Cognitive dysfunction in Parkinson's disease:

From early symptoms to diagnosis

Kumulative Dissertation

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Studies included in the cumulative dissertation

The present cumulative dissertation is a summary of the scientific results from three different studies. The comprehensive scientific articles were accepted/published in the following peer-reviewed journals:

I. **Fengler S**, Liepelt-Scarfone I, Schäffer E, Brockmann K, Berg D, Kalbe E (accepted). Cognitive dysfunction in prodromal Parkinson´s disease: a qualitative review. *Movement Disorders*.

II. **Fengler S**, Kessler J, Timmermann L, Zapf A, Elben S, Wojtecki L, Tucha O, Kalbe E (2016). Screening for Cognitive Impairment in Parkinson's Disease: Improving the Diagnostic Utility of the MoCA through Subtest Weighting. *Plos One,* 11(7): e0159318.

III. **Fengler S**, Roeske S, Heber I, Reetz K, Schulz J B, Riedel O, Wittchen HU, Storch A, Linse K, Baudrexel S, Hilker R, Mollenhauer B, Witt K, Schmidt N, Balzer-Geldsetzer M, Dams J, Dodel R, Gräber S, Pilotto A, Petrelli A, Fünkele S, Kassubek J, Kalbe E (2016). Verbal Memory Declines More in Female Patients with Parkinson's Disease: the Importance of Gender-Corrected Normative Data. *Psychological Medicine,* 19, 1-12.

List of Abbreviations

AD	Alzheimer's Disease
ANCOVA	Analysis of Covariance
AUC	Area under the Curve
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CSF	Cerebrospinal Fluid
DLB	Dementia with Lewy Bodies
GDS	Geriatric Depression Scale
LANDSCAPE	Langzeitbeobachtung dementieller Symptome und cognitiver Parameter sowie Anwendbarkeit neuer prognostischer Marker bei der Parkinson-Erkrankung
LEDD	Levodopa Equivalent Daily-dose
MCI	Mild Cognitive Impairment
MDS	Movement Disorder Society
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
NMS	Non-motor Symptoms
NPV	Negative Predictive Value
PD	Parkinson's Disease
PD-D	Parkinson's Disease Dementia
PD-N	PD Patients without Cognitive Impairment
PD-MCI	PD Patients with Mild Cognitive Impairment
PPV	Positive Predictive Value
RBD	Rapid Eye Movement Sleep Behavior Disorder
ROC	Receiver Operating Characteristic
SD	Standard deviation
UPDRS III	Unified Parkinson's Disease Rating Scale – Motor Symptoms

1. Introduction

1.1 Parkinson's disease

With over six million people being affected worldwide, Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD; Muangpaisan et al., 2011). It is a multisystem disorder which is characterized by two major disease processes: the accumulation of intraneuronal Lewy bodies/Lewy neurites containing misfolded fibrillar α-synuclein, and the degeneration of dopaminergic neurons in the substantia nigra pars compacta leading to the core motor symptoms bradykinesia, resting tremor, and rigidity (Fearnley and Lees, 1991). In the past decade, it has become more and more recognized that PD is a mixed motor, non-motor and multiorgan disorder rather than a pure movement disorder (Chaudhuri and Sauerbier, 2016), and that a variety of non-motor signs and symptoms may accompany motor parkinsonism. These include autonomic (gastrointestinal dysfunction, orthostatic hypotension, urinary and sexual dysfunction), sleep (impaired sleep initiation and maintenance, rapid eye movement behavior disorder, excessive daytime sleepiness), sensory (pain, hyposmia, visual dysfunction), and neuropsychiatric (cognitive dysfunction, anhedonia, depression, anxiety, and psychosis) disturbances (Goldman and Postuma, 2014, Schrag et al., 2015, Noyce et al., 2012).

1.2 Prevalence and relevance of cognitive dysfunction in Parkinson's disease

Mild cognitive impairment (PD-MCI) is one of the most common and relevant non-motor-symptoms with about 25% of PD patients being affected (Aarsland et al., 2010). Already a relatively high proportion of incident, drug-naïve PD patients exhibits cognitive dysfunction with different reported prevalence rates ranging from 10 to 23.5%, depending on the research criteria that were applied (Weintraub et al., 2015, Muslimovic et al., 2005, Poletti et al., 2012). Evidence suggests that cognitive dysfunction may even predate the development of motor symptoms in PD (e.g. Sanchez–Ferro et al., 2013, Webster Ross et al., 2012). However, research in this field is in its infancy and studies have been scarce and methodically heterogeneous.

PD-MCI is highly relevant, as it limits PD patients' quality of life (Reginold et al., 2013, Lawson et al., 2014), increases caregiver burden (Leroi et al., 2012) and is an important risk factor for Parkinson's disease dementia (PD-D; Emre et al., 2007, Litvan et al., 2011) which in turn is a crucial indication for institutionalization (Aarsland et al., 2004), and is related to worse disease prognosis (Velseboer et al., 2013, Bosboom et al., 2004) and mortality (Buter et al., 2008, de Lau et al., 2014).

