Aus dem Zentrum für Neurologie und Psychiatrie der Universität zu Köln
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Leiterin: Universitätsprofessorin Dr. rer. nat. E. Kalbe

# Development of a new CERAD Total Score in Individuals with Parkinson's Disease: Evidence from the LANDSCAPE Study

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Robert Alexander Lillig
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Dekan: Universitätsprofessor Dr. med. G. R. Fink
1. Gutachterin: Universitätsprofessorin Dr. rer. nat. E. Kalbe
2. Gutachter: Professor Dr. rer. soc. J. Kessler
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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AD | Alzheimer's disease |
| AUC | Area under the curve |
| CERAD | Consortium to Establish a Registry for Alzheimer's Disease |
| CERAD-Plus | Consortium to Establish a Registry for Alzheimer's Disease Plus |
| DLB | Dementia with Lewy bodies |
| EDS | Excessive daytime sleepiness |
| HRQOL | Health-related quality of life |
| LEDD | Levodopa equivalent daily dose |
| MCI | Mild cognitive impairment |
| MDS | Movement Disorder Society |
| MDRS-2 | Mattis Dementia Rating Scale Second Edition |
| MMSE | Mini Mental Status Examination |
| MoCa | Montreal Cognitive Assessment (MoCA) screening tool |
| MSA | Multiple system atrophy |
| PANDA | Parkinson Neuropsychometric Dementia Assessment |
| PCA | Principle component analysis |
| PD | Parkinson's disease |
| PD-CRS | Parkinson's Disease – Cognitive Rating Scale |
| PD-D | Dementia associated with Parkinson's Disease |
| PD-MCI | Mild cognitive impairment associated with Parkinson's Disease |
| PD-N | Parkinson's Disease without objective cognitive impairment |
| RBD | Rapid eye movement sleep behaviour disorder |
| ROC | Receiver operating characteristics |
| RCT | Randomized controlled trial |
| SD | Standard deviation |
| SCOPA-COG | Scale for Outcomes of Parkinson's Disease Cognition |
| SCD | Subjective cognitive decline |
| SNpc | Substantia nigra pars compacta |
| TMT | Trail Making Test |
| TS | Total Score |
| TS1 | CERAD TS by Chandler and colleagues: raw-score based |
| TS1z | CERAD TS by Chandler and colleagues: z-score based |
| TS2 | CERAD-Plus TS: z-score based |
| TS3 | CERAD-Plus TS: factor-score based |
| UPDRS | Unified Parkinson's Disease Rating Scale |

## ABSTRACT

**Introduction.** The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) is a renowned cognitive test battery for the assessment of cognitive functioning across various neurological conditions, including Parkinson's Disease (PD). Its German extension, the CERAD-Plus, with additional subscales assessing executive functions and processing speed might offer additional diagnostic value as these two cognitive domains rank among the most vulnerable in individuals with PD. The most established CERAD total score (TS) proposed by Chandler and colleagues is based on arbitrarily selected raw values of the restricted CERAD test battery.

**Objective**. The aim of the thesis project was the development of a new CERAD-TS in individuals with PD based on all available subtests of the extended CERAD-Plus test battery using age-, gender-, and education-corrected z-scores to ultimately test and compare its diagnostic utility with the established Chandler CERAD TS and common PD-screening tools.

**Methods**. The present thesis project analyzed baseline data of 679 individuals with PD of varying cognitive abilities (67.6% male, *n* = 277 with normal cognition (PD-N), *n* = 307 with impaired cognition (PD-MCI), *n* = 95 with dementia (PD-D)) from the multicenter, prospective DEMPREAK/LANDSCAPE cohort. For the comparisons of four different TS based either on the original CERAD or the CERAD-Plus battery with varying weighting of subtests (e.g., raw-scores, z-scores or factor-scores) receiver operating characteristics (ROC-) analyses were conducted. Comparisons of the areas under the curve (AUC) were run to identify the most parsimonious TS amongst the four tested TS.

**Results**. The newly designed CERAD-Plus TS based on equally-weighted z-scores proved to be the most accurate and parsimonious TS when discriminating between individuals with PD of varying cognitive impairment ($0.78 < AUC < 0.98$). Not only was this TS superior to the Chandler CERAD-TS, but the new CERAD-Plus TS also outperformed cognitive screening instruments, such as the Mini Mental Status Examination (MMSE) or the PD-specific Parkinson Neuropsychometric Dementia Assessment (PANDA).

**Conclusion**. Results of this thesis project highlight the importance of non-amnestic CERAD-Plus subscales (e.g., executive functions and processing speed) in the assessment of cognitive capacities in PD populations with different cognitive functioning, especially at an early stage of disease. An accurate and early diagnosis of PD is the prerequisite for early disease management and subsequent monitoring of disease progression. The new CERAD-Plus TS needs further validation and could prove to be of diagnostic value in non-PD populations as well.

# 1. ZUSAMMENFASSUNG IN DEUTSCH

**Einführung**. Kognitive Beeinträchtigungen sind vor allem im Krankheitsverlauf ein häufiges Symptom der Parkinson-Erkrankung, welches substanziell zur wahrgenommenen Schwere der Erkrankung beiträgt und den Alltag der Betroffenen maßgeblich beeinflusst. Parkinson ist die zweithäufigste sowie die am schnellsten wachsende neurodegenerative Erkrankung mit einer geschätzten Verdopplung der Fallzahlen bis zum Jahr 2040. Eine möglichst exakte Beurteilung kognitiver Fähigkeiten stellt dabei die Grundlage für eine frühzeitige Diagnosestellung und darauf aufbauend für gezieltes Krankheitsmanagement und Verlaufsbeobachtung dar. Eine umfassende Testung kognitiver Fähigkeiten von Patient*innen mit Morbus Parkinson wird meist durch den Einsatz von Testbatterien, wie z.B. der etablierten Consortium to Establish a Registry for Alzheimer's Disease (CERAD-) Testbatterie sichergestellt, die sich für die Untersuchung kognitiver Fähigkeiten von verschiedenen neurodegenerativen Pathologien eignet. In der deutschen Fassung existiert die CERAD-Plus-Testbatterie, die um Tests in Exekutivfunktionen und Verarbeitungsgeschwindigkeit erweitert wurde. Eine Möglichkeit Testwerte verschiedener Subskalen zu aggregieren, besteht in der Bildung eines Gesamtwertes (TS). Für die CERAD-Testbatterie existiert der etablierte Chandler CERAD-TS, ein von Chandler und Kollegen gebildeter Gesamtwert, der als Summe von selektierten Rohwerten der limitierten CERAD-Testbatterie gebildet wird. Da Exekutivfunktionen und Verarbeitungsgeschwindigkeit zu den vulnerabelsten kognitiven Funktionen bei Patient*innen mit Morbus Parkinson gehören, könnte die Verwendung der in der CERAD-Plus-Testbatterie zusätzlich enthaltenen Subskalen von besonderem, diagnostischen Wert in der Diagnostik kognitiver Beeinträchtigungen im Rahmen der Parkinson-Erkrankung sein.

**Zielsetzung**. Das Ziel dieser Doktorarbeit ist die Neuentwicklung eines CERAD-Plus TS, der auf allen Tests der CERAD-Plus-Testbatterie basiert, inklusive der Subtests in Exekutivfunktionen und Verarbeitungsgeschwindigkeit. Dieser neue CERAD-Plus TS, gebildet mit für Alter, Bildung und Geschlecht korrigierten z-Werten, soll hinsichtlich der diagnostischen Güte innerhalb von Parkinson-Populationen mit dem etablierten Chandler CERAD-TS sowie gängigen Screening-Instrumenten verglichen werden.

**Methoden**. Zu diesem Zweck wurden die Baseline-Daten von 679 Proband*innen (67.6% männlich) mit Parkinson-Erkrankung unterschiedlicher kognitiver Stadien (*n* = 277 mit normaler Kognition (PD-N), *n* = 307 mit eingeschränkter Kognition (PD-MCI), *n* = 95 mit Parkinson-Demenz (PD-D)) der DEMPRAK/LANDSCAPE-Kohorte analysiert. Für die Vergleiche von insgesamt vier verschiedenen CERAD TS, die entweder auf der limitierten CERAD-Testbatterie oder der erweiterten CERAD-Plus-Testbatterie basierten und deren

Gewichtung auf Rohwerten, z-Werten oder Faktor-Werten beruhte, wurden receiver operating characteristics (ROC-) Analysen durchgeführt. Anschließende Vergleiche der areas under the curve (AUC) dienten dazu den besten und dabei sparsamsten TS hinsichtlich der diagnostischen Güte zu identifizieren.

**Ergebnisse**. Der neu entwickelte CERAD-Plus TS auf der Basis von gleich gewichteten z-Werten stellte sich als der präziseste und zugleich sparsamste TS hinsichtlich der diagnostischen Differenzierung von Parkinson-Patienten heraus. Darin war er nicht nur dem etablierten Chandler CERAD-TS überlegen, sondern zeigte dies auch verglichen mit kognitiven Screening-Tests, wie dem Mini Mental Status Examination (MMSE) oder dem Parkinson-spezifischen Parkinson Neuropsychometric Dementia Assessment (PANDA).

**Schlussfolgerung**. Die Ergebnisse dieser Dissertation unterstreichen die Wichtigkeit der zusätzlichen, nicht-amnestischen Subtests der CERAD-Plus-Testbatterie (Exekutivfunktionen und Verarbeitungsgeschwindigkeit) in der Diagnostik kognitiver Fähigkeiten von Parkinson-Patient*innen, insbesondere zu einem frühen Erkrankungszeitpunkt. Eine frühzeitige Parkinson-Diagnose ist die Grundvoraussetzung für ein akkurates Krankheitsmanagement und eine nachfolgende Verlaufsbeobachtung. Der neue CERAD-PLUS TS benötigt weitere Validierung und könnte auch für andere neurodegenerative Erkrankungen von diagnostischem Wert sein.

# 2. INTRODUCTION

## 2.1. PARKINSON'S DISEASE

Parkinson's disease (PD) has been haunting mankind for thousands of years as early descriptions of motor symptoms date back to ancient Western and Eastern literature (until 2000 BC)[1]. Today PD is the most frequent motor disorder and ranks as the second most common neurodegenerative disorder right after Alzheimer's disease (AD)[2]. It has been calculated that globally 6.1 million individuals suffered from conditions of PD in 2016, a number that has more than doubled since 1990[3]. Current estimations project the number of individuals affected to double again until 2040 due to increasing life expectancy and population growth[3,4], making PD the fastest growing neurological disorder[5]. This highlights the need for effective treatment, cures and sufficient prevention as societal and economic PD-related burden will only increase in the future[6]. PD is caused by cell death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the accumulation of misfolded $\alpha$-synulcein-proteins[7-9]. The resulting neural deficiency causes the cardinal parkinsonian motor symptoms, non-motor symptoms and even prodromal symptoms, exceeding motor symptoms by years. After the first detailed description by James Parkinson in 1817[10], extensive research over the course of 200 years has revealed important landmarks in pathophysiology, diagnostics, therapy and disease-modifying factors, leading to the notion of PD as a heterogeneous[7], multisystem disorder[8].

### 2.1.1. Clinical characteristics of Parkinson's Disease

The clinical features of PD reflect the typical motor symptoms as well as a wide spectrum of non-motor-symptoms. These well-known cardinal motor symptoms are defined as the parkinsonian syndrome: bradykinesia or akinesia and one of the following three symptoms: muscle rigidity, postural instability or resting tremor[7] (Figure 1, adapted from Kalia & Lang, 2015). However, non-motor symptoms are almost as commonly found as motor symptoms in individuals with PD[11] and may emerge as autonomic dysfunction (e.g., orthostatic hypotension, gastrointestinal dysfunction or urinary tract symptoms), olfactory impairment, neuro-psychiatric conditions (e.g., depression, anxiety or fatigue), sleep disorders (e.g., insomnia, rapid eye movement sleep behaviour disorder (RBD)) and cognitive dysfunctions (e.g., mild cognitive impairment (MCI), dementia)[7,11,12]. It is noteworthy that non-motor symptoms are often underreported by individuals due to embarrassment or unawareness or focus on motor symptoms in neurological consultations[13]. With disease progression these non-motor symptoms may even prevail and severely define individuals' health-related quality of life[14]. While motor symptoms may initially be managed symptomatically, non-motor symptoms often remain staggeringly undertreated (e.g., one study found only 28% of individuals suffering from

depression and 13% suffering from urinary tract symptoms to be treated sufficiently)[11,15]. Further, in late stages of PD motor and non-motor symptoms are often treatment-resistant and include dysphagia, speech dysfunction, falls or the freezing of gait[7]. In the past years, prodromal PD markers (e.g., depression or olfactory impairment) have gained more and more attention. They potentially provide a time frame for disease-modifying treatment[7] as they can precede the onset of motor symptoms up to many years[7,12,16]. Although prodromal symptoms are not specific to PD, their co-occurrence increases the risk of a subsequent PD diagnosis[17].

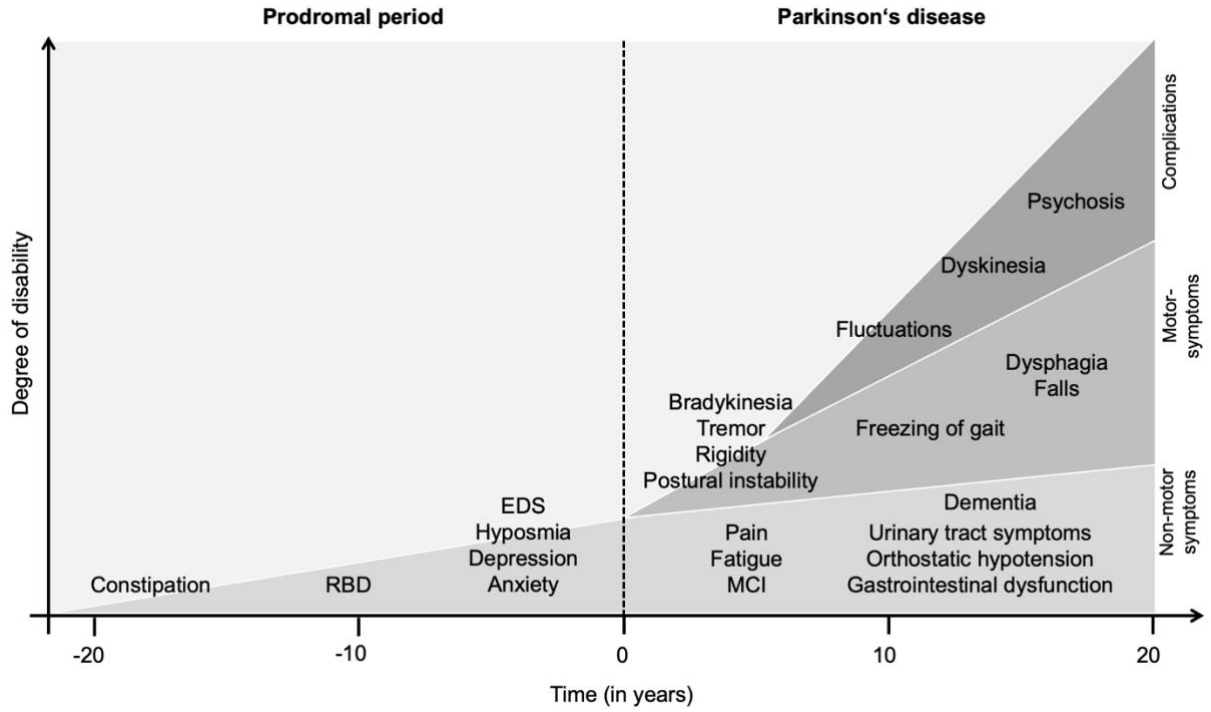


Figure 1. Clinical symptoms of Parkinson's disease over the course of years

The diagnosis of PD coincides with the onset of motor symptoms and can be preceded by a variety of non-motor symptoms up to twenty years. Additional non-motor symptoms develop with disease progression, causing significant disability. Axial motor symptoms, such as freezing of gait, postural instability or falls tend to occur in advanced stages of PD. Long-term complications of dopaminergic therapy, including fluctuations, psychosis and dyskinesia also contribute to disability. EDS = excessive daytime sleepiness, MCI = mild cognitive impairment, RBD = rapid eye movement sleep behaviour disorder. Adapted from Kalia and Lang (2015).

