomas Gasser directly via thomas.gasser@uni-tuebingen.de. The Ethics Committee has decided how the researchers should handle data of this particular study; however, the Ethics Committee does not have access to the actual data.

Results

Demographic data for the total sample, cognitive groups (PD-CN and PD-MCI), and Aβ42 (Aβ42+ and Aβ42–) groups are reported in Table 2. The proportion of patients classified as PD-MCI did not significantly differ between the Aβ42 groups ($\chi^2(1, N=45)=.024$, $p=1.00$).

Hippocampal volumes and cognition in PD-MCI vs. PD-CN

None of the demographic or clinical parameters differed significantly between cognitive groups. PD-MCI patients performed worse than PD-CN patients on the following RBANS subtests: semantic fluency ($U=143$, $p=.03$), and coding ($U=144.5$, $p=.04$). A non-significant trend towards the same direction was noted for list recognition ($U=156.5$, $p=.06$). Non-verbal recognition memory, as assessed by the PRM percent correct score, was also more affected in PD-MCI than PD-CN ($U=140.5$, $p=.03$). These results confirm the validity of our cognitive group assignment. PD-MCI patients had smaller HATA ($p=.04$) and a trend towards smaller CA1 ($p=.05$) volumes compared to PD-CN patients.

Hippocampal volumes in PD patients with high and low CSF Aβ42 levels

Mean disease duration was shorter in Aβ42+ than in Aβ42– patients. Demographic, clinical, and neuropsychological test parameters were not significantly different between groups, neither were any hippocampal subfield volumes.

Correlation analyses

Hippocampal subfields were significantly correlated to CANTAB subtests assessing memory ($-.53 \leq r \leq .37$, all $p<.05$) most notably the PAL test, the SOC subtest assessing executive functions ($.32 \leq r \leq .33$, all $p<.04$), and information sampling ($-.42 \leq r \leq .38$, all $p<.04$), independent of ICV (Table 3). Partial correlations revealed significant associations between RBANS memory subtests ($-.31 \leq r \leq .34$, all $p<.05$) and the hippocampal tail, subiculum, CA1, parasubiculum, and whole hippocampus (Table 4). Significant associations were also shown between RBANS language tests ($.32 \leq r \leq .41$, all $p<.04$) scores and the hippocampal tail, subiculum, presubiculum, parasubiculum and whole hippocampus.

Partial correlations between hippocampal subfields and CSF markers revealed significant associations between the volume of the subiculum and CSF total tau levels ($r=-.37$, $p=.01$). The correlations between hippocampal fissure volume and both, CSF total tau ($r=.28$, $p=.07$) and CSF phosphorylated tau ($r=-.28$, $p=.06$) approached significance.

Significant associations were found for the correlations between the FAQ total score and both the CA1 ($r=.31$, $p=.04$) and CA2-3 regions ($r=.38$, $p=.01$). Trends towards significance were observed for the correlations with the GC-DG ($r=.29$, $p=.06$) and whole hippocampus volume ($r=.30$, $p=.05$). The FAQ_C subscore was correlated only with the CA2-3 ($r=.32$, $p=.04$) region. The correlation between FAQ_C and CA1 ($r=.29$, $p=.06$) approached significance. The FAQ_M was correlated with the hippocampal tail ($r=.30$, $p=.04$), CA1 ($r=.33$, $p=.03$), CA2-3 ($r=.38$, $p=.01$), and whole hippocampus ($r=.33$, $p=.03$). Trends were observed for the correlations with molecular layer ($r=.29$, $p=.06$) and GC-ML-DG ($r=.28$, $p=.06$).

Discussion

This study examined whether hippocampal atrophy, a marker for AD, is associated with cognitive state and CSF Aβ42 levels in PD patients. The main findings of this study are (i) patients with PD-MCI have smaller HATA volumes than patients with PD-CN; (ii) PD patients with low and high CSF Aβ42 levels do not significantly differ regarding hippocampal subfield volumes and cognition; (iii) hippocampal subfield volumes in PD are correlated with memory, language, spatial working memory, and executive function performances; and (iv)

both the CA1 and CA2-3 volumes are positively correlated with cognition- and motor-associated ADLs in PD.

In contrast to our expectation, PD-MCI patients did not have smaller CA2-3 and CA4 volumes than had PD-CN patients; only the HATA region was smaller in PD-MCI. This result is, at least partly, comparable to a previous study that reported lower volumes of the right HATA in PD-MCI patients compared to PD-CN, with baseline left HATA volumes predicting conversion from PD-CN to PD-MCI[32]. The authors interpreted their finding in that way that HATA volume loss may be an early biomarker for visuospatial dysfunction in PD-MCI. Deficits in visuospatial functions have been shown to predict rapid decline to PDD[3], yet more studies are needed to examine the interplay between HATA, visuospatial deficits and cognitive decline.