1.3 Cognitive profile of PD patients

Executive dysfunction is a consistent finding in PD (Kudlicka et al., 2011), and the non-amnestic single domain MCI subtype with executive dysfunction is the most frequent MCI subtype in PD (Litvan et al., 2011, Kalbe et al., 2016) – also in drug-naïve de novo patients (Muslimovic et al., 2005). Memory impairment also occurs often (Muslimovic et al., 2005) but the frequency is less high than for executive dysfunction (Caviness et al., 2007). This pattern has also been described for drug-naïve newly diagnosed PD patients (Muslimovic et al., 2005, Poletti et al., 2012), although data are inconsistent, as memory was the most affected domain in a recent large sample of newly diagnosed PD patients (Weintraub et al., 2015).

1.4 (Early) Diagnosis of cognitive dysfunction

Next to pharmacological therapy which is available for PD-D (Wang et al., 2015) but not for PD-MCI yet, non-pharmacological treatments to enhance cognition in PD or to prevent a further deterioration of functioning of cognitively impaired PD patients have attracted increasing interest with promising results e.g. for cognitive training (Leung et al., 2015, Hindle et al., 2013, Kalbe and Folkerts, 2016) and physical exercise (Hindle et al., 2013, Leung et al., 2015, Reynolds et al., 2016). It can be assumed that patients with milder forms of cognitive impairment are the ideal target group for interventions aimed at preventing or slowing the onset of PD-D. Future interventions are in fact likely to yield the greatest benefit if initiated in an early phase, when cognitive deficits are mild (Pedersen et al., 2013).

Thus, for an optimal management of PD patients, early detection of cognitive symptoms in clinical practice is of utmost importance. Generally, a broad range of conventional neuropsychological test instruments can be used to detect cognitive impairment in PD. Next to comprehensive and psychometrically sound neuropsychological test batteries, which are the gold standard in the detection of cognitive impairment, cognitive screening tests have high value as a time-economic, easy-to-use tool for a first step in detecting cognitive impairment in clinical practice. The most frequently used cognitive screening instruments in PD are the Mini Mental State Examination (MMSE; Folstein et al., 1975) and the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), which has been developed specifically for the detection of milder cognitive deficits. Furthermore, PD-specific instruments have been developed, e.g. the PANDA (Kalbe et al., 2008).

1.5 Scientific research questions

This dissertation aims at providing scientific insight and knowledge regarding the manifestation and detection of cognitive impairment at different stages of PD and at different levels of cognitive impairment. The following topics were investigated:

- Study 1: Cognitive dysfunction in prodromal Parkinson's disease: a qualitative review
- Study 2: Screening for cognitive impairment in Parkinson's disease: Improving the diagnostic utility of the MoCA through subtest weighting
- Study 3: Verbal memory declines more in female patients with Parkinson's disease: The importance of gender-corrected normative data

2. Overview of the scientific contributions

The three studies have been prepared for publication and accepted/published in international peer-reviewed journals. Table 1 gives an overview of the individual scientific contributions of the doctoral candidate and the co-authors and the current status of publication.

Table 1. Overview of the scientific contributions in studies I, II, III

Study I: Cognitive dysfunction in prodromal Parkinson´s disease; a qualitative review							
Journal	**Status**	**Idea&Concept**	**Data collection**	**Data Analysis**	**Data Interpretation**	**Preparation Manuscript**	**Review&Feedback**
Movement disorders	Accepted on 26 June 2017	Fengler, Kalbe	Fengler	Fengler	Fengler, Kalbe	Fengler, Kalbe, Liepelt-Scarfone, Brockmann Schäffer	Fengler, Kalbe, Berg, Liepelt-Scarfone, Brockmann, Schäffer
Study II: Screening for cognitive impairment in Parkinson's disease: Improving the diagnostic utility of the MoCA through subtest weighting							
Journal	**Status**	**Idea&Concept**	**Data collection**	**Data Analysis**	**Data Interpretation**	**Preparation Manuscript**	**Review&Feedback**
Plos One	Published on 20 July 2016	Fengler, Kalbe	Fengler, Zapf	Fengler	Fengler, Kalbe	Fengler, Kalbe	Fengler, Kalbe, Tucha, Kessler, Timmermann, Zapf, Elben, Wojtecki
Study III: Verbal memory declines more in female patients with Parkinson's disease: The importance of gender-corrected normative data							
Journal	**Status**	**Idea&Concept**	**Data collection**	**Data Analysis**	**Data Interpretation**	**Preparation Manuscript**	**Review&Feedback**
Psychological Medicine	Published on 19 May 2016	Fengler, Kalbe	LANDSCAPE consortium	Fengler, Dams	Fengler, Kalbe	Fengler, Kalbe	Fengler, Kalbe, Roeske, Heber, Reetz, Schulz, Riedel, Wittchen, Baudrexel, Hilker-Roggendorf, Mollenhauer, Witt, Schmidt, Balzer-Geldsetzer, Dams, Dodel, Gräber, Pilotto, Petrelli, Fünkele, Kassubek

3. Summary of the scientific contributions

3.1 Study I: Cognitive dysfunction in prodromal Parkinson's disease: a qualitative review.

Background

Originally, PD was conceptualized as a motor disease, and its diagnosis is still based on the core motor features (Postuma et al., 2015). Today we know that 40-60% of the dopaminergic neurons are already degenerated at the time when motor symptoms allow a clinical diagnosis (Morrish et al., 1998, Fearnley and Lees, 1991, DeKosky and Marek, 2003). This timespan in which neurodegeneration is proceeding without leading to classical motor symptoms is termed "prodromal phase of PD" (Berg et al., 2014).