### 2.1.2. Diagnostic criteria in Parkinson's Disease

Typically, the diagnosis of PD is administered according to the criteria of the *United Kingdom Parkinson's Disease Society Brain Bank criteria*[18]. It requires (i) the diagnosis of the parkinsonian syndrome, (ii) the exclusion of alternative diagnoses and (iii) the inclusion of relevant disease features (e.g., such as unilateral onset, or present rest tremor). Recently, the Movement Disorder Society (MDS) has addressed the importance of prodromal and non-motor symptoms in PD by proposing more refined diagnostic criteria. These include non-motor symptoms for clinical[19] and prodromal criteria for scientific[17,20] use. Next to the presence of

parkinsonism, the clinical MDS criteria require at least two supportive criteria (e.g., the response to dopaminergic therapy, the presence of levodopa-induced dyskinesia or olfactory loss), the absence of red flags (e.g., the absence of non-motor features despite disease progression, the absence of severe autonomic dysfunction within first five years of PD) and the absence of absolute exclusion criteria (e.g., parkinsonian features limited to lower limbs for more than three years or documentation of alternative condition known to cause parkinsonism)[19].

### 2.1.3. Pathogenesis and etiology in Parkinson's Disease

Today PD is most likely seen as the result of an interplay of environmental and genetic factors, reflecting the heterogeneity of the disease. Two major neuropathological hallmarks are crucial to PD. First, the loss of dopaminergic neurons in SNpc, causing striatal dopaminergic deficiency, is associated with motor features of PD[7-9]. It is considered that approximately 50% of the SNpc has degenerated by the time clinical motor features become apparent[21,22]. Second, the intraneuronal aggregation of misfolded $\alpha$-synulcein-protein, the so-called Lewy bodies, leads to substantial neuronal loss[7-9,16]. Lewy pathology has been described by Braak and colleagues[23] as a progressing neurodegenerative process over the course of PD, suggesting preclinical stages of PD. Their *Six-Stage-Model of PD* proposes a specific temporal route of $\alpha$-synulcein-aggregation, starting from the peripheral nervous system, taking a caudal-to-rostral direction via medulla, pons and the limbic system towards central cortical areas. The fact that the olfactory bulb is affected in early stages highlights the correspondence to olfactory loss as a prodromal non-motor symptom of PD[24].

Apart from neuropathological correlates, various determinants of PD have been identified. The MDS research criteria for prodromal PD take into consideration different risk markers (e.g., male sex, gene mutations, plasma urate levels) and prodromal markers (e.g., non-motor symptoms such as depression, olfactory impairment, excessive daytime sleepiness (EDS), RBD, constipation, erectile dysfunction, and abnormal dopaminergic PET scans)[17,20]. Furthermore, environmental exposure to chemicals such as pesticides[25] and solvents[26], infectious diseases like Covid-19[27], or suffering from head injury over lifetime[28] may increase the risk of developing PD. While certain lifestyle factors like physical activities[29], and, strikingly, the consumption of coffee[30] or tobacco[31], are associated with a lower risk of PD, the consumption of dairy products[32] is associated with a higher risk of PD. A recent, genome-wide study found 90 independent risk factors across 78 genetic regions in 38 loci that affect PD risk, accounting for one third of heritable risk of PD[33]. Amongst others, there are genetic mutations causing specific damage at a cellular level: SNCA (altered alpha-synuclein gene)[34], PARKIN[35] & PINK1[36] (accumulation of dysfunctional mitochondria), DJ-1 (reduced antioxidant effect)[37] and GBA (reduced lysosomal activity)[38]. Interestingly, the most common genetic mutations for

PD have incomplete penetrance, highlighting the overall contribution of other environmental factors for the pathogenesis of PD[9]. Last, recent research has shown the associations of peripheral inflammation to PD, as inflammatory bowel disease[39] and diabetes[40] were linked to a higher PD risk. Taking the highly complex and multifactorial etiology of PD into account, the new conceptual framework *Triggers, Facilitators, and Aggravators* incorporates different findings and proposes a discrimination of different time stages in the pathogenesis of PD[41]. First, (i) triggers (e.g., viruses, bacteria, environmental risk factors) initiate the disease process in individuals that then require (ii) facilitators (e.g., peripheral neuroinflammation, mitochondrial dysfunction, genetic mutations), to promote the dissemination across the nervous system which is finally accelerated by aggravators (e.g., neural inflammation, impaired autophagy), so that symptoms exacerbate and neurodegeneration advances further in PD[41].

## 2.2. COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

Cognitive impairment in individuals with PD comes along with a broad range from subjective cognitive decline (SCD), MCI in PD (PD-MCI) to PD dementia (PD-D)[16]. While SCD refers to self-perceived cognitive decline in potentially different cognitive domains with simultaneously normative cognitive performance[42], the diagnoses of PD-MCI and PD-D are, amongst others, mainly based on objectively quantified, impaired performance in cognitive tests.

### 2.2.1. Clinical characteristics of cognitive impairment in Parkinson's Disease

Cognitive decline in PD may be present in various cognitive domains such as attention, executive functions, language, working memory or visuo-spatial functions[43-46] and arise in the form of single domain or multiple-domain impairment. According to the MDS criteria for PD-MCI, a single domain impairment requires abnormalities in two tests within a single cognitive domain with other domains remaining unimpaired. Multiple domain impairment then requires abnormalities in one test per domain in at least two cognitive domains[47]. A relative prevalence analysis (n = 269)[44] in the DEMPARK/LANDSCAPE cohort[48] found 46.1% of the PD-MCI study sample with a single-domain impairment (39.4% stemming from non-amnestic single domains, 6.7% from amnestic single domain) and 53.9% with multiple domain impairment (23.4% deriving from non-amnestic multiple domain impairment and 30.5% from amnestic multiple domain impairment). The authors further notice that non-amnestic deficits generally occur more frequently than amnestic impairment with executive functions being the most common symptom of cognitive impairment (65.3% of the PD-MCI sample) and visuo-spatial functions as the second most common (36.3%). Other studies have found working memory, executive functions and visuo-spatial functions amongst the most frequently affected domains in established PD-MCI populations[49] newly diagnosed PD-cases[45], but also in prodromal PD

cases[50]. Language impairment seems to be less frequent compared to other cognitive domains[44,45,50], but also compared with AD[51].

Recently, executive functions and visuo-spatial functions have been in the focus of PD-research lately as they are typical of early cognitive changes[16]. Executive functions are an umbrella term, commonly understood as mental flexibility, problem solving or reasoning[52] and describe a family of top-down processes surveying minor cognitive less effortful processes[52-54] Different sequential processes involved in executive functions are goal setting, strategy determination, progression monitoring as well as plan adjustments to changing circumstances[55]. Three underlying core features have been identified that are inherent to executive functions: inhibition, working memory and cognitive flexibility[53]. Executive functions are of general importance as early acquisition of executive functions in childhood is linked to lifelong wealth, health and quality of life[53]. To elderly they are of eminent importance for every-day-life as they direct complex, goal-oriented actions, such as cooking, dressing or housework[56]. With regard to PD, executive functions serve as a predictor for the transition from PD without objective cognitive impairment (PD-N) to PD-MCI[57] and interestingly also for the conversion from isolated RBD, a prodromal marker of PD, to PD and Dementia with Lewy bodies (DLB)[58].Taken together, they are ranked as one of the most vulnerable cognitive domains in PD[44,54].

Visuo-spatial functions involve different cognitive processes, such as visuo-spatial working memory, mental rotation or visuo-spatial problem solving[59]. Deficient visuo-spatial functions are linked to increasing freezing of gait behavior[60] and hinder individuals with PD from successfully navigating in everyday-life[61], causing problems such as bumping into objects and thereby possibly leading to injuries[59].

### 2.2.2. Diagnostic criteria of cognitive impairment in Parkinson's Disease

Both diagnoses, PD-MCI and PD-D, can be given in abbreviated (Level-1-diagnosis) and more comprehensive forms (Level-2-diagnosis; see Table 1 for an overview). The diagnosis of PD-MCI according to the *MDS Task Force Guidelines*[47] requires a PD-diagnosis based on the *United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria*[18] and reported cognitive decline by the individual or the clinician in the absence of significant interference with daily independence. For the Level-I-diagnosis, cognitive deficits need to emerge on a scale of global cognitive abilities (e.g., in the Montreal Cognitive Assessment (MoCA) screening tool[62]), for the Level-II-diagnosis in comprehensive neuropsychological assessment. The Level-II-diagnosis is based on cognitive impairment in at least two cognitive tests (within the same or in two different cognitive domains) with performance 1-2 standard deviations (SD) below appropriate norms. Each of the following five cognitive domains need to be examined by two tests: attention and working memory, executive functions, language,

memory and visuo-spatial functions[47]. Ultimately other explanations (e.g., stroke or delirium) or comorbid conditions (e.g., major depression, psychosis) need to be ruled out. The diagnosis of PD-D according to the *Movement Disorder Society Guidelines*[63,64] requires a PD-diagnosis based on the Queen Square Brain Bank criteria[65]. Cognitive impairment needs to be severe enough to impact individuals' daily lives beyond impairment by motor and autonomic symptoms and must be present in at least two of four cognitive domains: attention, executive function, visuo-constructive ability and memory. It is further essential that PD developed prior to the onset of dementia and is associated with global cognitive deficiency. PD-D may be subdivided into mild, moderate, severe referring to the degree of preserved daily functioning[16]. Of note, PD-D shares clinical and pathological features with DLB, so that both diseases are rather seen as different entities on a Lewy body spectrum[66]. As DLB accounts for four percent of all newly diagnosed dementia cases[67], it seems worth knowing that their cognitive profiles can be differentiated: while PD-D exhibits greater impairment in executive functions, DLB has a more pronounced impairment in memory and language[68].The one-year-rule in clinical use distinguishes both entities as following: dementia occurring more than 1 year after PD-diagnosis is classified as PD-D while parkinsonism occurring at or after dementia diagnosis is classified as DLB[69].

Table 1. Diagnostic procedures according to the Movement Disorder Society

| | PD-MCI criteria[47] | PD-D criteria[64] |
|---|---|---|
| Level-I-testing (abbreviated) | 1. PD-diagnosis based on UK brain bank criteria<br>2. Gradual cognitive decline, reported by patient, informant or clinician<br>3. Deficits not sufficient to interact with functional independence<br>4. Impairment on global cognitive scale (e.g., MoCa) or impairment on at least two neuropsychological tests when only limited testing is available | 1. PD-diagnosis based on UK Brain Bank criteria<br>2. PD developed prior to onset of dementia<br>3. PD associated with global cognitive deficiency (e.g., MMSE below 26)<br>4. Severe deficits impacting daily living<br>5. Impairment in more than one cognitive domain (attention, executive function, visuo-constructive ability, memory) |
| Level -II-testing (comprehensive) | Neuropsychological testing (two tests per domain) in five cognitive domains:<br>1. Attention and working memory<br>2. Executive functions<br>3. Language<br>4. Memory<br>5. Visuo-spatial skills<br>Impairment on two tests in one domain or one test in two different domains<br>Impairment by 1-2 SD below norms | Neuropsychological testing in four domains:<br>1. Decreased cognitive abilities<br>2. Subcorticofrontal features: executive functions, apathy, long-term memory<br>3. Instrumental functions: language, visuo-constructive, visuo-spatial, visuo-perceptive skills<br>4. Neuropsychiatric functions: apathy, depression, visual hallucinations, psychosis |

*Note*. Level-I-testing may be used by clinicians without particular expertise in neuropsychological methods. Once the PD-D diagnosis is established level-II-testing allows for a more refined characterization, but also for a greater diagnostic certainty. MCI = mild cognitive impairment, PD = Parkinson's disease, PD-D = Dementia associated with Parkinson's Disease, MMSE = Mini Mental Status Examination, MoCa = Montreal Cognitive Assessment screening tool.

### 2.2.3. Epidemiological data on cognitive impairment in Parkinson's Disease

Cognitive impairment occurs in great heterogeneity and may be present before the time of PD diagnosis[50], right at the time of diagnosis, decades after the initial diagnosis, or may even revert after becoming apparent (Figure 2, adapted from Aarsland & colleagues 2021). Cognitive domains affected and clinical impact vary interindividually so that individuals' quality of life as well as their caregivers may be severely affected[70]. Cognitive decline is up to six times more frequent in PD populations compared to healthy controls[71]. More specifically, prevalence rates for PD-MCI depend on individuals' time of assessment: in newly diagnosed populations prevalence rates for PD-MCI range from 10-33%[49,57,72], whereas established PD populations may exhibit rates up to 64%[43]. These numbers are reflected in a longitudinal cohort study with a PD-MCI-rate in a newly diagnosed PD population of 35%, and PD-MCI rates of 53% at a 3-year-follow-up, and 50% at 5-year-follow-up (due to some individuals converting from PD-MCI to PD-D), showing that prevalence increases with disease duration[73]. In contrast, the prevalence of MCI in the general population (aged 60-90) was found to be around 16-20%[74]. A recent meta-analysis found a pooled prevalence for PD-MCI of 40% in a total sample of 7053 individuals with PD[75], using the MDS task force criteria[47]. It further highlighted socioeconomic, disease-related and neuropsychiatric differences within PD populations between individuals without (PD-N) and with cognitive impairment (PD-MCI): PD-MCI was linked to older age, less years of education, longer disease duration, higher levodopa equivalent daily dose (LEDD), more severe motor symptoms, poorer quality of life and higher levels of apathy and depression[75].