The Aβ42+ and Aβ42– groups had comparable hippocampal subfield volumes and comparable cognitive test performances, which were unexpected results. Available studies on the influence of Aβ42 on cognitive impairment in PD have reported inconsistent results. A previous study found Aβ42 to be significantly lower in PD than in healthy controls but could not find significant correlations with ratings of neuropsychological testing[16]. As our study was cross-sectional, we cannot rule out that the Aβ42+ group may progress to PDD faster than the Aβ42– group, even if neuropsychological tests do not show a difference at baseline. It has previously been shown that patients with low CSF Aβ42 levels developed PDD within two years[33], highlighting a role for Aβ and the importance of following our cohort longitudinally.

As the Aβ42 groups did not differ with regard to hippocampal volumes, we also examined the relationship to CSF total and phosphorylated tau levels, which have been shown to be increased in PD patients[34]. We identified a moderate correlation between lower subiculum volumes and higher values of total tau in our PD sample. To date, only a few studies have examined the relationship between hippocampal volume and CSF biomarkers (specifically Aβ42, p-tau and t-tau) in PD[12,21]. Stav, et al. [21] did not find associations between CSF biomarkers and hippocampal volumes, even though subiculum volumes were reported to be smaller in PD patients compared to controls. Future studies should examine the relationship between both Aβ42 and tau in relation to longitudinal changes in hippocampal volume.

Further correlation analyses demonstrated that CANTAB memory subtests, specifically the PAL total number errors, showed moderate to high correlations with numerous hippocampal subfields, most importantly the CA1, CA2-3, CA4, and DG regions. Fewer significant correlations were found for the RBANS variables, but most notably CA1 and

subiculum volumes were positively correlated with list recognition. Atrophy of medial temporal lobe structures has been assumed to run in parallel and may even underlie the memory dysfunctions associated with PD[35]. Previous studies have shown that input hippocampal regions, such as the CA2-3 and DG, are associated with learning and encoding, output regions including the subiculum are related to recall, and the CA1 region is responsible for consolidation and later retrieval[10,36]. Our results reflect these findings, with errors made on the PAL test encompassing all aspects of memory. Notably, CA1 and subiculum atrophy has been shown to be present in very early stages of AD, predicting conversion to MCI and dementia[37]. Our results emphasize the potential of hippocampal subfield atrophy as a promising biomarker for cognitive worsening in PD, which needs to be verified in future longitudinal studies.

Interestingly, poorer spatial working memory performance, expressed by a higher number of errors, was correlated to smaller parasubiculum, CA4, DG and fimbria volumes in our sample. While the hippocampus may be important for encoding spatial components of memory, it is unclear to what extent working memory, especially the SWM task, is related to executive functions and mediated by frontal circuits[3]. Upon further examination of the data, we found a correlation between executive function (SOC subtest) and the molecular layer, the DG, and the fimbria, as well as correlations between information sampling task variables, which measure impulsivity, and the DG, CA4, fimbria, HATA and whole hippocampus. Executive dysfunctions and hippocampal atrophy have been sparsely studied; one study did not confirm correlations between frontal functions and hippocampal volumes[38]. Our results also indicate that computerized tests are more sensitive than paper-and-pencil tests in relation to hippocampal volume, as CANTAB subtests are potentially less reliant on motor functions than the RBANS. Both computerized and paper-and pencil tests may also reflect AD pathology differently, although more research is necessary to examine sensitivity of both types of tests for detecting cognitive impairment and hippocampal atrophy in PD.

Recently, mild impairments in activity of daily living (ADL) function have been proposed as a risk marker for PDD. PD-MCI patients presenting with mild cognitive-driven ADL dysfunction potentially characterize those at high risk for PDD[29]. Interestingly, greater severity of ADL impairment was associated with larger hippocampal subfield volumes. As we only included non-demented PD patients in our sample, ADL impairment assessed with the FAQ was only at a mild stage. Our finding, at a first view surprising, may mirror compensation strategies of the hippocampus, to counteract already occurring daily relevant

cognitive deficits in a vulnerable phase of the disease. This hypothesis may serve as a basis for longitudinal evaluation of this phenomenon.