During the prodromal phase of PD, a wide variety of clinical "non-motor symptoms" (NMS) may occur, including gastrointestinal symptoms such as constipation, olfactory dysfunction (hyposmia), sleep disorders (rapid eye movement behavior disorder and excessive daytime sleepiness), and neuropsychiatric symptoms such as depression and anxiety (Goldman and Postuma, 2014, Noyce et al., 2012, Schrag et al., 2015; see chapter 1.1).

Given the high amount of neuronal damage present at the time of clinical diagnosis of PD, it is not surprising that the effectiveness of currently available interventions on disease modulation is limited. In this context, the understanding of NMS in the prodromal phase of the disease may perspectively help to reliably identify at-risk individuals, and by this means foster the understanding of pathomechanisms as well as the development of disease-modifying interventions (Olanow and Obeso, 2012).

Therefore, the aim of the review was to identify and critically evaluate the current knowledge with regard to prodromal cognitive symptoms in PD and thus provide the first comprehensive literature review on this topic. Findings from different kinds of human studies were gathered to provide evidence on the occurrence, frequency, and type of cognitive dysfunction in this phase as well as on the best suited neuropsychological assessments to identify these symptoms.

Data stemming from studies with individuals with a later clinical diagnosis of PD, with genetic variations associated with PD, hyperechogenicity of the nucleus subthalamicus or a family history of PD, and finally individuals with PD pathology or cerebrospinal fluid (CSF) markers of PD were presented.

Method

A systematic literature search for peer-reviewed articles in English language with studies published until February 2017 using the databases PubMed and PsycINFO was performed. A wide range of keyword combinations was used (see full article for comprehensive presentation of keywords). Studies were included if either a clinician`s statement on the subjects' cognitive state (medical records) or cognitive testing was applied. The latter studies needed to include either a clear cut-off value to rate normal or impaired cognitive state, standard scores allowing to classify presence of cognitive impairment, or a comparison of cognitive data of the target group with that of a control group. Moreover, studies focusing on the relation between cognitive functions and imaging data were included, i.e. studies in which cognition-related imaging data of the target group were compared with that of a control group or with reference values in the respective brain areas. Studies were categorized into four main subtypes: (i) prospective and retrospective studies in individuals (with or without prodromal markers) with future PD diagnosis, (ii) prodromal PD at-risk cohort studies (individuals with combinations of PD risk and/or prodromal markers), (iii) studies referring to populations with genetic, or other, risk factors for the later development of PD (except for a genetic vulnerability and SN hyperechogenicity, other risk markers were not considered, because those markers are related to a lower risk of PD development), and (iv) studies on patients with verified PD pathology, but without a clinical diagnosis of PD. The results were presented and discussed in a narrative review.

Main Results

In total, 286 articles from 5094 hits were retrieved for detailed analysis, and 60 fulfilled all inclusion criteria: Nine studies with individuals with a later clinical diagnosis of PD, four prodromal PD at-risk cohort studies (individuals with combinations of PD risk and/or prodromal markers), 26 studies with individuals with genetic risk markers of PD, twelve studies with individuals with hyperechogenicity of the nucleus subthalamicus or with a family history of PD, and nine studies with individuals with PD pathology or CSF markers of PD.

The following conclusions with regard to the presence and profile of cognitive dysfunction in prodromal PD can be derived from these studies: (i) Evidence indicating prodromal executive dysfunction is the most frequent finding, irrespective of the methodical approach (ii), memory deficits appear to be the second most frequently affected cognitive domain in the prodromal phase of PD (iii), attention seems to be less affected but is also less frequently investigated,

and (iv), no evidence for visuospatial or language deficits exists so far. Finally, (v) global cognition was also reduced in a substantial number of studies at least in some participants of the study sample, but this reduction seems less frequent than impairment in executive functions or memory.

Discussion

The data indicating that a substantial part of the patients may have cognitive problems in the prodromal phase of PD is in line with evidence from newly diagnosed drug-naïve PD patients showing that a relatively high proportion of incident PD patients exhibits cognitive dysfunction (Weintraub et al., 2015, Muslimovic et al., 2005, Poletti et al., 2012). Also the profile of prodromal cognitive problems with executive dysfunction as the most frequently and memory as the second most frequently affected domain matches the previously described cognitive profile of early-stage PD patients, also in drug-naïve newly diagnosed PD patients (Muslimovic et al., 2005, Poletti et al., 2012, Litvan et al., 2011, Caviness et al., 2007).

However, knowledge on prodromal cognitive dysfunction in PD is limited due to the small number of prospective studies and other investigations with individuals with a later established PD diagnosis. Further research is needed, especially with regard to prospective longitudinal study designs to assess the emergence of cognitive symptoms over time and evaluate their validity as predictive markers for subsequent onset of motor symptoms, and to determine the most sensitive cognitive markers. Looking for compensatory functional brain changes might also be a fruitful approach to unravel early changes of cognitive processing (Vemuri et al., 2009), particularly since the potential at-risk groups may be too early in the disease process to have clinically assessable cognitive symptoms.

Despite these limitations, the results of the current review suggest that it might be worthy to consider the incorporation of cognitive tests, especially assessing executive dysfunction, as additional non-motor markers into PD “risk scores” which are algorithms screening for combinations of prodromal features sensitive for the identification of individuals at high risk for PD (Winkler et al., 2011).