Regarding prevalence rates for PD-D, different reviews have found them to be close to 30%[76,77] The cumulative prevalence of PD-D is increasing immensely with disease duration. One longitudinal cohort study for example shows that 27% of individuals met PD-D criteria at baseline, 45% at 4 years-follow-up, 56% at 8-years- follow-up and 60% at 12-years-follow-up[78] while another multicentre study found 83% of study survivors to be diagnosed with PD-D 20 years after initial diagnosis[79]. Compared to an overall prevalence for dementia of 5-7% in the general population over 60 years[80], the identified prevalence of PD-D highlights the massive threat of developing dementia that individuals, suffering from PD-MCI, have to face.

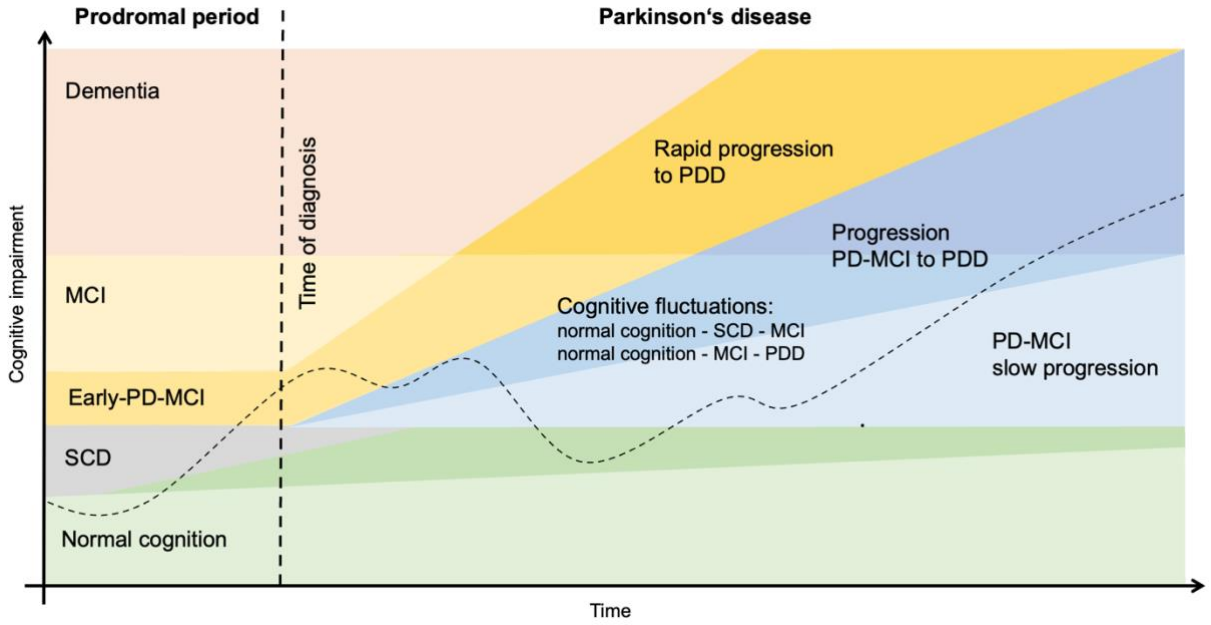


*Figure 2.* The progression of cognitive impairment in Parkinson's disease

Over the course of years cognitive decline usually becomes evident in the form of subjective cognitive decline or mild cognitive impairment. These changes may evolve prior to or decades after a PD diagnosis. Cognitive fluctuations depict the variability of disease progression, so that individuals with PD-MCI may even revert to normal cognition for a time span, but then develop cognitive impairment again. MCI = mild cognitive impairment, PD = Parkinson's disease, PDD = Dementia associated with Parkinson's Disease, SCD = subjective cognitive decline. Adapted from Aarsland and colleagues (2021).

The study of risk factors for cognitive decline in PD has already been of interest as they possibly identify vulnerable individuals, but also offer the potential of prevention in the general population. Already the perceived subjective cognitive decline of de-novo PD individuals was found to be a valid predictor of developing PD-MCI onwards[81,82]. It is noteworthy that cognitive decline itself has been characterized as a new prodromal PD marker in the update of the MDS research criteria for prodromal PD[20], highlighting the importance of understanding underlying features of cognitive decline. A meta-analysis (*n* = 4011) on conversion rates from normal cognition to PD-MCI or PD-D identified PD-MCI as a risk factor for the progression to PD-D with a conversion-rate of 20% (95% CI 13-30%) within three years and a conversion rate of 34% (95% CI 27-43%) for follow-ups of more than three years[83]. A review on risk factors for cognitive impairment in PD ranked the following risk factors according to their relative impact across studies (ranked in descending order of weight) by using z-scores: hallucinations, older age, overall severity of motor symptoms, speech impairment, older age at onset of Parkinson's disease, bradykinesia severity, higher Hoehn and Yahr stage, axial impairment, a low level of education, depression, and male sex[84].

To account for differences in the variation of cognitive decline, the concept of cognitive reserve, e.g., operationalized by higher educational or occupational levels in early life, but recently also with social engagement in later life[85], has been proposed. Cognitive reserve is

not only associated with better cognitive performance but also with decelerated cognitive decline[85-87] and a decreased risk of developing PD-D[85]. Apart from the severity of motor symptoms[84,88,89], the quality of motor symptoms has also been linked to poorer cognitive test performance. More specifically, cognitive decline is linked to certain motor subtypes in PD: individuals exhibiting more postural instability and gait difficulty symptoms were cognitively more impaired than individuals with tremor-dominant symptoms[90], so that the former motor subtype is considered a risk factor for PD-D[91]. There is further evidence that particular dysfunctions in frontal and executive processing comes at a higher risk for the conversion to dementia[87,92-94]. This is supported by functional imaging showing that thinning in the frontal cortex was found to be a conversion marker to PD-D[93]. Besides that, the Campaign study found posterior cortical deficits operationalized by poor performance in semantic fluency tasks to be predictive of PD-D[95].

As the Lancet commission points out, about 40% of all different dementia cases in the population are associated with hypertension, diabetes, obesity, physical inactivity excessive alcohol consumption or low social contact[96]. This additionally highlights the need for prevention programs for individuals at risk, precise diagnostics to identify those at risk, and individually tailored interventions to benefit those suffering from the burden cognitive decline is causing in individuals with PD.

### 2.2.4. Neuropathology of cognitive impairment in Parkinson's Disease

Next to the disease-defining PD neuropathologies of dopaminergic loss in substantia nigra and $\alpha$-synulcein-aggregation in Lewy bodies (initially in cholinergic and monoaminergic brainstem regions and the olfactory system[97]), there are different degenerative processes involved with cognitive decline in PD[16]. The majority of cases in PD post-mortem studies shows a mixed neuropathology[79]. In an attempt to integrate heterogeneous trajectories of cognitive decline and various findings on cognitive impairment patterns in individuals with PD, Kehagia and colleagues postulated the *Dual Syndrome Hypothesis*[98,99]. The Dual Syndrome Hypothesis states that there are two hypothetically independent and partially overlapping syndromes of MCI and dementia in PD: the dopamine-regulated and probably also noradrenaline-regulated fronto-striatal syndrome and the acetylcholine-regulated posterior and temporal lobe dementia syndrome[99]. The early fronto-striatal syndrome, associated with PD-MCI and deficits in executive functions, working memory and attention, is subject to dopamine therapy, but also to possible overdosing effects[98,99]. The posterior and temporal lobe syndrome, associated with rapid cognitive decline to PD-D and deficits in memory, visuo-spatial functions, and semantic fluency, seems to benefit from cholinergic treatment[98,99]. It is noted that PD-D cannot be considered isolated from dopaminergic neurotransmission as nigrostriatal neuron loss is the

neuropathological core of PD, so that individuals with PD-D may, but do not necessarily have to share features of the early fronto-striatal syndrome[99].

A recent review further specifies that in PD-MCI dopaminergic loss occurs particularly in the striatal dorsal nucleus caudatus with other dopaminergic systems potentially being preserved, whilst in PD-D these dopaminergic systems (e.g., frontal, parietal and temporal) are substantially affected[100]. With regard to noradrenergic pathways neural loss in the locus coeruleus (e.g., the frontal cortex and hippocampus) has been found to be correlated with the presence of PD-MCI[101]. A post-mortem brain tissue examination of individuals with PD-D found reduced noradrenergic levels in all of the eight investigated brain areas, whereas only six regions exhibited dopaminergic and four serotonergic alterations[102], undermining the idea that noradrenergic pathways play a role in advanced stages of PD. Cortical cholinergic neuronal loss is independently associated with cognitive decline in PD [16], but it also interacts with dopaminergic loss in the nucleus caudatus to contribute to greater cognitive decline[103], highlighting the possibility of independent and interactive contributions of dopaminergic and cholinergic loss to cognitive decline. Of note, serotonergic dysfunction is not directly related to cognitive decline in PD[16].

### 2.2.5. Pharmacological treatment of cognitive impairment in Parkinson's Disease

Specific treatment options for cognitive impairment in individuals with PD consist of pharmacological medication and a broad variety of non-pharmacological treatment approaches including cognitive interventions, physical exercise, non-invasive and invasive brain stimulation, or a combination of them.

To date, the only officially approved pharmacological treatment option solely exists for individuals with PD-D in the form of cholinesterase inhibitors (e.g., rivastigmine or donepezil)[104-106]. They reversibly inhibit the enzyme acetylcholinesterase and decelerate the metabolism of acetylcholine in the synaptic cleft, thus enhancing cholinergic neurotransmission[16]. Different meta-analyses have shown that they overall improve global cognition and particular cognitive domains, such as attention, memory, processing speed and executive functions while potentially causing adverse effects, such as nausea, vomiting, tremor or neuropsychiatric conditions (e.g., hallucinations or sleep disturbance)[104-106]. Moreover, they exhibit considerable variance in efficacy between individuals, sometimes only providing very little benefit[107]. Unfortunately, there is no officially approved pharmacological treatment for cognitive impairment for earlier stages of PD and PD-MCI. It is also important to note that cholinesterase inhibitors are not curative, but rather symptomatic and disease-defining, common non-motor symptoms remain to be treated, nevertheless.

The initial use of different PD medication against motor symptoms (e.g., levodopa, dopamine agonists or monoamine oxidase-B inhibitors) does not seem to impact cumulative PD-D rates[108]. Interestingly, the same study found individuals initially treated with levodopa at disease-onset to outperform those treated with dopamine agonists or monoamine oxidase-B inhibitors at the three-years-follow-up in the Mini Mental State Examination (MMSE)[108]. The general effect of dopamine levels on cognitive abilities in PD has been thoroughly discussed as not only beneficial, but also detrimental effects on cognition have been found, determined as states of dopamine overdose or dopamine depletion[109]. This has led to the assumption of an inverted u-shaped relation between dopamine levels and cognitive performance[109,110]. However, individuals' dopamine levels seem to depend on complex factors such as disease progression, genotypes and thereby resulting individual baseline dopamine levels, and on the interplay between pharmacotherapy and genetic polymorphisms (e.g., such as in COMT: catechol-O-methyltransferase), making it hard to predict individuals' cognitive response to dopaminergic treatment[110]. Additionally, on an individual level depleted dopaminergic neural routes benefit from dopaminergic therapy while others are subject to dopamine overdose, resulting in impaired cognition (e.g., dopaminergic therapy might benefit the depleted dorsal striatum, while overdosing the intact ventral striatum)[109,110].

Surprisingly, a cross-sectional analysis on prescription errors in PD treatment found that 29% of PD patients, irrespective of cognitive status, received at least one potentially inappropriate medication that is not suited for use in PD-MCI or PD-D[111]. Among these, especially anticholinergic medication (e.g., common antihistamines or antidepressants) has a detrimental effect on cognition as they are associated with worse long-term cognition in PD[111] and elevated risk of developing dementia in PD[112]. Regarding hospitalization, a recent analysis revealed that failures of medication administration in hospitalized PD patients, such as antidopaminergic medication, delayed, reduced or failed administration of dopaminergic medication cause different negative backlashes such as prolonged stays, readmissions and even increased mortality[113].

### 2.2.6. Non-pharmacological treatment of cognitive impairment in Parkinson's Disease

Due to limited pharmacological treatment options for cognitive impairment in PD, various non-pharmacological treatment options have been studied. Although there is evidence that cognitive training, physical exercise and non-invasive brain stimulation have at least short-term effects on some cognitive domains, criticism has been raised due to methodological shortcomings of involved studies in the field (e.g., small sample sizes, problematic diagnostic criteria for PD-MCI od PD-D or lack of rigorous design standards for randomized controlled trials (RCT))[16,114]. A recent meta-analysis[115] addressed this issue by classifying studies of

different non-pharmacological approaches into different degrees of effectiveness, following established rating criteria[116]. Strikingly, no intervention matched class A level evidence and only cognitive trainings reached class B, probable effectiveness, for the cognitive domains of attention, memory and working memory. While physical exercise reached class C, possible effectiveness, non-invasive brain stimulation failed to reach any type of recommendation at all. Other meta-analyses and reviews likewise found cognitive trainings[117,118], computer-based cognitive trainings[119,120] and physical exercise[121] to ameliorate cognitive abilities in individuals with PD with combined multimodal physical and cognitive training programs[122] even bearing the potential to outperform single modality training programs. Of note, exergaming (e.g., videogames with visuo-sensory feedback) has gained significant attention lately as it has the potential to not only improve motor abilities, but also cognitive abilities in PD in a potentially home-based scenario[123]. As some the above-mentioned analyses focus on earlier stages in PD and include cognitively unimpaired PD populations more recent meta-analyses investigated the effects of cognitive trainings on individuals with PD-MCI or PD-D[120,124]. Orgeta and colleagues report seemingly unpromising results without statistically significant effects on cognition for PD-MCI and PD-D, potentially due to a small number of studies (*n* = 7) with few participants (*n* = 225) meeting inclusion criteria of the meta-analysis, thus calling for methodologically robust and adequately powered studies for individuals with PD-MCI and PD-D[124]. However more recently, Gavelin and colleagues included more studies (*n* = 17) with a larger set of participants (*n* = 679), exhibiting an overall effect for global cognition not only for PD-N, but also for PD-MCI[120]. With regard to the importance of executive functions in PD, a RCT with a multidomain training setup found cognitive training compared to physical exercise to ameliorate executive functions in PD-MCI[125]. The same multimodal cognitive training set-up was able to increase physical activity measured by accelerometry at home in PD-MCI, possibly caused by improved executive functioning[126]. Taking a more generalist approach, a systematic overview analysed 46 reviews on cognition-oriented interventions in the general older population, including healthy and cognitively impaired individuals with different dementia pathologies[127]. The authors found small pooled-effect sizes for improved cognitive performance in cognitive trainings in healthy older adults, MCI and dementia[127], supporting the idea that specific studies on efficacy of cognitive trainings in PD-MCI and especially in PD-D might need more large-scale studies to identify small-scale effect sizes.