Limitations

This study faces some limitations. First, we used automated segmentation of the hippocampus. Although this analysis technique guarantees highly standardized and objective results, the technique may still have downsides compared to manual segmentation[39]. To minimize risk of miss-segmentation, all Freesurfer calculations were manually counter-checked. Second, we used the MoCA score for PD-MCI classification, although more complex classification strategies are available [24]. Based on the CANTAB and RBANS results (PD-MCI patients performed worse on measures of attention and language), we argue that our approach is still valid. Deficits in attention and language have been shown to be associated with shorter time to conversion to PDD[2,40]. Third, results are based on a cross-sectional study design. However, we feel that our results are useful for the design of specifically designed prospective longitudinal studies, and our cohort will also be followed longitudinally. Finally, certain cognitive assessments, such as the figure copy/recall test and the digit-symbol test, may be influenced by motor impairment especially when paper-pencil tests are used. Consequently, future studies should evaluate motor dysfunction, and how those deficits interfere with neuropsychological test results.

Conclusion

In non-demented PD patients, hippocampal subfields showed associations with memory, spatial working memory, language, and executive functions, and to CSF tau levels. Interestingly, no relevant association was found between hippocampal sub regions and CSF Aβ42 levels. Our results suggest that the HATA has the potential to differentiate cognitive status in PD, and that CSF total tau levels are associated with hippocampal atrophy. These pilot results should be confirmed in future prospective studies, preferably with a longitudinal design.

Appendix 1. Authors

Name	Location	Role	Contribution
Sara Becker, M.Sc.	Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, and German Center for Neurodegenerative Diseases	Author	Major role in data collection; major role in data analysis; drafted the manuscript for intellectual content
Oliver Granert, Dipl.-Inf.	Department of Neurology, Christian-Albrechts-University	Author	Data analysis; revision of manuscript
Maarten Timmers, PhD	Janssen Research and Development, a Division of Janssen Pharmaceutica N.V., and Reference Center for Biological	Author	Design and conceptualization of study

	Markers of Dementia, Institute Born-Bunge, University of Antwerp		
Andrea Pilotto, MD	Department of Clinical and Experimental Sciences, University of Brescia, and Parkinson's disease Rehabilitation Centre, FERB ONLUS Sant'Isidoro Hospital, Trescore Balneario	Author	Data collection; revision of manuscript
Luc Van Nueten, MD	Janssen Research and Development, a Division of Janssen Pharmaceutica N.V.	Author	Design and conceptualization of study
Benjamin Roeben, MD	Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, and German Center for Neurodegenerative Diseases	Author	Data collection; revision of manuscript
Giacomo Salvadore, MD	Janssen Research and Development LLC	Author	Design and conceptualization of study
Wendy R. Galpern, MD, PhD	Janssen Research and Development LLC	Author	Revision of manuscript
Johannes Streffer, MD	Janssen Research and Development, a Division of Janssen Pharmaceutica N.V., and Translational Medicine Neuroscience, UCB Biopharma SPRK	Author	Design and conceptualization of study
Klaus Scheffler, PhD, Prof.	Magnetic Resonance Center, Max Planck Institute for Biological Cybernetics, and Department of Biomedical Magnetic Resonance, University Hospital Tübingen	Author	Design and conceptualization of study
Walter Maetzler, MD	Department of Neurology, Christian-Albrechts-University	Author	Design and conceptualization of study; data collection; revision of manuscript
Daniela Berg, MD, Prof.	Department of Neurology, Christian-Albrechts-University	Author	Design and conceptualization of study
Inga Liepelt-Scarfone, PhD, PD	Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, and German Center for Neurodegenerative Diseases	Author	Design and conceptualization of study; revision of manuscript for intellectual content

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Table 1. *Description of CANTAB subtests*

Test	Domain	Function Measured	Description	Outcome Measures
PAL	Memory	Visual memory and new learning	Boxes are displayed on the screen and show patterns (2,4,6, and 8 patterns) in a randomized order. Patterns are then shown on the screen and participants select the box in which the pattern was located originally.	Total Errors Total Errors 6 Shapes
PRM	Memory	Visual pattern recognition memory	Participants are presented with a series of visual patterns. They are then instructed to choose between a pattern they have just seen and a novel pattern.	Percent Correct
SWM	Memory	Strategy and working memory	A number of colored boxes are shown on the screen. Aim is to select boxes and, by using a process of elimination, find a blue 'token' in each of the boxes.	Between Errors
MTS	Attention	Visual searching, accuracy, reaction time	Complex visual pattern is shown to participant who is then instructed to choose a matching pattern from a varying number of similar patterns.	Percent Correct Total Correct
SOC	Executive Functions	Problem-solving	Two displays show stockings containing colored balls arranged in different patterns. Participants move the balls in one display to copy the pattern shown in the other display.	Problems solved in minimum Moves
IST	Information Sampling	Impulsivity and decision making	Participants are presented with a 5x5 array of gray boxes and told that they are playing a game for points. They select boxes randomly, one at a time, to reveal one of two colors shown at the bottom of the screen. When participants have made their decision about which color is in the majority, they select the appropriate color panel to indicate their choice and the remaining gray boxes display a message whether or not the choice was correct.	Mean Number of Boxes opened per Trial Mean Percent Correct at Decision Mean Box Opening Latency