3.2 Study II: Screening for cognitive impairment in Parkinson's disease: Improving the diagnostic utility of the MoCA through subtest weighting

Background

As already outlined in chapter 1.2, cognitive dysfunction is frequent in PD and has become increasingly recognized as major contributor to worse patient outcomes, quality of life, caregiver burden (Leroi et al., 2012), and institutionalization (Aarsland et al., 2004), and is related to disease prognosis (Velseboer et al., 2013) and mortality (Buter et al., 2008, de Lau et al., 2014). Thus, for an optimal management of symptoms in PD patients, early detection of cognitive symptoms in clinical practice is highly relevant.

The Montreal Cognitive Assessment (Nasreddine et al., 2005) is a widely used cognitive screening tool that has been recognized to be efficient in detecting cognitive symptoms in PD patients (Chou et al., 2010, Dalrymple-Alford et al., 2010, Hoops et al., 2009). It has been shown to be more sensitive than the Mini Mental State examination (Folstein et al., 1975), especially for detecting milder cognitive symptoms (Dalrymple-Alford et al., 2010, Nazem et al., 2009, Lessig et al., 2012).

The subtests of the MoCA include visuospatial and executive function tasks (alternating trail making, a cube copy task, clock-drawing), a naming task (animal naming), attention tasks (digit span, target tapping, serial subtraction), language tasks (repetition, verbal fluency), an abstraction task, memory tasks (verbal learning and delayed recall task of five words), and finally six global orientation questions (see Appendix 1 for a German version of the test). The combination of subtests can be regarded as a strength of the MoCA, given that a broad range of cognitive domains is covered and assessed with established test paradigms, including very sensitive tasks for the evaluation of executive dysfunction (Ismail et al., 2010) which is especially relevant in PD (Caviness et al., 2007, Dirnberger and Jahanshahi, 2013). However, it is striking that the scoring procedure of the MoCA does not reflect the discriminant power of the individual subtests but is rather based on the raw scores of the subtests which are simply summed up to a total score of 30 points.

The aim of the study was thus to develop an alternative scoring procedure for the MoCA which considers the subtests' individual power to detect cognitive symptoms in PD, and to test whether it improves the ability to discriminate patients with PD-MCI and PD-D from PD patients without cognitive impairment (PD-N). A scoring algorithm was developed and tested in a first study including a sample of PD patients and then evaluated in a second study on an independent sample of PD patients. The diagnostic accuracy of the "classical" MoCA and the

MoCA with the revised scoring system was calculated and compared in both the original dataset (study 1) and the validation dataset (study 2).

Method

In both studies, data from neuropsychological routine testing of consecutively recruited inpatients with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (Hughes et al., 1992) seen at the Parkinson's Disease and Movement Disorders Unit of the Department of Neurology, University Hospital of Cologne, Germany, were included. Patients were classified as PD-N or as PD-MCI or PD-D patients according to the Movement Disorder Society (MDS) Task Force Level II criteria for PD-MCI (Litvan et al., 2012) and MDS criteria for PD-D (Emre et al., 2007), respectively. The neuropsychological examination was conducted by an experienced neuropsychologist. In accordance with the MDS task force criteria for PD-MCI and PD-D, each cognitive domain (memory, executive functions, attention, language, and visuospatial functions) was assessed with two neuropsychological tests.

In order to develop the new scoring system, the diagnostic accuracy of each MoCA subtest was assessed with receiver operating characteristic (ROC) by calculating the area under the curve (AUC). In a first step, the AUC values of the subtests were divided into six groups in which minor AUC values of ≤ 0.5 received the minimum of 0 points and in which each further decimal AUC value received one additional point. Thus, each MoCA subtest was assigned to one of the six groups described and received the according sum of points. In a second step, the relative weight of every MoCA subtest was calculated. In the third and final step, the new weight was multiplied by 30 and rounded to an integral number in order to retain a total score of 30. The conversion table for scoring of the MoCA subtests can be found in Appendix 6.2. The diagnostic accuracy of the original and the revised MoCA total score were compared by means of their sensitivity, specificity, Youden's Index, positive predictive value (PPV), and negative predictive value (NPV).

Results

In study 1, forty PD patients were recruited (n=15 with PD-N, n=14 with PD-MCI, n=11 with PD-D). Mean age was 65.4 years (*SD*=9.8). The AUCs for the MoCA subtests ranged between 0.51 and 0.83. Sensitivities and specificities of the original and the weighted MoCA score were compared using the original cutoff of 26/30 for cognitive impairment. Analyses showed that

the original MoCA total score discriminated PD patients with preserved cognition (PD-N) from those with cognitive impairment (PD-MCI and PD-D) with a sensitivity of 62.5% and a specificity of 77.7% Youden's Index=0.41), while the weighted MoCA total score had an increased sensitivity of 92% and a slightly reduced specificity of 73% (Youden's Index=0.65). The PPV of the original MoCA for the detection of any cognitive disorder was 75%, and the NPV was 52.6%. The PPV of the weighted MoCA increased to 88.5%, and the NPV increased to 77.8%.