Apart from direct treatment of motor symptoms and cognitive impairment, the management and treatment of non-motor symptoms is important, not only because it may define disease-burden, but also because of their association with cognitive performance (e.g. orthostatic hypotension, obstructive sleep apnoe, depression, EDS, RBD) and their potential to improve cognitive abilities in PD, even at later stages[16]. A recent MDS review gives an extensive overview on treatment options, their efficacy and safety for non-motor symptoms in

PD[128]. It further seems to be beneficial to offer group cognitive behavioural therapy[129] not only to tackle anxiety and depression as non-motor symptoms in PD, but also to increase therapy adherence thereby. Following a multifaceted treatment approach the utilization of complementary therapies, such as Tai Chi, Qi Gong and Yoga[130] or circadian interventions, such as light therapy or melatonin treatment[131] should be considered as additional treatment options, as they can at least offer short-term benefits on non-motor and motor symptoms.

## 2.3. COGNITIVE ASSESSMENT IN PARKINSON'S DISEASE

Accurate diagnosis of cognitive capacities in individuals with PD is crucial for adequate treatment. Currently, it is not uncommon to examine cognitive dysfunction in PD with assessments, originally developed for use in AD. These assessments include for example the MMSE[132] as a cognitive screening instrument or the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[133] as a cognitive test battery. The CERAD test battery has been successfully used for the discrimination of PD-D[134,135] and PD-MCI[135] from PD-N in PD populations. It covers the following cognitive domains: memory (Word List Learning, Word List Recall, Word List Recognition, Figure Recall), language (Modified Boston Naming Test), visuo-construction (Figure Copy) and executive functions (Animal Naming)[133]. The German CERAD-Plus extension[136,137] offers additional subscales in executive functions (Phonemic Fluency, Trail Making Test B (TMT-B)) and processing speed (Trail Making Test A (TMT-A)). With executive functions as one of the most vulnerable cognitive domains in PD, it provides promising potential for the improvement of diagnostic accuracy in PD populations.

As recommended by the MDS criteria for PD-MCI[47], neuropsychological evaluation can be based on testing global cognition or on more comprehensive testing of cognitive domains. Global cognitive performance is usually assessed by screening instruments. While they require less resources, professional training and are easily accessible, they offer less detailed information on cognitive functions affected[16]. The MDS criteria for PD-MCI[47] provide four examples of global cognitive instruments validated in PD population without further specifying psychometric properties: the MoCA[62], the Parkinson's Disease – Cognitive Rating Scale (PD-CRS)[138], the Mattis Dementia Rating Scale[139] and the Scale for Outcomes of Parkinson's Disease Cognition (SCOPA-COG)[140]. According to a more recent MDS review on twelve cognitive global scales in PD populations[51], there are currently three cognitive screening instruments covering multiple cognitive domains that meet certain diagnostic standards (e.g., scale validated in PD population, data available other than from developers and sufficient reliability, validity and sensitivity to change in PD) and are thus recommended: the MoCa[62], the Mattis Dementia Rating Scale Second Edition (MDRS-2)[139,141] and the PD-CRS[138]. All instruments provide good internal consistency, test-retest-reliability, convergent validation and normative data[51,142-144] with the MoCA being the most frequent screening instrument in PD research and clinical use[16]. The SCOPA-COG was only recommended with caveats, as

information on sensitivity to cognitive change was insufficient[51]. Even though the MDS committee does not recommend its use because of inadequate assessment of executive functions and visuo-spatial abilities[51], the MMSE[132], originally designed for the diagnosis of cognitive dysfunction in Alzheimer's disease, is still commonly used in PD populations. Apart from the MDS recommendations, the German Parkinson Neuropsychometric Dementia Assessment (PANDA) screening tool[145] offers good psychometric properties and accuracy in distinguishing PD populations with and without cognitive impairment.

More comprehensive neuropsychological testing is usually comprised of raw-scores turned into z-scores based on normative data adjusting for demographic variables such as age, education and sex. Although there is a broad range of cognitive tests across different domains proposed for comprehensive testing by the MDS criteria for PD-MCI[47] and by the MDS criteria for PD-D[64], psychometric properties or sensitivity to cognitive change, especially essential for the early detection of PD-MCI, are not addressed in consensus guidelines. A recent prevalence study[44] analyzed the most sensitive tests to detect cognitive dysfunctions in PD, finding the following amongst the most frequently impaired tests: Modified Card Sorting Test (executive functions)[146], digit span backwards (executive functions)[147], word list learning (memory)[133] and figure recall (visuo-constructive memory)[133]. A pooled analysis on neuropsychological testing in undemented PD populations revealed that current cognitive test batteries are not sensitive enough to cognitive decline in PD[148], highlighting the need for more accurate neuropsychological assessment. Across 30 cognitive tests within 20 studies the authors found a high degree of between-study variability in cognitive performance of undemented PD individuals and cognitive overperformance of healthy controls, calling for validated, PD-specific cognitive test batteries. To date, the implementation of comprehensive cognitive testing in PD research relies on the use of different neuropsychological tests designed to study single cognitive domains, resulting in an enormous heterogeneity of test protocols[148-150], even though MDS guidelines[47] recommend specific neuropsychological tests for each cognitive domain. However, clinicians often use existing, more coherent test batteries, such as the CERAD[133], as one advantage of such test batteries is that they were developed and standardized on a large normative sample, while individual tests and their norm values are based on various normative samples. Aggregating data of the CERAD test battery, different total scores (TS) have been developed[151,152] to further simplify the diagnostic process, offering a cut-off score for clinicians. So far the Chandler CERAD TS[152] has proven useful in populations of different neuropathologies and severity[136,153,154], but recently also in PD populations[134]. While Camargo and colleagues successfully discriminated PD-N from PD-D & PD-MCI in a combined group in their study sample, the Chandler CERAD TS still needs to be validated in a greater PD population which incorporates more refined discriminations, such as PD-N vs. PD-MCI or PD-MCI vs. PD-D.

### 2.3.1. Weighting of cognitive test performance in Parkinson's Disease

The neuropsychological assessment of cognition may result in single test scores as described above or by composite test scores, representing either single cognitive domains or a global cognition score. Composite scores are combined of several test scores in certain ways and often reflect factor scores from a measurement model[150]. In the educational context, composite scores may be designed implicitly, based on the sum of raw scores or item response theory modelling or explicitly, referring to weighting based on difficulty, reliability or validity[155]. In general, composite scores offer advantages as they gather multiple test scores and potentially offer greater reliability, yet the choice of contributing subtests or items as well as their weighting onto the composite score needs to be theoretically reasonable[150]. In theory, composite scores rely on equal or differential weighting. In practice however, the use of composite scores, such as the sum of raw scores, implying weighting components by their maximum score[156], is not uncommon. Adding raw scores does not recognize the relative importance of contributing components to the composite score, thus calling for standardized scores[155]. Next to standardized scores as a prerequisite, underlying distributions or measurement scales should be similar to each other to impede distorted composite scores[150].

In their article on factor scores, DiStefano and colleagues differentiate between non-refined, rather easily computed and interpretable methods and refined methods, rather exact and complex methods to build composite scores based on factor scores[157]. Among non-refined methods deriving sum scores from adding raw scores reflects the simplest building procedure followed by adding standardized scores and by adding weighted scores[157]. Refined procedures include the use of regression scores, Bartlett scores or Anderson-Rubin scores when using exploratory factor analysis, with regression scores providing maximum correlation to the estimated factor[157]. Whether using equal or differential weights, refined or non-refined methods when building composite scores, the use of methods and weighting should be the result of a rational process evaluating contributions and trade-offs of chosen procedures[155].

So far, two composite scores have been developed for the assessment of cognitive dysfunction in AD[151,152] on the basis of CERAD subscales[133]. While Chandler and colleagues implemented six out of seven of the original set of CERAD subscales for their TS, omitting the subscale Figure Recall, Seo and colleagues included all seven CERAD subscales for theirs. These two global CERAD TS have been examined regarding their diagnostic utility in discriminating between individuals with different pathologies and stages of cognitive impairment[136,151-153] with the Chandler CERAD-TS appearing to be the most feasible. The Chandler CERAD-TS is composed of the sum of raw scores, resulting in a maximum raw score of 100 points (with single maximum raw scores ranging from 10 to 24 points). As the Chandler CERAD-TS has proved to successfully discriminate between PD-D and a combined group of PD-MCI and PD-N in a Brazilian PD sample[134], it needs to be validated in a larger PD

population with more refined diagnostic discriminations (e.g. PD-N vs PD-MCI, PD-MCI vs. PD-D). Further, Camargo and colleagues criticize the Chandler CERAD-TS for its lacking assessment of fronto-striatal functions (e.g., executive functions), which were found to be the most vulnerable cognitive functions in PD[44,98]. The CERAD-Plus extension for the German-speaking market, adding non-amnestic subscales in processing speed (e.g., TMT-A) and executive functions (e.g., TMT-B, Phonemic Fluency), has shown superior diagnostic accuracy over the original CERAD battery in dementia of different pathologies[136]. To date, these additional subscales have not yet been included in the original Chandler CERAD-TS and thus could potentially foster diagnostic accuracy in PD populations of varying cognitive profiles.

# 3. PUBLICATION

## 3.1. AIM OF THESIS PROJECT

The aim of this thesis project was to investigate how possible additions and alterations of the existing Chandler CERAD-TS could possibly increase diagnostic accuracy in discriminating PD individuals with different cognitive functioning (PD-N, PD-MCI, PD-D). A more sensitive and accurate diagnosis of PD-associated cognitive decline is the prerequisite for early disease management and subsequent monitoring of disease progression. Especially the early identification of PD-MCI is crucial to ameliorate possible long-term outcomes in light of the inevitable disease progression to PD-D in many cases.

Therefore, different alterations were made to the original Chandler CERAD TS, resulting in three additional CERAD TS (see Table 2 for a comparison of all tested TS): (i) TS1z: application of equal weights to the original Chandler CERAD TS by using age-, gender-, and education-corrected z-scores (ii) TS2: development of a new global CERAD-TS on the basis of the CERAD-Plus test battery (e.g., extended by TMT-A, TMT-B and Phonemic Fluency) and the omitted CERAD subscale Figure Recall by using age-, gender-, and education corrected z-scores (iii) TS3: application of differential weights to all subscales of the newly developed CERAD TS by using factor scores in a principle component analysis (PCA), subsequently loading onto one global factor[157]. Finally, these TS were compared to the established Chandler TS regarding their diagnostic ability to discriminate between the cognitive subgroups, to identify the most feasible TS.

### 3.1.1. Hypotheses

It is hypothesized that the inclusion of CERAD-Plus subscales in processing speed (e.g., TMT-A) and executive functions (TMT-B and Phonemic Fluency) and the reintegration of the omitted CERAD subscale Figure Recall to a new global CERAD-Plus based either on equally weighted z-scores (TS2) or optimally weighted factor-scores (TS3) improves diagnostic accuracy over the original Chandler CERAD (TS1). As corrected z-scores were calculated for the TS2 anyways, the TS1z was built to see whether standardization already improves diagnostic accuracy with an exploratory intention.

Table 2. Synopsis of all four CERAD total scores and used CERAD-Plus subtests

| **CERAD – Plus** test battery | | **TS1** | **TS1z** | **TS2** | **TS3** |
|---|---|---|---|---|---|
| Executive Functions | Animal Naming | max. 24 | z-score | z-score | factor-score |
| | Phonemic Fluency | | | z-score | factor-score |
| | Trail Making Test A | | | z-score | factor-score |
| | Trail Making Test B | | | z-score | factor-score |
| Memory | Word List Learning | max. 30 | z-score | z-score | factor-score |
| | Word List Recall | max. 10 | z-score | z-score | factor-score |
| | Word List Recognition | max. 10 | z-score | z-score | factor-score |
| | Figure Recall | | | z-score | factor-score |
| Language | Modified Boston Naming Test | max. 15 | z-score | z-score | factor-score |
| Visuoconstruction | Figure Copy | max. 11 | z-score | z-score | factor-score |
| Total Score | | raw score | mean z-score | mean z-score | weighted factor-score |

*Notes*: z-scores were obtained from a large database of 1100 healthy subjects based on three age groups, two education groups and gender[137]. CERAD, Consortium to establish a Registry for Alzheimer's Disease; TS1, CERAD total score by Chandler and colleagues[152]; TS1z, z-score based CERAD total score by Chandler and colleagues[152]; TS2, z-score based CERAD-Plus total score; TS3, factor-score-based CERAD-Plus total score.

### 3.1.2. The DEMPRAK/LANDSCAPE database

The thesis project used the baseline data of the German DEMPARK/LANDSCAPE longitudinal cohort study, which was designed to investigate and characterize the progression of and contributing factors to cognitive impairment in PD (for more detailed information please see[48]). A total of 711 individuals with PD was recruited across nine movement disorder centers in Germany and underwent comprehensive clinical and cognitive assessment as well as imaging and genetic modules.

Inclusion criteria for study enrollment into the DEMPRAK/LANDSCAPE cohort were (i) age between 45 and 80 years at baseline assessment and (ii) a diagnosis of idiopathic PD according to UK Parkinson's Disease Society Brain Bank criteria[65]. Exclusion criteria for study participation were (i) evidence for atypical Parkinson syndromes (e.g., Multiple System Atrophy (MSA)), (ii) other causes of dementia (e.g., AD, vascular dementia), (iii) PD patients with

cognitive impairment impeding consent. After study enrollment, individuals' cognitive status was classified according to the available diagnostic criteria for cognitive impairment in PD available at the time of study set-up[158,159]: PD-N, PD-MCI, or PD-D. Individuals were diagnosed with PD-MCI[158] when (i) subjective cognitive dysfunctions were reported by the patient, (ii) daily life activities were reported as non-significantly impaired, and (iii) performance in at least one cognitive test relevant for diagnosis was ≤1.5 SD below the mean of published normative data. Individuals were diagnosed with PD-D[159] when (i) criteria for PD according to Queen Square Brain Bank were met, (ii) onset of cognitive deficits was insidious and progression was slow, (iii) deficits were present in two cognitive domains with one test per domain being ≤1.5 SD below normative data, (iv) impairment represented a decline from a premorbid level, and (v) deficits were severe enough to impair daily life independent of motor or autonomic symptoms.