CANTAB, Cambridge Neurological Test Automated Battery; MTS, Match to Sample Visual Search; IST, Information Sampling Task; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; SOC, Stockings of Cambridge; SWM, Spatial Working Memory

Table 2. *Demographic and clinical characteristics of the population*

	Total Sample *N*=45	PD-CN *n*=29	PD-MCI *n*=16	*p*-value	Aβ42– ≥ 600 pg/ml *n*=19	Aβ42+ < 600 pg/ml *n*=26	*p*-value
Male Gender: n (%)	28 (62.2)	17 (58.6)	11 (68.8)	.54	12 (63.2)	16 (61.5)	1.00
Age (years)	64.27 (50.52-79.02)	64.27 (50.52-79.02)	64.49 (53.52-75.06)	.65	65.51 (51.98-77.37)	63.53 (50.52-79.02)	.56
Education Years	13 (9-21)	14 (9-21)	12.5 (10-19)	.24	12 (9-21)	15 (11-19)	.08
Age at Onset (years)	57.12 (39.85-77.63)	56.55 (39.85-77.63)	59.58 (48.35-71)	.33	59.58 (39.85-72.94)	57.04 (42.53-77.63)	.92
Disease Duration (years)	4.30 (1-14.36)	4.99 (1.26-14.36)	4.08 (1-11.94)	.58	5.13 (2.92-14.36)	3.94 (1-12.68)	**.04**
LEDD	565 (100-1505)	520 (105-1505)	610 (152-1122)	.37	620 (100-1505)	450 (105-1055)	.07
UPDRS-III	22 (5-50)	21 (5-50)	26.5 (10-40)	.69	24 (5-50)	20.50 (10-40)	.56
Hoehn & Yahr: n (%)				.13			1.00
1	1 (2.2)	0 (0)	1 (6.3)		0 (0)	1 (3.8)	
2	37 (82.2)	26 (89.7)	11 (68.6)		16 (84.2)	21 (80.8)	
3	7 (15.6)	3 (10.3)	4 (25)		3 (15.8)	4 (15.4)	
BDI-II	5 (0-27)	6 (0-27)	5 (0-25)	.76	7 (0-19)	5 (0-27)	.86
PD-NMS-Q	7 (0-21)	6 (0-20)	8.5 (3-21)	.43	7 (2-16)	6 (0-21)	.41
MoCA	27 (21-30)	28 (26-30)	23 (21-25)	–*	27 (21-30)	26.5 (22-30)	1.00
MMSE	29 (24-30)	29 (26-30)	28.50 (24-30)	.52	28 (24-30)	29 (26-30)	.30
FAQ Total Score	0 (0-19)	0 (0-19)	1 (0-9)	.23	0 (0-19)	0 (0-10)	.48
FAQ_C	0 (0-.67)	0 (0-.67)	0 (0-.33)	.38	0 (0-.67)	0 (0-.33)	.66
FAQ_M	0 (0-.57)	0 (0-.57)	0 (0-.33)	.20	0 (0-.57)	0 (0-.33)	.40

Results are expressed as *Median (Range)* except where noted; Boldface denotes statistically significant correlations

*As the MoCA was used to split cognitive groups, astatistical comparison was not applicable

BDI-II, Beck Depression Inventory-II; FAQ, Functional Activities Questionnaire; FAQ_C, Functional Activities Questionnaire cognitive subscore; FAQ_M, Functional Activities Questionnaire motor subscore; LEDD, Levodopa-Equivalent Daily Dose; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; PD-CN, Parkinson's Disease Cognitively Normal; PD-NMS-Q, Parkinson's Disease Non-Motor Symptoms Questionnaire; PD-MCI, Parkinson's Disease with Mild Cognitive Impairment; UPDRS-III, Unified Parkinson's Disease Rating Scale-III