In study 2, twenty-four PD patients were recruited (n=8 with PD-N, n=10 with PD-MCI, n=6 with PD-D). Mean age was 65.1 years (*SD*=10.4). The original MoCA discriminated patients with PD-N from those with impaired cognition (both the PD-MCI and the PD-D group) with a sensitivity of 68.8% and a specificity of 75% (Youden's Index=0.43). In contrast, the new, weighted total score reached a sensitivity of 81.3%, while specificity remained unchanged at 75% (Youden's Index=0.56). The original MoCA score had a PPV of 84.6% and a NPV of 54.6%, while the score based on the new algorithm had a PPV of 86.7% and a NPV of 66.7%.

Discussion

Analysis of the data revealed that the new weighted MoCA total score yields a higher diagnostic accuracy than the original MoCA total score and that it discriminates cognitively preserved from cognitively impaired PD patients more accurately. This result was found both in the original dataset and the validation dataset. This can be explained by the fact that the relatively easy items, for which the probability of a correct response is very high, became less influential in the new weighting. Consequently, those patients that are indeed cognitively impaired do no longer receive numerous points for very easy items that lack a high diagnostic value. As a result, deficits in relevant domains are no longer "masked" or hidden within the total score of the MoCA, and cognitive dysfunctions are more easily detected.

With regard to the specific subtests which are weighted stronger in the new MoCA scoring procedure on the basis of their predictive values, our results correspond largely to findings concerning the typical cognitive deficits associated with PD. The trail making subtest as an executive and the clock-drawing subtest as an executive and visuospatial task were the subtests with the highest predictive value, followed by the cube copy (again a visuospatial task), verbal fluency (again an executive task), and the memory subtests learning and recall. In line with these findings, executive functions are the functions that are most frequently impaired in the early stages of PD (Williams-Gray et al., 2009, Zgaljardic et al., 2006, Henry and

Crawford, 2004), as well as visuoconstructive functions (Galtier et al., 2009, Uc et al., 2005), and memory (Weintraub et al., 2004, Whittington et al., 2006).

With this study, it has been demonstrated that weighting the MoCA subtests according to their respective diagnostic values can optimize diagnostic accuracy in the assessment of cognitive impairment of PD patients. One of the strengths of the proposed approach lies in improving the detection of patients with milder forms of cognitive impairment, who are the ideal target group for interventions aimed at preventing or slowing the onset of dementia. Correspondingly, the study has high clinical relevance. Further studies with larger sample sizes are needed to confirm the higher diagnostic value of the new MoCA scoring algorithm.

3.3 Study III: Verbal memory declines more in female patients with Parkinson's disease: The importance of gender-corrected normative data

Background

Phenotypic heterogeneity in PD is being increasingly recognized (van Rooden et al., 2011). Recently, gender differences have attracted interest as a potential contributing factor to this heterogeneity. There is general agreement that both incidence and prevalence of PD are higher in men than in women (e.g. de Lau et al., 2004, Taylor et al., 2007, Van Den Eeden et al., 2003), women have a higher average age at disease onset (Twelves et al., 2003) and may be more likely to exhibit the tremor-dominant PD phenotype (Haaxma et al., 2007). Next to the core motor symptoms, non-motor symptoms of PD are receiving increasing attention, particularly for their important role in disability and reduction of quality of life. Cognitive impairment is one of the most common and relevant symptoms, with about 25% of PD patients being affected (Aarsland et al., 2010), as already mentioned above.

Studies concerning gender differences in cognition have been scarce and inconsistent. While some studies did not find any effect of gender (Amick et al., 2006, Crizzle et al., 2012, Schendan et al., 2009), other reports indicate that differences exist (Hariz et al., 2003, Lyons et al., 1998, Uc et al., 2009, Hu et al., 2014, Nazem et al., 2009, Szewczyk-Krolikowski et al., 2014). Regarding specific domains, females with PD were found to be superior in both semantic and phonemic verbal fluency (Locascio et al., 2003, Szewczyk-Krolikowski et al., 2014) and inferior in visuospatial abilities (Riedel et al., 2008, Carey et al., 2002, Locascio et al., 2003). In the largest investigation on this topic so far (Pasotti et al., 2012), including 162 male and 144

female PD patients, it was reported that women with PD had significantly higher scores on a delayed verbal recall task, whereas men had better visuospatial abilities.

Contrary to the research design of previously published studies on gender differences in PD, it has to be clarified whether the observed effects are really PD specific or rather reflect a more general gender effect. It has to be taken into account that cognitive functions are known to be different also in healthy men and women (Munro et al., 2012, van Hooren et al., 2007), and that the described gender-specific profiles in PD patients so far resemble those in healthy adults.

Two alternative methods exist to control for gender-related performance differences in the healthy population and thus separate 'regular' gender effects from a disease-specific deterioration of functioning. (i) To include a healthy control group and compare male and female PD patients to healthy men and women, respectively, and (ii) to include only patients but to use gender-corrected normative data. Gender-corrected Z-scores have several advantages; the most important one is that they enable us to quantitatively compare disease-specific cognitive deficits between men and women.

The aim of the current study was to define gender-related cognitive profiles in PD (above and beyond gender differences in healthy adults) in a large and well-defined cohort of patients taken from the LANDSCAPE study (Balzer-Geldsetzer et al., 2011) including patients with different levels of cognitive functions, i.e., PD-N, PD-MCI, and PD-D. We hereby controlled for the most important possible influencing factors age, education, severity of motor symptoms, disease duration, depression and levodopa equivalent daily dose (LEDD).