## 3.2. ORIGINAL PUBLICATION: LILLIG, OPHEY ET AL. (2021)

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* contributed equally

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# A new CERAD total score with equally weighted *z*-scores and additional executive and non-amnestic „CERAD-Plus“ tests enhances cognitive diagnosis in patients with Parkinson's disease: Evidence from the LANDSCAPE study

Robert Lillig [a,1], Anja Ophey [a,1], Jörg B. Schulz [b,c], Kathrin Reetz [b,c], Jennifer Wojtala [b,c], Alexander Storch [d], Inga Liepelt-Scarfone [e,f,g], Sara Becker [e], Daniela Berg [e,h], Monika Balzer-Geldsetzer [i], Jan Kassubek [j], Rüdiger Hilker-Roggendorf [k], Karsten Witt [l], Brit Mollenhauer [m], Claudia Trenkwalder [m], Sandra Roeske [n], Hans-Ullrich Wittchen [o], Oliver Riedel [p], Richard Dodel [q,r], Elke Kalbe [a,*]

[a] University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Medical Psychology | Neuropsychology & Gender Studies, Center for Neuropsychological Diagnostic and Intervention (CeNDI), 50937, Cologne, Germany
[b] Department of Neurology, RWTH Aachen University, Pauwelsstraße 30, Aachen, Germany
[c] JARA-BRAIN Institute Molecular Neuroscience and Neuroimaging, Forschungszentrum Jülich GmbH and RWTH Aachen University, 52074, Aachen, Germany
[d] Department of Neurology, University of Rostock and German Center for Neurodegenerative Diseases (DZNE) Rostock, Gehlsheimer Str. 20, 18147, Rostock, Germany
[e] Hertie Institute for Clinical Brain Research Department of Neurodegenerative Diseases, Otfried-Müller-Straße 27, 72076, Tübingen, Germany
[f] German Center for Neurodegenerative Diseases (DZNE), Otfried-Müller-Straße 23, 72076, Tübingen, Germany
[g] IB-Hochschule für Gesundheit und Soziales, Paulinenstraße 45, 70178, Stuttgart, Germany
[h] Department of Neurology, Christian-Albrechts-University of Kiel, Arnold-Heller-Straße 3, 24105, Kiel, Germany
[i] Ethikkommission, Ludwig-Maximilians-Universität München, Pettenkoferstr. 8, 80336, München, Germany
[j] Department of Neurology, University of Ulm, Oberer Eselsberg 45, 89081, Ulm, Germany
[k] Department of Neurology, Klinikum Vest, Dorstener Str. 151, 45657, Recklinghausen, Germany
[l] Department of Neurology and Research Centre of Neurosensory Sciences, Carl von Ossietzky University, Carl-von-Ossietzky-Straße 9, 26129, Oldenburg, Germany
[m] Paracelsus-Elena Klinik, Kassel, Department of Neurosurgery, University Medical Center, Goettingen, Klinikstraße 16, 34128, Kassel, Germany
[n] German Center for Neurodegenerative Diseases (DZNE), Department of Clinical Research, Bonn, Sigmund-Freud-Str. 27, 53127, Bonn, Germany
[o] Department of Psychiatry & Psychotherapy, University Hospital Munich, Ludwig-Maximilians-University Munich, Nußbaumstraße 7, 80336, München, Germany
[p] Leibniz Institute for Prevention Research and Epidemiology – BIPS, Department of Clinical Epidemiology, Achterstraße 30, 28359, Bremen, Germany
[q] Department of Neurology, Philipps University Marburg, Baldingerstraße, 35043, Marburg, Germany
[r] Department of Geriatric Medicine, University Hospital Essen, Germaniastrasse 1-3, 45356, Essen, Germany

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ABSTRACT

*Introduction:* The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) is a renowned cognitive test battery, which has been extended in its German version to the CERAD-Plus including tests of executive functions and processing speed. The most commonly used total score (TS) is based on the restricted CERAD version and reflects the sum of selected raw-values (Chandler et al., 2005). The CERAD-Plus extensions might be of particular diagnostic utility for cognitive assessments in Parkinson's Disease (PD), as executive functions and processing speed belong to the most vulnerable domains in PD.

* Corresponding author. Kerpener Str. 68, 50937, Cologne, Germany.
*E-mail addresses:* rlillig@smail.uni-koeln.de (R. Lillig), anja.ophey@uk-koeln.de (A. Ophey), jschulz@ukaachen.de (J.B. Schulz), kreetz@ukaachen.de (K. Reetz), jwojtala@ukaachen.de (J. Wojtala), alexander.storch@med.uni-rostock.de (A. Storch), inga.liepelt@uni-tuebingen.de (I. Liepelt-Scarfone), becker.sara4@gmail.com (S. Becker), Daniela.Berg@uksh.de (D. Berg), Monika.balzergeldsetzer@med.uni-muenchen.de (M. Balzer-Geldsetzer), jan.kassubek@uni-ulm.de (J. Kassubek), ruediger.hilker-roggendorf@klinikum-vest.de (R. Hilker-Roggendorf), karsten.witt@evangelischeskrankenhaus.de (K. Witt), brit.mollenhauer@pk-mx.de (B. Mollenhauer), trenkwalder@pk-mx.de (C. Trenkwalder), Sandra.Roeske@dzne.de (S. Roeske), hans-ulrich.wittchen@tu-dresden.de (H.-U. Wittchen), riedel@leibniz-bips.de (O. Riedel), Richard.Dodel@uk-essen.de (R. Dodel), elke.kalbe@uk-koeln.de (E. Kalbe).
[1] first two authors contributed equally.

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*Objective:* The aim was to develop a CERAD-TS based on the extended CERAD-Plus' age-, gender-, and education-corrected z-scores and to evaluate its diagnostic accuracy compared to the established CERAD-Chandler-TS.
*Methods:* Baseline data of $n = 679$ patients with PD (69% male, $n = 277$ PD without cognitive impairment, $n = 307$ PD-MCI, $n = 95$ PD-D) from the multicenter, prospective DEMPARK/LANDSCAPE study were analyzed. ROC-analyses were conducted for four different TS that were either based on the original CERAD or CERAD-Plus, on raw-values or z-scores, and equally-weighted or based on factor scores. AUC-comparisons were conducted to determine the best yet most parsimonious TS.
*Results:* The newly designed CERAD-Plus-TS based on equally-weighted z-scores outperformed both the CERAD-Chandler-TS and cognitive screening instruments when differentiating between individuals with PD of varying cognitive impairment ($0.78 \leq AUC \leq 0.98$).
*Conclusion:* Results suggest a high relevance of non-amnestic subscales for the cognitive assessment in PD populations. The proposed CERAD-Plus-TS needs further validation. The extensions might offer diagnostic potential for non-PD populations as well.

## 1. Introduction

Cognitive decline represents a common non-motor symptom of Parkinson's disease (PD) with severe implications for individuals' quality of life and possible independency in activities of daily living [1]. Due to the subsequent vulnerability for developing PD dementia (PD-D), an early diagnosis of potential cognitive decline is crucial for early intervention and monitoring clinical progression.

Currently, several cognitive assessments developed for the diagnosis of cognitive dysfunction in Alzheimer's disease are utilized to examine cognitive decline in individuals with PD. These include for example the Mini-Mental State Examination (MMSE) [2] as a cognitive screening, and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [3] as a cognitive test battery. Next to single subscores, global CERAD total scores (TS) have been developed [4,5]. After comparing their diagnostic utility for discriminating between individuals with different pathologies and stages of cognitive impairment [4–7], the CERAD-TS proposed by Chandler and colleagues [4] emerged as the most viable. It comprises six out of seven CERAD subscales (i.e., all subscales except Figure Recall). The subscales' raw scores are summed, adding up to an arbitrarily weighted maximum raw score of 100 points (the maximum single test raw scores range from 10 to 24, see Table 1).

**Table 1**
Synopsis of all four different CERAD total scores.

| CERAD-Plus test battery | | TS1 | TS1z | TS2 | TS3 |
|---|---|---|---|---|---|
| Executive Functions | Animal Naming | 24 | z-score | z-score | factor-score |
| | Phonemic Fluency | | | z-score | factor-score |
| | Trail Making Test A | | | z-score | factor-score |
| | Trail Making Test B | | | z-score | factor-score |
| Memory | Word List Learning | 30 | z-score | z-score | factor-score |
| | Word List Recall | 10 | z-score | z-score | factor-score |
| | Word List Recognition | 10 | z-score | z-score | factor-score |
| | Figure Recall | | | z-score | factor-score |
| Language | Modified Boston Naming Test | 15 | z-score | z-score | factor-score |
| Visuoconstruction | Figure Copy | 11 | z-score | z-score | factor-score |
| Total Score | | raw score | mean z-score | mean z-score | weighted factor-score |

*Notes.* For TS1, the maximum raw score per subtest is indicated. For the other subtests, standardized z-scores were obtained from a large database of 1100 healthy subjects based on three age groups, two education groups and gender [11]. CERAD, Consortium to establish a Registry for Alzheimer's Disease; TS1, CERAD total score by Chandler and colleagues [4]; TS1z, z-score based CERAD total score by Chandler and Colleagues [4]; TS2, z-score based CERAD-Plus total score; TS3, factor-score-based CERAD-Plus total score.

Recently, the Chandler CERAD-TS was shown to successfully differentiate between patients with PD-D and patients with PD without dementia, including both patients without any clinically relevant cognitive decline yet (PD-N) and patients with mild cognitive impairment (PD-MCI) [8]. However, the authors discuss one central shortcoming of the traditional CERAD for the assessment of cognition in PD: it lacks a broad assessment of frontostriatal functions, such as executive functions, which constitute the most vulnerable cognitive functions in PD [9,10].

For the German-speaking market, the CERAD has been extended by further subtests to gauge more detailed information on non-amnestic cognitive domains, e.g., executive functions and processing speed. The resulting CERAD-Plus test battery [7,11] strongly improved diagnostic accuracy for dementia with different etiologies [7]; however, its additional subtests are not yet included in the common CERAD-TS.

Therefore, our aim was to develop a CERAD-TS based on the extended CERAD-Plus [7,11] and to evaluate its diagnostic accuracy compared to the established Chandler CERAD-TS. Using data from a large multicenter, prospective, observational cohort study, the DEMPARK/LANDSACPE study [12], we had access to a representative number of patients with PD across different levels of cognitive impairment, from PD-N to PD-MCI, and PD-D, that underwent extensive clinical and neuropsychological testing. We hypothesized that the inclusion of further subtests (measuring executive functions and processing speed) and the subscale Figure Recall to a global CERAD-Plus-TS based on age-, gender-, and education-corrected z-scores, either equally weighted or optimally weighted using factor scores, will improve diagnostic accuracy and might constitute a valid score to differentiate global levels of cognitive functioning in PD.

## 2. Method

### 2.1. DEMPARK/LANDSCAPE database and participants

For this study, baseline data of the German DEMPARK/LANDSCAPE project, which aimed at characterizing the natural progression of cognitive impairment in PD, were used [12]. The database included 711 patients with PD recruited via nine movement disorder centers across Germany and assessed with a comprehensive clinical and cognitive test battery. Inclusion criteria were (i) age between 45 and 80 years at baseline assessment and (ii) a diagnosis of idiopathic PD according to UK Parkinson's Disease Society Brain Bank criteria [13]. More detailed information about the study can be found in Balzer-Geldsetzer et al. [12].

Patients were allocated to three subgroups following diagnostic criteria for cognitive impairment in PD available at time of study set-up [14,15]: PD-N, PD-MCI, or PD-D. Patients were diagnosed with PD-MCI [14] when (i) subjective cognitive dysfunctions were reported by the patient, (ii) daily life activities were reported as non-significantly impaired, and (iii) performance in at least one cognitive test relevant for diagnosis was ≤1.5 SD below the mean of published normative data.

The cognitive tests relevant for diagnosis included several (but not all) CERAD-Plus subtests plus additional neuropsychological tests. For details, please refer to the Supplementary Material Table 1. Cognitive screening instruments were not relevant for diagnosis. Patients were diagnosed with PD-D [15] when (i) criteria for PD according to Queen Square Brain Bank were met, (ii) onset of cognitive deficits was insidious and progression was slow, (iii) deficits were present in two cognitive domains with one test per domain being ≤1.5 SD below normative data, (iv) impairment represented a decline from a premorbid level, and (v) deficits were severe enough to impair daily life independent of motor or autonomic symptoms.

For this study, we only included patients from the LANDSCAPE database without missing values in the MMSE [2], the Parkinson Neuropsychometric Assessment (PANDA) [16], and, after imputation of values in the Trail Making Tests (TMT),[2] the German CERAD-Plus [7,11].

### 2.2. Ethical approval

The DEMPARK/LANDSCAPE project was carried out in accordance with the World Medical Association Declaration of Helsinki (1997). The study procedure was approved by the Ethics Committee of Philipps University Marburg (approval No. 178/07) in March 2009 and thereupon by the ethics committees of the participating centers in Germany.

### 2.3. Clinical assessment

PD diagnosis was documented by recording the duration of symptoms, the date of initial diagnosis, and the severity of motor impairment, using the Unified Parkinson's Disease Rating Scale (Part III) [17] and the Hoehn & Yahr scale [18]. Drug therapy was documented regarding start of therapy, medication taken over the last three months before enrolment and total dopaminergic treatment calculated as the L-dopa equivalent daily dose (LEDD).

### 2.4. Cognitive assessment

Global cognitive functions were assessed with the cognitive screening instruments MMSE [2] and the PD-specific PANDA [19]. Furthermore, the test battery CERAD-Plus [7,11] evaluated cognitive performance across several cognitive domains: memory (Word List Learning, Word List Recall, Word List Recognition, Figure Recall), language (Modified Boston Naming Test), visuoconstruction (Figure Copy), executive functions (Animal Naming, Phonemic Fluency, Trail Making Test B (TMT-B)) and processing speed (Trail Making Test A (TMT-A)). Age-, gender-, and education-corrected normative *z*-scores for all subtests, derived from a database of 1100 healthy control subjects, were used [11].

### 2.5. CERAD total scores

#### 2.5.1. CERAD total score 1 (TS1)

The Chandler CERAD total score 1 (TS1) was constructed based on the procedure proposed by Chandler et al. [4] and is based on six out of seven of the original CERAD subscales: Animal Naming, Modified Boston Naming Test, Word List Learning, Word List Delayed Recall, Word List Recognition, and Figure Copy, adding up to a total raw score of exactly 100 points (see Table 1), while excluding the subscale Figure Recall [4]. We used the corrected version of the total raw score by controlling for age, gender, and education. Instead of using the correction formula proposed by Chandler and colleagues [4] we used the correction formula proposed by Ehrensperger and colleagues [6], that was based on the German CERAD version.

#### 2.5.2. CERAD total score 1z (TS1z)

For the CERAD total score 1z (TS1z), we sought equal weighting of the six subscales used in the TS1 to circumvent the arbitrary weighting of subscales. Therefore, the TS1z was calculated as the mean *z*-score of all six subscales (Animal Naming, Modified Boston Naming Test, Word List Learning, Word List Delayed Recall, Word List Recognition and Figure Copy). *Z*-scores were previously determined using published normative data of the German CERAD-Plus, adjusting for age, gender, and education [11].

#### 2.5.3. CERAD total score 2 (TS2)

To determine whether the additional subtests of the German CERAD-Plus (TMT A, TMT B, and Phonemic Fluency) and previously excluded subtests of the original CERAD (Figure Recall) improve discriminative ability between the cognitive subgroups, the CERAD total score 2 (TS2) was created. The TS2 was computed as an equally weighted mean score of *z*-scores of all subtests included in the German CERAD-Plus.