Table 3. *Correlation coefficients between CANTAB values and hippocampal subfields, controlling for ICV*

	Memory				Attention		Executive Functions	Information Sampling		
	PAL Total Errors*	PAL Total Errors 6 Shapes*	PRM Percent Correct	SWM Between Errors*	MTS Percent Correct	MTS Total Correct	SOC Problems solved in min. Moves	IST Mean Number of Boxes opened per Trial	IST Mean Percent Correct at Decision	IST Mean Box Opening Latency*
Hippocampal tail	**-.40**	**-.47**	.15	-.08	-.17	-.17	.03	-.20	-.14	-.18
Subiculum	-.23	-.27	.22	-.26	.15	.15	.23	.07	.23	-.20
CA1	**-.45**	**-.45**	**.35**	-.21	.19	.19	.21	.14	.18	**-.32**
Hippocampal fissure	.16	.20	-.27	**.31**	.12	.12	-.22	.14	.07	.11
Presubiculum	-.03	-.08	.05	-.05	.15	.15	.11	.13	.24	-.17
Parasubiculum	-.24	-.29	.07	**-.35**	-.05	-.05	.24	.18	.29	-.04
Molecular layer	**-.44**	**-.44**	.29	-.29	.12	.12	.29	.00	.10	-.19
Dentate Gyrus	**-.50**	**-.47**	**.37**	**-.33**	.13	.13	**.33**	.11	.19	**-.42**
CA2/3	**-.37**	**-.31**	.24	-.12	.19	.19	.14	.04	.08	-.31
CA4	**-.53**	**-.48**	**.31**	**-.32**	.16	.16	.28	.08	.16	**-.41**
Fimbria	**-.51**	**-.50**	.29	**-.49**	.12	.12	**.32**	.09	.19	-.28
HATA	**-.35**	**-.33**	**.30**	-.19	.26	.26	.16	**.32**	**.38**	**-.34**
Whole Hippocampus	**-.48**	**-.49**	**.31**	-.28	.12	.12	.25	.05	.16	**-.32**

Asterisks identify tests where higher values indicate worse performance; Boldface denotes statistically significant correlations

CA, cornu ammonis; CANTAB, Cambridge Neurological Test Automated Battery; HATA, Hippocampal-amygdaloid Transition Region; MTS, Match to Sample Visual Search; ICV, Intracranial volume; IST, Information Sampling Task; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; SOC, Stockings of Cambridge; SWM, Spatial Working Memory

Table 4. *Correlation coefficients between RBANS z scores and hippocampal subfields, controlling for ICV*

	List learning	Story learning	Figure copy	Line orientation	Picture naming	Semantic Fluency	Digit span	Coding	List recall	List recognition	Story recall	Figure recall
Hippocampal tail	.00	-.26	-.15	-.04	**.41**	-.09	-.11	.06	.08	**.30**	-.10	.10
Subiculum	.04	-.01	.07	.07	**.34**	.09	-.04	.25	.15	**.34**	.07	.00
CA1	-.08	-.10	-.09	.15	.21	.07	-.01	.23	.06	**.33**	-.05	.00
Hippocampal fissure	-.06	-.06	-.15	-.20	-.15	-.26	.08	-.08	-.11	-.09	-.30	-.25
Presubiculum	-.10	-.07	.19	-.08	**.32**	.00	-.11	.02	-.02	.19	.02	-.12
Parasubiculum	**-.31**	-.15	.00	-.03	.07	**.32**	.05	-.09	-.17	-.05	.03	-.11
Molecular layer	-.11	-.03	.08	.12	.27	-.02	-.05	.15	-.00	.28	.05	.02
Dentate Gyrus	-.14	.02	-.09	.23	.22	.22	.02	.17	.03	.16	.10	-.02
CA2/3	-.16	-.02	-.19	.18	.05	.14	.03	.12	-.03	.08	-.09	-.10
CA4	-.12	.02	-.13	.19	.17	.22	.06	.19	.05	.19	.09	-.04
Fimbria	-.15	-.03	.13	.19	.05	.19	-.01	.18	.07	.23	.05	.11
HATA	-.21	.03	.01	.11	.01	.17	-.01	.13	-.07	.16	-.02	-.16
Whole Hippocampus	-.10	-.10	-.03	.11	**.33**	.08	-.05	.19	.06	**.32**	.00	.00

Boldface denotes statistically significant correlations

CA, cornu ammonis; HATA, Hippocampal-amygdaloid Transition Region; ICV, Intracranial volume; RBANS, Repeated Battery for the Assessment of Neuropsychological Status