Method

Data came from the LANDSCAPE study which is a multicentre, prospective, observational cohort study of PD patients that focuses on the natural progression of cognitive impairment in PD and on the identification of factors that contribute to the evolution and/or progression of cognitive impairment. Idiopathic PD patients according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (Hughes et al., 1992) were recruited in eight specialized movement disorder centres across Germany (Aachen, Bonn, Dresden, Frankfurt/Main, Kassel, Kiel, Marburg, and Tübingen) and assessed with a comprehensive clinical and neuropsychological test battery.

Diagnosis of PD-MCI was defined according to the criteria proposed by Petersen (2004), and PD-D was diagnosed according to the consensus guidelines by Emre et al. (2007),

operationalized by Dubois et al. (2007). Neuropsychological assessment was carried out by trained neuropsychologists. The analysis of gender differences in cognitive functions was based on the results of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Plus test battery.

All analyses were performed for the whole group of PD patients included in the study and for each diagnostic group separately (PD-N, PD-MCI, and PD-D). The analyses were carried out in two steps: (1) the association between gender and raw values on the individual neuropsychological tests was evaluated with analysis of covariance (ANCOVA). The following covariates were controlled for: age, disease duration, Unified Parkinson's Disease Rating Scale (UPDRS) III, Geriatric Depression Scale (GDS)-15 score, and LEDD. (2) Gender comparisons of the corrected Z-scores for the individual neuropsychological tests were performed using ANCOVA. In this analysis, again disease duration, UPDRS III, GDS-15 score, and LEDD were controlled for.

Main results

In total, 656 PD patients were included: 267 with PD-N, 292 with PD-MCI, and 97 with PD-D. Average age was 67.2 (*SD*=7.8) for female and 67.9 (*SD*=7.8) for male patients. Female patients had 10.1 (*SD*=1.7) years of formal education and male patients 10.6 (*SD*=1.7) years.

The raw score analysis showed that women performed better on the verbal learning (p=0.01) and verbal recall (p=0.02) task, whereas men outperformed women on the visuoconstructive test (constructional praxis, p=0.002) and figural memory (recall of figures, p=0.006). The differentiated group analysis demonstrated that women's superiority in verbal learning and verbal recall was only significant in the PD-N group (p=0.0005 and p=0.008, respectively), while there were no differences in the two groups with cognitive impairment (PD-MCI, PD-D). In the visuospatial domain (constructional praxis and figural memory), men significantly outperformed women only in the PD-MCI group (p=0.002 and p=0.01, respectively), while no significant differences were found in the other groups.

The pattern that emerged in Z-score analyses was substantially different from that in the raw score analysis: In the overall patient group analysis, men had significantly higher Z-scores on all three verbal memory tests, i.e. verbal learning (p=0.04), verbal recall (p=0.02) and verbal recognition (p=0.05). In contrast, there were no significant differences between men and women for the visuospatial tasks. The differentiated group analysis showed a similar picture: men were significantly superior to women in verbal learning and verbal recall in the PD-MCI

group (p=0.02 and p=0.04, respectively) and for verbal learning also in the PD-D group (p=0.04).

Discussion

One main finding is that the gender-specific cognitive pattern described in other studies could be replicated based on a raw score analysis. This means women perform better in verbal memory while men outperform women in visuospatial abilities. This could be demonstrated both in the analysis of the overall group as well as for the differentiated group analysis (for the PD-N group for verbal learning and verbal recall and for the PD-MCI group for visuospatial skills). The second main finding of our study is that gender-corrected Z-score analysis showed a markedly different pattern: Women were more affected in verbal memory while the difference between genders in visuospatial skills disappeared. This was demonstrated in the overall analysis and the differentiated analysis – for verbal learning in both impaired groups (PD-MCI and PD-D), for verbal recall only in PD-MCI and for visuospatial skills in all three groups.

The fact that using gender-corrected normative data changes the picture of gender-specific cognitive profiles in such a substantial way is striking. It is important to note that our raw score analysis is in line with previous studies showing that women with PD outperform men with PD in the verbal memory domain, while male patients are superior in visuospatial tasks (Carey et al., 2002, Locascio et al., 2003, Pasotti et al., 2012, Szewczyk-Krolikowski et al., 2014). Importantly, although these gender-specific cognitive profiles in PD patients are based on raw score analyses and could thus simply represent a drop of ‘normal‘ performance, they have been interpreted as PD related. Our gender-corrected Z-score analysis clearly demonstrates that raw score analyses are misleading and that the interpretation of these profiles should be taken with caution. We conclude that the profile described so far may have to be revised.

Remarkably, although longitudinal data from the LANDSCAPE study are not yet available, the cross-sectional data provide preliminary evidence that this decline may accelerate from the stage of PD-MCI to that of PD-D, as the discrepancy between men and women increases. In other words, the advantage in verbal memory that healthy women and female PD patients without cognitive impairment typically show disappears with increasing disease progression, and in later stages this domain becomes even more vulnerable compared to male healthy individuals and PD patients.

Possible explanations for this may be a different cognitive reserve in men and women, the effects of endogenous sex hormones, or differential effects of levodopa treatment on men and women.

Despite a very careful study design, the present study may carry several limitations. First, our neuropsychological test battery was limited, as both visuoconstruction and figural memory were tested with only one test each. Second, with regard to the development of affected domains, it should be noted that longitudinal data from our patients were not yet available. Third, severely demented PD patients were not included, limiting conclusions to only mild stages of PD-D. Finally, the recently established PD-MCI criteria according to Litvan et al. (2012) were not used, as these criteria were published after onset of the LANDSCAPE study.