#### 2.5.4. CERAD total score 3 (TS3)

The CERAD total score 3 (TS3) was developed, to examine whether a differential weighting of all CERAD-Plus tests included in TS2 further improves discriminative ability between the subgroups of PD-N, PD-MCI, and PD-D. Based on the idea that there is a global cognition factor underlying patients' test performances, we employed a principle component analysis (PCA) extracting one factor to obtain weights for each of the CERAD-Plus subtests' *z*-scores and calculate factor scores accordingly. During an initial PCA without rotation and the maximum number of ten components, only one component had an eigenvalue over Kaiser's criterion of 1 and explained 38.7% of the variance, supporting the rational of a global CERAD TS. In the subsequent PCA without rotation with maximum likelihood estimation, all factor loadings on this one component were greater than the commonly used cutoff of 0.3, with the lowest loading being 0.48 for the Modified Boston Naming Test. Factor scores for each individual, i.e., the TS3, are then computed by multiplying each CERAD-Plus subtest z-value by the product of the standardized loading and the corresponding weight of the subtest and summing up the results across the ten CERAD-Plus subtest scores. The extracted factor scores then equal a weighted sum score of *z*-scores of all subtests included in the German CERAD-Plus. While summing up raw scores or calculating equally weighted means does not take into account the differential diagnostic accuracies of neuropsychological tests, this regression factor score method assigns optimal weights to each subtest loading onto the global cognition factor [20]. Further details on the CERAD TS3 can be obtained from the Supplementary Material.

### 2.6. Statistical analysis

All statistical analyses were conducted in R (https://www.r-project.org). Data were checked for normal distribution using Shapiro-Wilk tests. Demographic, clinical, and cognitive characteristics between PD-N, PD-MCI, and PD-D were compared using univariate analyses of variances (ANOVAs) or $\chi^2$-tests as appropriate. In case of a significant main effect of cognitive group, Bonferroni-corrected post-hoc *t*-tests were performed. Receiver operating characteristics (ROC) analyses were performed with the R-package *pROC* [21]. Sensitivity, specificity, positive and negative predictive values, and the area under the curve (AUC) were calculated for each CERAD-TS. An AUC of 0.5 corresponds to

[2] We had to cope with missing values within the CERAD-Plus. Of n = 711 patients, complete CERAD-Plus data sets were available for only n = 626 (i.e. for 12% of participants, data of at least one CERAD-Plus subtest was missing). For n = 53 (7.5%), only data in TMT-A and/or TMT-B was missing. As in Schmid and colleagues [7], particularly cognitively more impaired patients did not complete the TMT subtests. Therefore, we substituted missing values in TMT-A and TMT-B by the lowest possible value (TMT-A: 180 s, TMT-B: 300 s) to ensure a non-random penalty for non-completion in these subtests. TMT-A data was imputed for 1.6% of patients, and TMT-B data for 7.5% of patients.

predictive ability equal to that of chance, whereas an AUC of 1.0 represents perfect predictive ability [22]. Optimal cutoff points maximizing the sensitivity – specificity criterion were extracted using the R-package *OptimalCutpoints* [23]. ROC-analyses were performed for 4 diagnostic group comparisons: (i) PD-N vs. PD-MCI & PD-D, (ii) PD-N vs. PD-MCI, (iii) PD-N vs. PD-D and (iv) PD-MCI vs. PD-D. For each contrast, we compared the AUC between all four CERAD-TS by using the roc.test function as implemented in *pROC* using the DeLong method [24]. Furthermore, the AUC of the best possible CERAD-TS was compared to the AUC of established cognitive screenings, the MMSE and the PD-specific PANDA. The alpha-level was Bonferroni-adjusted within each diagnostic group comparison to $\alpha = 0.00625$ according to 8 comparisons: (i) TS1 vs. TS1z, (ii) TS1 vs. TS2, (iii) TS1 vs. TS3, (iv) TS1z vs. TS2, (v) TS1z vs. TS3, (vi) TS2 vs. TS3, (vii) "best TS" vs. PANDA, (viii) "best TS" vs. MMSE.

## 3. Results

### 3.1. Sample characteristics

Our final sample consisted of $n = 679$ patients with PD, of which $n = 277$ were diagnosed with PD-N, $n = 307$ with PD-MCI, and $n = 95$ with PD-D. On average, patients were 67.58 ± 7.82 years old and 67.6% were male. Total years of formal education were significantly higher for patients with PD-N compared to PD-MCI and PD-D. Disease-related characteristics indicated significantly longer disease duration and more severe motor impairment for patients with PD-D compared to PD-MCI, and PD-MCI compared to PD-N. Likewise, across all cognitive tests, patients with PD-N performed significantly better than patients with PD-MCI, and patients with PD-MCI performed significantly better than patients with PD-D. Further details on sociodemographic, clinical, and cognitive characteristics are displayed in Table 2.

### 3.2. ROC-analysis of CERAD total scores

For all CERAD-TS, the pattern of performance of PD subgroups was comparable: patients with PD-N significantly outperformed patients with PD-MCI, who likewise outperformed patients with PD-D (*ps* ≤ .001, for details, see Table 1). Table 3 shows the results of ROC analyses for all CERAD-TS, with ROC curves visualized in Fig. 1. A similar pattern emerged for all four comparisons ((i) PD-N vs. [PD-MCI & PD-D], (ii) PD-N vs. PD-MCI, (iii) PD-N vs. PD-D (iv) PD-MCI vs. PD-D), with TS2 and TS3 outperforming TS1 and TS1z regarding AUC values as well as specificity and sensitivity. Diagnostic accuracy for differentiating

**Table 2**
Demographic, clinical, and cognitive characteristics.

| | | PD-N ($n = 277$) | PD-MCI ($n = 307$) | PD-D ($n = 95$) | $p$ value* |
|---|---|---|---|---|---|
| Age in years | | 65.55 (8.58) | 68.17 (7.34) | 71.59 (5.11) | ≤.001 (PD-N < PD-MCI < PD-D) |
| Sex female (in %) | | 91 (32.9) | 100 (32.6) | 29 (30.5) | .913 |
| male (in %) | | 186 (67.1) | 207 (67.4) | 66 (69.5) | |
| Education in years | | 13.93 (3.26) | 13.12 (3.05) | 12.28 (3.01) | ≤.001 (PD-N > PD-MCI and PD-D) |
| Disease duration in years | | 5.57 (4.60) | 7.06 (5.43) | 9.38 (6.59) | ≤.001 (PD-N < PD-MCI < PD-D) |
| Age of initial diagnosis | | 59.92 (8.92) | 61.03 (8.78) | 62.20 (8.04) | .069 |
| Levodopa Equivalent Daily Dose in mg/day | | 705.63 (535.20) | 805.29 (534.64) | 848.90 (507.28) | .027 (PD-N < PD-MCI and PD-D) |
| UPDRS-III | | 19.86 (10.41) | 23.23 (11.84) | 31.36 (14.73) | ≤.001 (PD-N < PD-MCI < PD-D) |
| Hoehn & Yahr stage | 1 | 51 (18.5%) | 47 (15.4%) | 2 (2.1%) | ≤.001 |
| | 2 | 167 (60.5%) | 135 (44.3%) | 31 (33.0%) | |
| | 3 | 52 (18.8%) | 96 (31.5%) | 41 (43.6%) | |
| | 4 | 5 (1.8%) | 22 (7.2%) | 16 (17.0%) | |
| | 5 | 1 (0.4%) | 5 (1.6%) | 4 (4.3%) | |
| MMSE (max. 30) | | 28.89 (1.31) | 27.97 (1.71) | 25.09 (2.75) | ≤.001 (PD-N > PD-MCI > PD-D) |
| PANDA (max. 30) | | 24.74 (4.13) | 21.00 (5.12) | 13.64 (5.08) | ≤.001 (PD-N > PD-MCI > PD-D) |
| CERAD-TS1 (max. 100) | | 95.18 (6.97) | 87.81 (8.90) | 73.11 (11.05) | ≤.001 (PD-N > PD-MCI > PD-D) |
| CERAD-TS1z | | 0.22 (0.53) | −0.37 (0.66) | −1.43 (0.86) | ≤.001 (PD-N > PD-MCI > PD-D) |
| CERAD-TS2 | | 0.25 (0.53) | −0.43 (0.66) | −1.55 (0.70) | ≤.001 (PD-N > PD-MCI > PD-D) |
| CERAD-TS3 | | 0.61 (0.59) | −0.13 (0.72) | −1.34 (0.72) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Boston Naming Test raw (max. 15) | | 14.71 (0.58) | 14.21 (1.13) | 12.89 (1.98) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Boston Naming Test z | | 0.53 (0.73) | 0.16 (1.03) | −0.69 (1.44) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Semantic Verbal Fluency raw | | 23.64 (6.02) | 19.76 (6.09) | 13.98 (5.46) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Semantic Verbal Fluency z | | 0.19 (1.13) | −0.39 (1.14) | −1.29 (1.10) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Phonemic Verbal Fluency raw | | 15.31 (5.11) | 11.60 (5.21) | 7.34 (4.21) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Phonemic Verbal Fluency z | | 0.51 (1.05) | −0.21 (1.21) | −1.10 (1.16) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Word List Learning raw (max. 30) | | 21.37 (3.49) | 18.16 (4.18) | 12.87 (4.65) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Word List Learning z | | 0.08 (0.95) | −0.76 (1.29) | −2.19 (1.48) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Word List Recall raw (max. 10) | | 7.53 (1.74) | 6.04 (2.22) | 3.62 (2.34) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Word List Recall z | | 0.15 (0.93) | - 0.49 (1.16) | −1.53 (1.28) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Word List Recognition raw (max. 100%) | | 98.07 (3.71) | 95.41 (6.71) | 88.63 (11.21) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Word List Recognition z | | 0.15 (0.91) | −0.26 (1.17) | −1.14 (1.50) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Figure Copy raw (max. 11) | | 10.59 (0.93) | 9.83 (1.45) | 8.05 (2.36) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Figure Copy z | | 0.20 (1.00) | −0.50 (1.31) | −1.74 (1.65) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Figure Recall raw (max. 11) | | 9.61 (1.78) | 7.87 (2.62) | 5.13 (3.33) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Figure Recall z | | 0.20 (1.20) | −0.66 (1.37) | −1.69 (1.39) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Trail Making Test A in sec. (max. 180) | | 43.00 (21.58) | 56.36 (27.87) | 106.75 (53.60) | ≤.001 (PD-N < PD-MCI < PD-D) |
| Trail Making Test A z | | 0.24 (1.24) | −0.49 (1.21) | −2.12 (1.06) | ≤.001 (PD-N > PD-MCI > PD-D) |
| Trail Making Test B in sec. (max. 300) | | 103.03 (52.87) | 152.57 (75.47) | 257.91 (75.32) | ≤.001 (PD-N < PD-MCI < PD-D) |
| Trail Making Test B z | | 0.22 (1.25) | −0.74 (1.27) | −2.01 (0.72) | ≤.001 (PD-N > PD-MCI > PD-D) |

*Notes.* Data is reported as mean (SD); p-values of univariate ANOVAs or $\chi 2$-tests are reported as appropriate. In case of significant results, Bonferroni-corrected post-hoc tests are shown in brackets.
CERAD, Consortium to establish a Registry for Alzheimer's Disease; MMSE, Mini-mental state examination; PANDA, Parkinson neuropsychometric dementia assessment; PD-D, Parkinson's disease with dementia; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-N, Parkinson's disease without cognitive impairment; TS1, CERAD total score by Chandler and colleagues [4]; TS1z, z-score based CERAD total score by Chandler and colleagues [4]; TS2, z-score based CERAD-Plus total score; TS3, factor-score-based CERAD-Plus total score; UPDRS-III, Unified Parkinson's Disease Rating Scale Part 3.

**Table 3**
ROC analyses of CERAD total scores.

| | TS1 | TS1z | TS2 | TS3 | PANDA | MMSE |
|---|---|---|---|---|---|---|
| | **PD-N vs. [PD-MCI & PD-D]** | | | | | |
| Optimal cutoff | 91.13 | −0.09 | −0.12 | 0.25 | 23.00 | 28.00 |
| Sensitivity | 0.71 | 0.72 | 0.75 | 0.75 | 0.71 | 0.65 |
| Specificity | 0.71 | 0.72 | 0.75 | 0.75 | 0.69 | 0.72 |
| Positive predictive value | 0.78 | 0.79 | 0.82 | 0.81 | 0.77 | 0.77 |
| Negative predictive value | 0.63 | 0.64 | 0.68 | 0.68 | 0.62 | 0.59 |
| AUC | 0.79 | 0.78 | 0.84[abc] | 0.84[ab] | 0.78 | 0.73 |
| | **PD-N vs. PD-MCI** | | | | | |
| Optimal cutoff | 92.02 | −0.05 | −0.03 | 0.32 | 23.00 | 28.00 |
| Sensitivity | 0.67 | 0.68 | 0.72 | 0.72 | 0.62 | 0.57 |
| Specificity | 0.67 | 0.68 | 0.72 | 0.72 | 0.69 | 0.72 |
| Positive predictive value | 0.69 | 0.70 | 0.74 | 0.74 | 0.69 | 0.69 |
| Negative predictive value | 0.65 | 0.66 | 0.70 | 0.70 | 0.62 | 0.60 |
| AUC | 0.74 | 0.75 | 0.79[abc] | 0.79[ab] | 0.72 | 0.67 |
| | **PD-N vs. PD-D** | | | | | |
| Optimal cutoff | 86.36 | −0.48 | −0.53 | −0.32 | 19.00 | 27.00 |
| Sensitivity | 0.88 | 0.89 | 0.93 | 0.94 | 0.86 | 0.78 |
| Specificity | 0.88 | 0.90 | 0.93 | 0.94 | 0.88 | 0.88 |
| Positive predictive value | 0.72 | 0.75 | 0.81 | 0.84 | 0.71 | 0.69 |
| Negative predictive value | 0.96 | 0.96 | 0.97 | 0.98 | 0.95 | 0.92 |
| AUC | 0.96 | 0.95 | 0.98[bc] | 0.98[ab] | 0.95 | 0.91 |
| | **PD-MCI vs. PD-D** | | | | | |
| Optimal cutoff | 80.74 | −0.80 | −0.97 | −0.71 | 17.00 | 27.00 |
| Sensitivity | 0.78 | 0.75 | 0.80 | 0.78 | 0.75 | 0.78 |
| Specificity | 0.78 | 0.75 | 0.80 | 0.78 | 0.74 | 0.69 |
| Positive predictive value | 0.52 | 0.48 | 0.55 | 0.52 | 0.47 | 0.44 |
| Negative predictive value | 0.92 | 0.91 | 0.93 | 0.92 | 0.90 | 0.91 |
| AUC | 0.85 | 0.84 | 0.88[b] | 0.88[b] | 0.82 | 0.84 |

*Notes.* Optimal cutoff points maximizing the sensitivity – specificity criterion were carried out using the R-package OptimalCutpoints [30]. Results of AUC-comparisons [22] can be found in the Results section.
AUC, area under the curve; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MMSE, Mini-mental state examination; PANDA, Parkinson neuropsychometric dementia assessment; PD-D, Parkinson's disease with dementia; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-N, Parkinson's disease without cognitive impairment; ROC, receiver operating characteristics; TS1, CERAD total score by Chandler and colleagues [4]; TS1z, z-score based CERAD total score by Chandler and colleagues [4]; TS2, z-score based CERAD-Plus total score; TS3, factor-score-based CERAD-Plus total score.
[a]AUC-Score was better than TS1 ($p \leq .001$).
[b]AUC-Score was better than TS1z ($p \leq .001$).
[c]AUC-Score was better than MMSE/PANDA ($p \leq .001$).

between patients with PD-N vs. [PD-MCI & PD-D] was acceptable for TS1 (AUC = 0.79) and TS1z (AUC = 0.78), and excellent for TS2 and TS3 (both AUC = 0.84). While the discriminative performance for the comparison PD-N vs. PD-MCI was acceptable for all TS ($0.74 \leq$ AUC $\leq 0.79$), differentiating between PD-MCI vs. PD-D was excellent ($0.84 \leq$ AUC $\leq 0.88$) and differentiating between PD-N vs. PD-D outstanding for all TS ($0.95 \leq$ AUC $\leq 0.98$).