In conclusion, the results of our study disclose that in contrast to the findings of previous studies, women may be more detrimentally affected by PD in verbal memory, and this effect may increase with the progression of cognitive dysfunction. Furthermore, men and women with PD seem not differentially affected in the visuospatial domain. Finally, the high relevance of gender-corrected data in the evaluation of cognitive deterioration in PD was emphasized.

4. Discussion and Outlook

The three studies cover multiple facets from the spectrum of cognitive (dys-)function in PD: The nature and frequency of cognitive dysfunction in the prodromal phase of PD, early recognition of cognitive impairment by means of a revised scoring algorithm of a frequently used screening instrument in PD, and finally the description of cognitive gender profiles of PD patients with both normal cognition and at different stages of cognitive deterioration (PD-MCI and PD-D).

4.1 Study I

As already mentioned above, an adequate and early-stage detection of cognitive impairment in PD is of both scientific and clinical relevance. Clinically, identification of cognitive dysfunction is highly relevant since it constitutes a requirement for all kinds of interventions aimed at preventing deterioration of cognitive functions, slowing down the progression of impairment, or even extenuating it. Regarding neuroprotective interventions, it is increasingly recognized that it is essential for interventions to be implemented at the earliest stages of the disease to impact neurodegeneration. This awareness is largely based on the fact that the effectiveness of interventions with encouraging preclinical data could not be confirmed in a

variety of disease-modification trials with PD patients (Athauda and Foltynie, 2015). Scientifically, the detection of prodromal PD and its associated symptoms, including early cognitive dysfunction, is of utmost importance for the definition of sensitive risk markers and thus the selection of suitable candidates for intervention trials.

There are reviews that summarize the existing evidence on several prodromal markers of PD, e.g. for autonomic disorders (Palma and Kaufmann, 2014), REM sleep behavior disorder (RBD; Boeve, 2013), and sleep-wake changes and impaired olfaction (Iranzo, 2013). To my knowledge, Study I is the first comprehensive literature overview that specifically gathers and critically evaluates the available evidence on prodromal cognitive dysfunction in PD in a systematic and comprehensive way. One important contribution of this literature review was that the main limitations of the currently available data on this topic and accordingly the requirements for future studies were compiled:

1. Although studies on individuals carrying genetic risk variants, asymptomatic individuals with PD pathology or CSF markers, and individuals with a family history of PD or hyperechogenicity of the substantia nigra make an important contribution to the field, subsequent development of PD in these individuals is not clear. Only studies on individuals with a later clinical diagnosis of PD can reliably provide information on the prodromal phase of the disease.
2. Studies need to carefully define the prevalence of cognitive dysfunction with established test instruments and clearly defined criteria for impairment.
3. The basic age adjusted prevalence of cognitive dysfunction in the normal population and age-corrected normative data should not be neglected.
4. The distinction between PD and dementia with Lewy bodies (DLB) – another alpha synucleinopathy that is assumed to follow a similar pathophysiological pathway (Berg et al., 2014, Goldman et al., 2014, Walker et al., 2015) – is still under discussion, and it is increasingly accepted that these diseases along the spectrum of Lewy body disorders might represent a continuum rather than independent entities. Accordingly, for most of the at-risk groups mentioned in Study I, conversion to DLB is theoretically possible. Until this issue is resolved, this uncertainty needs to be taken into account.
5. Studies are needed to investigate the influence of neuropathological features on cognitive aspects prior to the clinical diagnosis of PD.

Recently, the limitations in longitudinal studies focusing on prodromal markers in PD have been summarized (Heinzel et al., 2016). Largely congruent with the conclusions drawn from Study I, the authors reported that the major limitations were found in the domains of PD

diagnosis, prodromal marker assessments, and temporal information on prodromal markers or PD diagnosis. Additional limitations were found to be generalizability of results, statistical methods, study design, and sample size.

The second main contribution of Study I is the finding that despite these limitations, there are strong indications that cognitive and especially executive dysfunction in the prodromal phase of PD exists. Taken together with the heightened awareness of the weaknesses of the available data, this may serve to propel research in this area, especially due to the potential application in clinical and scientific practice: If executive dysfunction proves to be a consistent finding in future studies on prodromal PD fulfilling the above mentioned requirements, it should be considered to include executive dysfunction as additional non-motor marker in PD risk scores, such as recently proposed by Winkler et al. (2011). Although executive dysfunction alone may not be specific enough on its own, it may constitute one component that can be combined with other risk markers for the detection of at-risk groups and therefore suitable candidates for intervention trials. The MDS research criteria for prodromal PD (Berg et al., 2015) which have recently been tested for usefulness in the general elderly community, and were found to be a promising tool to identify cases of incident PD over 5 years (Mahlknecht et al., 2016), may be supplemented by early executive dysfunction if it proves to be predictive in future studies. There are several ongoing studies that will hopefully contribute to fill this knowledge gap and shed light on the yet undefined aspects of prodromal symptoms in PD, once that follow-up data will be available (Jennings et al., 2014, Siderowf et al., 2012, Berg et al., 2012, Liepelt–Scarfone et al., 2013, Gaenslen et al., 2014).