### 3.3. AUC-comparison of CERAD total scores

Results of the comparisons of the AUC of the different TS for each diagnostic group comparison can be found in the Supplementary Material Table 2. While TS1z did not improve diagnostic accuracy over TS1 for any of our diagnostic group comparisons ($.261 \leq p \leq .420$), diagnostic accuracy significantly improved for TS2 and TS3 compared to TS1 and TS1z. TS2 did so compared to TS1 for the comparisons PD-N vs. [PD-MCI & PD-D] ($Z = -3.72$, $p \leq .001$) and PD-N vs. PD-MCI ($Z = -3.41$, $p \leq .001$). For the comparison PD-N vs. PD-D, discriminative accuracy improved only marginally ($Z = -2.70$, $p = .007$), and no significant improvement in discriminative accuracy could be observed for the comparison PD-MCI vs. PD-D ($Z = -1.76$, $p = .079$). TS3 improved diagnostic accuracy compared to TS1 for the comparisons of PD-N vs. [PD-MCI & PD-D] ($Z = -3.66$, $p \leq .001$), PD-N vs. PD-MCI ($Z = -3.31$, $p \leq .001$), and PD-N vs. PD-D ($Z = -2.88$, $p = .004$), but not for PD-MCI vs. PD-D ($Z = -2.25$, $p = .024$). TS3 did not improve diagnostic accuracy significantly compared to TS2 for any of the comparisons ($.138 \leq p \leq .683$). Therefore, as the TS2 is the more parsimonious CERAD-TS, it was chosen as the best possible CERAD-TS and further compared to discriminative accuracy of common cognitive screening tools.

### 3.4. Comparison of TS2 to cognitive screening tools

When compared to the cognitive screening tools MMSE and PANDA, whose ROC curves are displayed in Fig. 1 as well, the CERAD-TS2 yielded better discriminative performance for three of the four comparisons: PD-N vs. [PD-MCI & PD-D], PD-N vs. PD-MCI, and PD-N vs. PD-D ($ps \leq .001$). For the comparison PD-MCI vs. PD-D, no significant improvement in discriminative performance of TS2 compared to neither MMSE ($Z = 2.26$, $p = .024$) nor PANDA ($Z = 1.85$, $p = .064$) was observed.

## 4. Discussion

This study aimed to develop and evaluate a novel CERAD-TS based on the CERAD-Plus using a representative, multicenter, prospective, observational database of 679 individuals with PD across different levels of cognitive impairment. Our main findings are that (1) the CERAD-TS2 was the best and most parsimonious total score for discriminating the PD subgroups compared to the established Chandler CERAD-TS1 and other evaluated CERAD-TS and (2) including non-amnestic cognitive subscales in executive functions, processing speed, and the subscale Figure Recall from the CERAD-Plus significantly improved diagnostic accuracy in patients with PD.

Our findings revealed the superiority of the newly developed CERAD-TS2 compared to the established Chandler CERAD-TS1 and the CERAD-TS1z regarding diagnostic accuracy and compared to the CERAD-TS3 regarding parsimony. The CERAD-TS2 included a broader spectrum of cognitive domains and was computed by equally weighting the age-, gender-, and education-corrected normative z-scores of the corresponding subscores. Interestingly, Chandler and colleagues [4] originally left out the subscale Figure Recall in the CERAD-TS1 without any further theoretical remarks. As previous findings found Figure Recall to be among the most frequently impaired subscales in PD-MCI [9] and to be highly capable of differentiating PD-N from (PD-MCI & PD-D) [8], it seems reasonable to utilize Figure Recall when applying the CERAD in individuals with PD. Moreover, the CERAD-TS1 did not imply any theory-based weighting of subscales as they were simply summed up to a raw score of 100 points. The equally weighted CERAD-TS1z, however, did not show any improvement compared to the CERAD-TS1 stressing the fact that solely weighting subscales equally is not sufficient to yield better discrimination in PD populations. The broader CERAD-TS2 enhanced diagnostic accuracy over the CERAD-TS1, especially for the comparison PD-N vs. PD-MCI, probably as cognitive impairment in individuals with PD is highly heterogeneous [9,10,25].

Optimally weighted subscales in the CERAD-TS3 did not improve diagnostic accuracy over equally weighted subscales in the CERAD-TS2, which indicates that the CERAD subscales are of equal importance for the TS across most patients with PD. Nevertheless, for a given individual patient some tests might be more sensitive in detecting clinically relevant cognitive decline than others, depending on the individual cognitive profile.

The fact that our CERAD-TS2 only marginally improved diagnostic

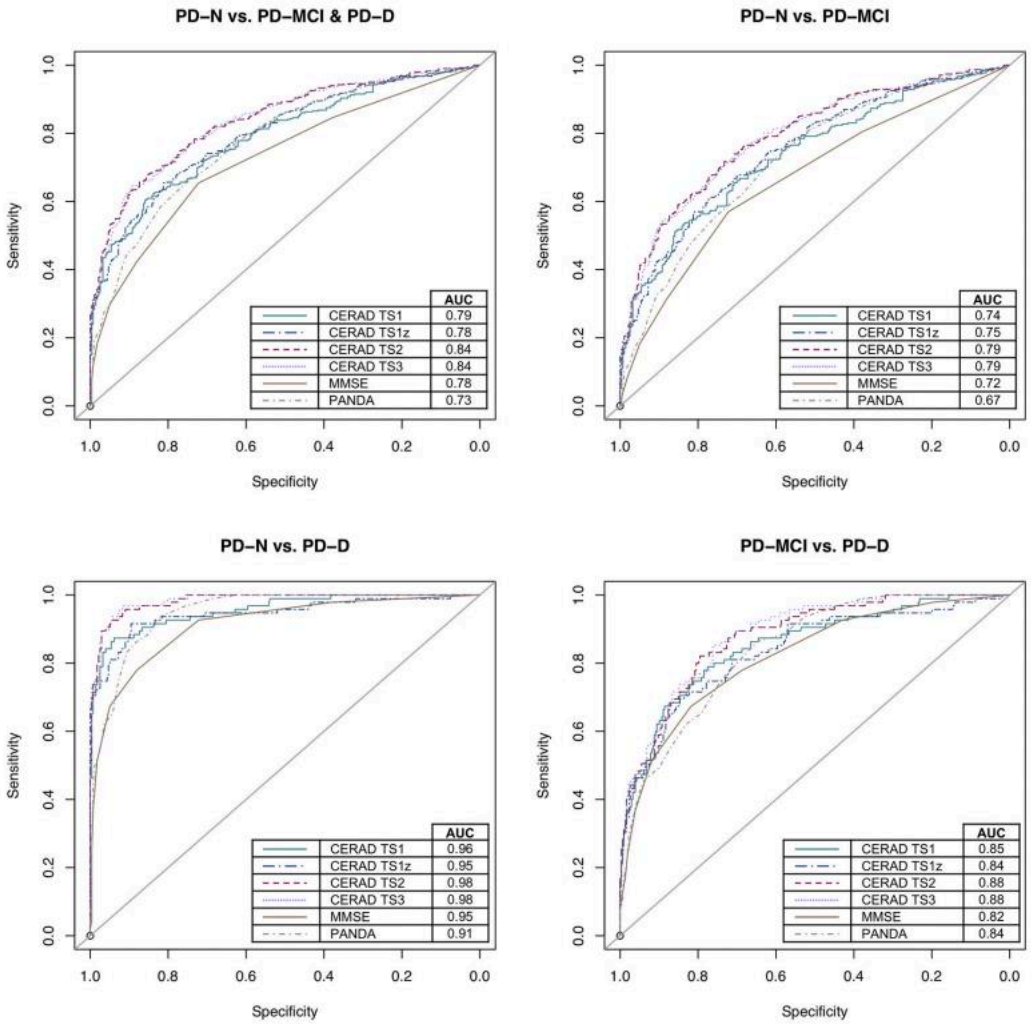


**Fig. 1.** Receiver Operating Characteristics for four comparisons: PD-N vs. [PD-MCI & PD-D], (ii) PD-N vs. PD-MCI, (iii) PD-N vs. PD-D, (iv) PD-MCI vs. PD-D. AUC, area under the curve; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MMSE, Mini-mental state examination; PANDA, Parkinson neuropsychometric dementia assessment; PD, Parkinson's disease; PD-D, Parkinson's disease with dementia; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-N, Parkinson's disease without cognitive impairment; TS1, CERAD total score by Chandler and colleagues [4]; TS1z, z-score based CERAD total score by Chandler and colleagues [4]; TS2, z-score based CERAD-Plus total score; TS3, factor-score-based CERAD-Plus total score.

accuracy for the comparison PD-N vs. PD-D compared to CERAD-TS1 might be due to the already near perfect diagnostic accuracy of the CERAD-TS1 for this comparison. Likewise, our CERAD-TS2 could not significantly improve diagnostic accuracy for the comparison PD-MCI vs. PD-D when compared to TS1, PANDA, or MMSE. It is well known that executive functions are the most vulnerable cognitive domain in patients with PD [26], which is due to frontostriatal, predominantly dopaminergic, impairments. Therefore, the addition of executive functions subscales appears to be more fruitful to detect impairment in earlier stages of PD. Further research should try to examine how the comparison PD-MCI vs. PD-D could be more accurately diagnosed to better grasp the transition from PD-MCI to PD-D.

As a recent meta-analysis noted, the most important risk factor for developing PD-D is the presence of PD-MCI [27]. This underlines the importance of and the need for accurately assessing the comparison PD-N vs. PD-MCI, as demonstrated by the superiority of the CERAD-TS2 over CERAD-TS1, MMSE, and PANDA. Less education has also been marked as a potential risk factor for PD-D [28], alluding to the concept of cognitive reserve. It postulates that higher levels of education correlate with better cognitive performance and decelerated cognitive decline in PD [29]. Interestingly, more years of education were observed in our sample of patients with PD-N compared to both PD-MCI and PD-D. As education-corrected CERAD-scores have been found to increase sensitivity for detecting PD-MCI and PD-D [30], controlling for education should be considered of high importance when cognitive assessments in PD populations are conducted. Our CERAD-TS2 is inherently education corrected, as it was based on age-, gender-, and education-corrected standardized *z*-scores [11].

### 4.1. Strengths and limitations

The main strength of this study was the representative database of 679 individuals with PD across different levels of cognitive impairment and the elaborated clinical and neuropsychological characterization. Further strengths include the use of age-, gender-, and education-corrected normative *z*-scores for all subtests, the utilization of robust and rather conservative statistical procedures and adjustments, and the evaluation of the data-based optimally weighted CERAD-TS3. A limitation of the study was that the diagnosis of PD-MCI was not based on the contemporary criteria by Litvan and colleagues [31], but on MCI criteria available at the time of study set-up [14]. These were less conservative as they only required one impaired test score compared to two required

for a Level-II diagnosis according to the current criteria. This might have led to an overidentification of patients with PD-MCI.

### 4.2. Conclusion

Summarizing, we were able to introduce a new CERAD-Plus-TS with equally weighted *z*-scores of all subtests included in the CERAD-Plus test battery for the cognitive assessment of PD, which was validated in a large, cognitively heterogeneous PD population. ROC-analyses demonstrated that the additional subscales reflecting executive functions, processing speed, and visuospatial memory might be of high relevance when differentiating between different levels of cognitive functioning in PD. Especially in early disease stages with heterogeneous cognitive profiles, a broad assessment of cognitive domains seems highly relevant. The proposed CERAD-Plus-TS still needs further validation and might offer diagnostic potential for non-PD populations as well.

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## Contributorship statement

RL conceptualized the analyses, interpreted the data, drafted the first version of the manuscript, revised the manuscript for intellectual content, and approved the final version of the manuscript.

AO conceptualized the analyses, analyzed and interpreted the data, drafted the first version of the manuscript, revised the manuscript for intellectual content, and approved the final version of the manuscript.

JBS, KR, JWoj, ASt, ILS, SB, DB, MBG, JKa, RHR, KW, BM, CT, SR, HUW, OR, and RD conceptualized and supervised the DEMPARK/LANDSCAPE study, contributed to data collection, revised the manuscript for intellectual content, and approved the final version of the manuscript.

EK conceptualized and supervised the DEMPARK/LANDSCAPE study as well as the current analyses, interpreted the data, contributed to data collection, revised the manuscript for intellectual content, and approved the final version of the manuscript.

## Declaration of competing interest

RL, AO, JBS, KR, JWoj, ASt have nothing to disclose.

ILS reports grants from International Parkinson Fonds (Deutschland) GmbH (IPD), grants from Johnson & Johnson, grant from the Michael J Fox Foundation, grants from European Commission, H2020-TWINN-2015, outside the submitted work.

SB, DB, MBG have nothing to disclose.

JKa has received fees as speaker and/or advisor from UCB Pharma, Desitin, Novartis, Bial, Zambon, Medtronic, Desitin, AbbVie, NeuroDerm, and Teva Pharmaceuticals.

RHR has nothing to disclose.

KW has received lecture honoraria from BIAL, Desitin and UCB, we serves as an advisory broad member of Stadapharm, outside the submitted work.

BM, CT, SR, HUW, OR have nothing to disclose.

RD reports personal fees from AbbVie, personal fees and non-financial support from Axon Neuroscience, non-financial support from Akademie für medizinische Fortbildung, personal fees from Agentur Süß, personal fees and non-financial support from Bayer, grants from Baxter, personal fees from Bial, personal fees and non-financial support from Biogen, personal fees and non-financial support from Bayer Vital, personal fees and non-financial support from BB-Biotech, grants and non-financial support from Deutsche Gesellschaft für Neurologie, non-financial support from Deutscher Hausärzteverband, personal fees from Deutsches Zentrum für neurodegenerative Erkrankungen, grants and non-financial support from Deutsche Parkinson Vereinigung, non-financial support from Deutsche Gesellschaft Parkinson, personal fees and non-financial support from Desitin, non-financial support from European Brain Council, grants from EU-Horizon, grants, personal fees and non-financial support from Eisai, personal fees from Elsevier, grants from Ernst und Margot Faber Stiftung, personal fees and non-financial support from Gemeinsamer Bundesausschuss, personal fees and non-financial support from GE Healthcare, grants from GE Healthcare General Electric, personal fees and non-financial support from International Parkinson and Movement Disorder Society, personal fees and non-financial support from Institut für hausärztliche Fortbildung im Deutschen Hausärzteverband, personal fees and non-financial support from IAK+, personal fees and non-financial support from Johanniter, personal fees from Kohlhammer, grants and personal fees from Lilly, grants from Michael J. Fox Foundation, grants, personal fees and non-financial support from Novartis, personal fees from Ono Pharma, personal fees and non-financial support from Pfitzer, personal fees and non-financial support from Paul-Martini-Stiftung, non-financial support from Programm Demenz Prävention, personal fees and non-financial support from Roche, personal fees and non-financial support from Schwabe, personal fees from Springer Verlag, grants from Stichting International Parkinson Fonds, personal fees from Thieme Verlag, personal fees and non-financial support from UCB Pharma, personal fees from Hummingbird, grants from BMBF, outside the submitted work; In addition, Dr. Dodel has a patent Alpha-Synuclein Epitopbereiche (Bindungsstellen) natürlich vorkommender humaner Alpha-Synuclein Autoantikörper zur Diagnostik und Therapie von Morbus Alzheimer und anderen neurodegenerativen Erkrankungen issued, a patent Diagnosis of Alzheimer's Disease and other neurodementia diseases of AD-type and AD-therapeutic application issued, a patent Diagnosis, Prohylaxis and Therapy of Alzheimer's Disease and other neurodementing disorders issued, a patent ELISA-Test zur Bestimmung von Amyloid Beta Auto-Antikörpern in humanen Serum-/Plasma-/CSF-Proben issued, a patent Herstellung von oligomeren (trimeren) beta-Amyloid Molekülen mittels spezifischer Mutationen issued, a patent Künstliche Mini-Amyloide zur Diagnose und Behandlung der Alzheimer Demenz issued, a patent Naturally occurring autoantibodies against alpha-synuclein that inhibit the aggregation and cytotoxicity of alpha-synuclein mit Dr. Rentschler Holding GmbH & Co KG issued, and a patent Verfahren, insbesondere Enzyme-linked Immunosorbent Assay (ELISA) zum in vitro Nachweis von Amyloid beta Autoantikörpern, Mikrotiterplatte und Testkit issued, outside the submitted work.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.07.034.

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# 4. DISCUSSION

This thesis project developed a new CERAD-TS based on the entire CERAD-Plus test battery using a large database of 679 individuals with PD and varying cognitive status from the multicenter, prospective, DEMPRAK/LANDSCAPE study. After evaluating and comparing different TS regarding their diagnostic accuracy in discriminating PD subgroups, the following two main findings of this project were identified: (1) the CERAD-TS2 emerged as the best and most parsimonious total score compared to other CERAD TS including the established Chandler CERAD-TS1 and (2) the addition of non-amnestic CERAD-Plus subscales in executive functions and processing speed and the reintegration of the omitted visuo-spatial CERAD subscale Figure Recall significantly ameliorated diagnostic accuracy in individuals with PD.

## 4.1. Diagnostic accuracies of CERAD TS in the DEMPRAK/LANDSCAPE population

AUC-comparisons of the investigated PD-subgroups showed the superiority of the newly developed CERAD-TS2 over the original Chandler CERAD-TS1, the CERAD-TS1z and the MMSE and PANDA as cognitive screening tools with respect to diagnostic accuracy and over the CERAD-TS3 regarding parsimony. The CERAD-TS2 covers a broad variety of cognitive domains and is calculated with equal weights using age-, gender-, and education-corrected normative z-scores. More specifically, the CERAD-TS2 was able to enhance diagnostic discrimination over the CERAD-TS1z for all contrasts and over the CERAD-TS1 for the comparisons: PD-N vs. (PD-MCI & PD-D) and for PD-N vs. PD-MCI. Especially the diagnostic improvement for the latter comparison suggests that cognitive impairment in individuals with PD is highly heterogeneous[44,98]. As opposed to the Chandler CERAD-TS1, the novel CERAD-TS2 reintegrated the CERAD subscale Figure Recall, originally omitted by Chandler and colleagues[152] without specific remarks. Taking into consideration the facts that the visuo-spatial-amnestic subscale Figure Recall ranks amongst the most commonly impaired cognitive tests in PD-MCI[44] and shows outstanding qualities in distinguishing diagnostic groups of PD-N and (PD-MCI & PD-D)[134], the application of Figure Recall when diagnosing PD populations should be considered as highly useful.

At first glance it seems surprising that the CERAD-TS2 only marginally improved diagnostic accuracy for the contrast PD-N vs. PD-D compared to the Chandler CERAD-TS1. Considering the already outstanding, near-perfect, diagnostic accuracy of the CERAD-TS1 for this comparison (AUC = 0.96) the marginal significance of the CERAD TS-2 might be due to a ceiling effect. Further, the CERAD-TS2 failed to yield better discriminative performance for the comparison PD-MCI vs. PD-D compared to the CERAD-TS1, PANDA and MMSE. Given the fact that executive functions are most susceptible to decline in earlier stages of PD caused by

fronto-striatal, dopaminergic impairments[99], the integration of executive functions subscales seems most beneficial to investigate cognitive impairment in earlier stages of PD. Future research should address how the comparison PD-MCI vs. PD-D could be more precisely differentiated to better understand the later transition from PD-MCI to PD-D. The importance of this transition becomes even more evident as research has shown that PD-MCI is the most important risk factor for developing PD-D[83]. This in turn shows that accurate diagnosis of the comparison PD-N vs. PD-MCI, demonstrated by superior diagnostic accuracy of the CERAD-TS2 over the CERAD-TS1, PANDA and MMSE, is fundamental to detect those at risk of developing PD-D later on.

## 4.2. Weighting of different CERAD TS

As the Chandler CERAD-TS1[152] implies data aggregation on the basis of summing up raw scores to an arbitrary total of 100 points and is thus lacking theory-based weighting, the CERAD-TS1z sought equal weighting through a mean of z-scores. However, the CERAD-TS1z did not improve diagnostic accuracy for any of the investigated contrasts over the CERAD-TS1, suggesting that the mere application of equal weights is inadequate to promote better diagnostic discrimination in PD populations. The original Chandler CERAD-TS1[152] implies maximum raw scores of 24 for the subscale Animal Naming and 30 for the subscale Word List Learning, accounting for more than half of the TS1 maximum of 100 points. This could have led to an unintentionally sound weighting of subscales in PD populations, as Word List Learning was found to be the most commonly impaired memory scale in PD-MCI and Animal Naming to rank among the most commonly impaired executive functions scale in PD-MCI[44]. Taken together, when developing novel aggregate scores, reasonable weighting of subscales plays an important role[150] and at least z-score-transformation should be considered. Interestingly, the introduction of optimal weights to the CERAD-TS2 in form of the CERAD-TS3 using a two-way regression factor score method[157] did not yield improved discrimination in the PD sample, leading to the notion that CERAD-Plus subscales might be rather equally important for CERAD-TS in PD populations as cognitive impairment might simply be too heterogeneous across PD populations. This is supported by the fact that all ten subscales exhibited factor loadings far above the commonly accepted cutoff of 0.3, ranging from 0.48 to 0.72 (and optimal weights ranging from 0.09 to 0.22). It still should be noted that the most sensitive subscales might differ interindividually and depend on individual cognitive profiles and disease progression.

## 4.3. The role of education in Parkinson's Disease populations

A lack of education has been identified as a potential risk factor for the development of PD-D already a long time ago[71]. Extending this finding, the concept of cognitive reserve[85,86] has been established over the course of years, suggesting that higher educational levels correlate with better cognitive performance and decelerated cognitive decline. Interestingly, individuals with PD-N in the DEMPRAK/LANDSCAPE sample had more years of education compared to individuals with PD-MCI or PD-D. The importance of using education-corrected test-scores in PD population is only further highlighted by the fact that education-corrected CERAD-scores have proven to be more sensitive in the detection of PD-MCI and PD-D[135]. The CERAD-TS2 with age-, gender- and education-corrected z-scores[137] thus provides a promising tool for the cognitive assessment of PD populations for the German-speaking market that should be further implemented in other languages. It should be noted that TMT-A and TMT-B are both available in many different languages (e.g., Chinese, Indian or Arab) with normative data[160]. Likewise, Phonemic Fluency is internationally available (e.g., in Iran) with normative data[161,162]. According to a recent workgroup paper cognitive reserve can be understood as an interplay of differences in innate properties (e.g., genetics) and lifetime exposure (e.g., exercise and activities) resulting in a dynamic model that enables brain processes to deal with cognitive impairment interindividually[163]. This highlights the general need for elderly to participate in and to benefit from leisure activities, physical exercise, or social engagement to possibly absorb degenerative changes in their brain processing.

## 4.4. Strengths & limitations

The major strength of this thesis project was the use of the large, representative DEMPRAK/LANDSCAPE database with 679 individuals of varying cognitive capacities and their extensive neuropsychological characterization, resulting in refined group comparisons. Further strengths reflect that the development of different TS followed clear conceptual guidelines, made use of age-, gender-, and education- corrected normative z-scores for all CERAD-Plus subscales and that the analysis applied conservative statistical procedures. A limitation of this thesis project was that the diagnosis of PD-MCI was made according to criteria available at study set-up[158] and not on more recent, commonly used criteria[47]. As the criteria at study set-up were more liberal and requested only one impaired test score as opposed to two impaired test scores for a Level-II-diagnosis following the current criteria, the sample of this thesis project could potentially include too many individuals with PD-MCI as a result of overidentification with PD-MCI.

## 4.5. Future Directions

Given the multifactorial aetiology of cognitive dysfunction in PD with various ways of inflicting disease burden individually tailored, multimodal disease management, including direct measures based on pharmacological and non-pharmacological treatments and indirect measures based on treating risk factors and comorbidities will ensure best possible patient care[16]. The accurate assessment of cognitive capabilities in individuals at risk or with PD is a prerequisite for this objective and gets further highlighted as non-motor symptoms including cognitive impairment have a bigger impact on health-related quality of life (HRQOL) than motor symptoms[164]. The authors further notice that the decline in HRQOL is stronger influenced by non-motor symptoms than by motor symptoms, even though they define individuals' disease stages [164]. While motor symptoms are subject to common dopaminergic pharmacological treatment options non-motor symptoms often remain untreated[11,15] or unreported[13], even though MDS guidelines on the treatment of non-motor symptoms exist[128] and cognitive trainings are able to elevate cognitive abilities in individuals with PD-MCI[120]. An extensive and accurate assessment of possible non-motor symptoms thus seems to be the fundament for individual disease management.

On a global scale, the impact of PD is immense as PD is the fastest growing neurological disorder regarding prevalence, disability, and death[5] with the global south being hit the hardest as resources and treatment options are often scarce, but also as prevalence rates are expected to rise in particular in the global south[16]. This makes it imperative to address differences found between white and black individuals with PD[165], but also to globally improve the accessibility to health care. With telecommunications being an important driver of socioeconomic development in the global south, remotely based disease management via smart-phones could potentially provide an important development step for lower-income countries.

The Covid-19-era has powerfully catalyzed the use and evaluation of telemedicine as discontinuity in therapy had negatively affected motor and non-motor symptoms in individuals with PD[166]. So far PD research has successfully established virtual visits over videoconferences[167] with recent adaptations in developing countries[168], disease monitoring via smartphones[169,170] or accelerometers[126], the use of various apps covering domains like rehabilitation, motivation or medication adherence[171] and different training forms, such as multi-domain cognitive trainings[126]. Regarding diagnostics in PD the administration of the MoCa as a cognitive screening instrument via video conferencing has been successfully tested[172] and an app-based electronic version of the MoCA shows adequate convergent validity to its pen and paper version[173]. PD-Specific, comprehensive, cognitive test batteries using remote measurements technologies have not yet been introduced for the accurate assessment in PD populations. Fully digitalized cognitive test batteries, including device- and

online-based batteries covering varying cognitive domains, however, have been successfully designed for AD and are in use already[174]. Interestingly, some of them include executive functions subscales from the CERAD-Plus battery, namely TMT-A and TMT-B[175,176], showing their potential to be administered online. This calls for the development of remote, comprehensive, PD-specific, cognitive test batteries that can differentiate between diagnostic PD groups and are sensitive to cognitive change at early disease stages. The CERAD-Plus test battery could be used as a promising start for the development of a remote PD-specific cognitive test battery with the CERAD-Plus-TS, inherently offering age-, gender-, and education-adjusted test scores.

It is important to keep in mind that cognitive assessment needs to rely on validated, established measures and may not be entirely replaced by telemedicine and still needs to be based on clinicians' expertise and intuition. There are also challenging bottlenecks to telemedicine like access to internet, network reliability or device usability skills of patients and caregivers amongst others[174]. Still, when patients' frailty makes in-clinic consultations impossible or when simple disease progression monitoring seems valuable, telemonitoring might enhance the diagnostic process with relatively simple means at low cost. This potential was proven by a webcam-based approach, showing that simple motor tasks performed by individuals with PD were rated almost as precise by artificial intelligence as by trained experts[177]. Further, speech monitoring analysis via mobile phone networks proved to correctly estimate individuals' UPDRS scores[178]. Another remote, smartphone-based approach is currently gathering active and passive data to detect early sensor-based PD markers[179]. Moreover, eye-tracking seems like a promising technology as it has successfully classified PD populations into cognitive subtypes of PD-N, PD-MCI and PD-D[180]. Further research could try to establish home-based eye-tracking via video recordings on mobile devices to provide regular follow-up diagnostics, but potentially also to introduce cheap first-line diagnostics in low-income countries where trained neurologists are scarce.

Looking ahead into a perfect future device-based remote technology will be able to enhance disease management by extensively assessing and monitoring motor and non-motor symptoms of individuals with PD or of individuals at risk and will use multimodal, artificial intelligence-based diagnostic procedures that are currently outperforming single modality diagnostic approaches[181]. At the same time device-based remote technology will be able to provide individually tailored direct measures in the form of multimodal trainings or indirect measures in the form of medication adherence support or preventive lifestyle trainings, including the boostering of cognitive reserves. Asking for the moon, the sun and the stars, this extensive form of disease management will then be realized within a single application and offered in multiple languages for free so that the global burden of PD can be rightfully handled.

## 4.6. Conclusion

This thesis project was the first to establish and validate the CERAD-Plus test battery with its executive function subscales, integrated in the newly developed CERAD-Plus-TS, in a large, representative PD population of heterogeneous cognitive functioning. ROC-analyses demonstrated the ability of the CERAD-Plus-TS to successfully discriminate PD groups of varying cognitive capacities. This highlights the role of non-amnestic cognitive subscales, reflecting executive functions, processing speed and visuo-spatial functions, in diagnosing PD populations and should thus be considered for a broader application in clinical context. The CERAD-Plus-TS still needs further validation and should be tested in PD populations, diagnosed according to the most recent diagnostic criteria for PD-MCI and could also be considered of interest in non-PD populations

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