It can be concluded from the above that research on the prodromal phase of PD has great potential to further change and explicate the evolving disease concept and therapeutic possibilities in a substantial way and may help exploit the potential of treatment at a stage when it is still possible. Study I contributed to this by summarizing the available evidence and making recommendations for highly needed future studies.

4.2 Study II

For the correct and early detection of cognitive dysfunction as described above, test instruments that are sensitive and tailored to the patient group in question are a crucial component of the diagnostic process. In the context of PD, the MoCA is used frequently (Dalrymple-Alford et al., 2010, Hoops et al., 2009, Chou et al., 2014) and has been

recommended by the MDS Task Force Guidelines (Litvan et al., 2012) and in the French consensus procedure for assessing cognitive function in PD (Dujardin et al., 2016).

Despite its frequent use and promising results regarding diagnostic power (Nazem et al., 2009, Lessig et al., 2012, Dalrymple-Alford et al., 2010), the MoCA has a weakness that has been described in detail above: the weighting of the items in the total score does not take into account their individual discriminatory power. Previous studies have investigated the MoCA on a subtest basis (Koski et al., 2009, Koski et al., 2011, Cecato et al., 2016, Freitas et al., 2015) or suggested a short form of the test (Horton et al., 2015, Roalf et al., 2016). To my knowledge, however, there has not been a study examining the items in a systematic and transparent way and also making a practical proposal for future scoring of the original test in the PD population. The proposed algorithm has the potential to substantially improve the diagnostic accuracy for cognitive dysfunction, and especially PD-MCI, in both future research trials and clinical practice. The methodical approach has been described in such a transparent and replicable way that it may serve as incentive for other research groups to develop algorithms for the MoCA tailored to specific diseases, and possibly even for other test instruments that also lack an appropriate weighting of subtests (nearly all cognitive screening instruments, except for some test instruments using a weighted approach for the subtests: DemTect, PANDA, MUSIC, and EASY; Kalbe et al., 2013). This is not a problem that is restricted to cognitive screening instruments. For example, depression screening instruments often have the same difficulty.

With this method, it is possible to exploit the potential of the MoCA more effectively. Because all items from the original test are still included in the revised version and only the weighting has been changed, comparability of raw values to previous studies is warranted. Furthermore, no administrative burden is placed and no major change in implementation has to be taken into account. The implementation of this approach may thus aid to improve the diagnostic process of cognitive dysfunction in PD – with only minor additional cost in terms of time and workload. In clinical practice, only the additional conversion table (see Appendix 6.2) will be necessary to implement the revised MoCA scoring into daily routine.

4.3 Study III

As important as the selection of an appropriate and sensitive test instrument and a meaningful weighting of subtests is the adequate evaluation of scores and the involvement of an adequate reference group. This includes gender-corrected data which were addressed in Study III. The results of the study demonstrate two important things:

Psychometrically, this was the first study that described cognitive gender profiles of PD patients with different states of cognitive functioning by means of gender- (and also age- and education-) corrected normative data based on a large healthy control group. Accordingly, it can be assumed that this is the first study that adequately describes PD-specific cognitive gender profiles. It may thereby raise awareness of the general problem of neglecting gender differences in the normal population when describing specific patient groups. This is a serious methodological flaw and previous studies should be carefully re-evaluated for informative value and meaningfulness. Furthermore, this is not a problem that only affects studies on cognition but it also applies to other studies on the topic of gender differences with regard to PD or other mental or physical illnesses.

With regard to the described gender profile, the finding that – contrary to previous findings – verbal memory declines more in women with PD is striking. Next to the above described necessity to question the previously reported gender-related cognitive profile of PD patients, it also has implications for clinical practice. It may have practical consequences for the non-pharmacological treatment of cognitive impairment in PD, e.g. cognitive training. It can increase the awareness of verbal memory dysfunction in female PD patients and may thereby lay the foundation for the development of specific interventions aimed at preserving verbal memory functions in female PD patients – or at least give information about the different indications of men and women with PD for specific cognitive training modules. Furthermore, it may explain a potentially differential degree of benefit from cognitive training focusing on verbal memory.

A highly relevant topic for future research will be the investigation of intra-individual changes of cognitive (dys-)function in men and women with PD. The LANDSCAPE database offers an ideal framework for this, and the follow-up data will provide important information about the different degree and nature of intra-individual cognitive deterioration in men and women with PD as the disease progresses.

Furthermore, an interesting topic for further investigations would be the pathophysiological basis of verbal memory impairment in female PD patients, as well as the relationship to endogenous sex hormones.

4.4 Conclusion

In conclusion, all three studies are of innovative nature and have the potential to shed further light on the manifestation of cognitive impairment at different stages of PD – from cognitive

symptoms in the prodromal phase to the early detection of mild cognitive dysfunction and finally the detection and description of gender-specific cognitive symptoms in PD patients at different states of cognitive functioning. For the first time, it could be demonstrated that

(i) despite serious limitation and heterogeneity in terms of research design, prodromal and especially executive dysfunction may occur frequently in the prodromal phase of PD

(ii) a revised MoCA scoring algorithm tailored to the cognitive profile of PD patients increases the diagnostic power of the screening instrument

(iii) verbal memory declines more in women with PD and gender-corrected normative data are highly important when describing the gender profile of cognitive functions in PD.

All three studies may lay the foundation for future research and have implications for clinical practice in the treatment of PD patients with (developing) cognitive impairment.

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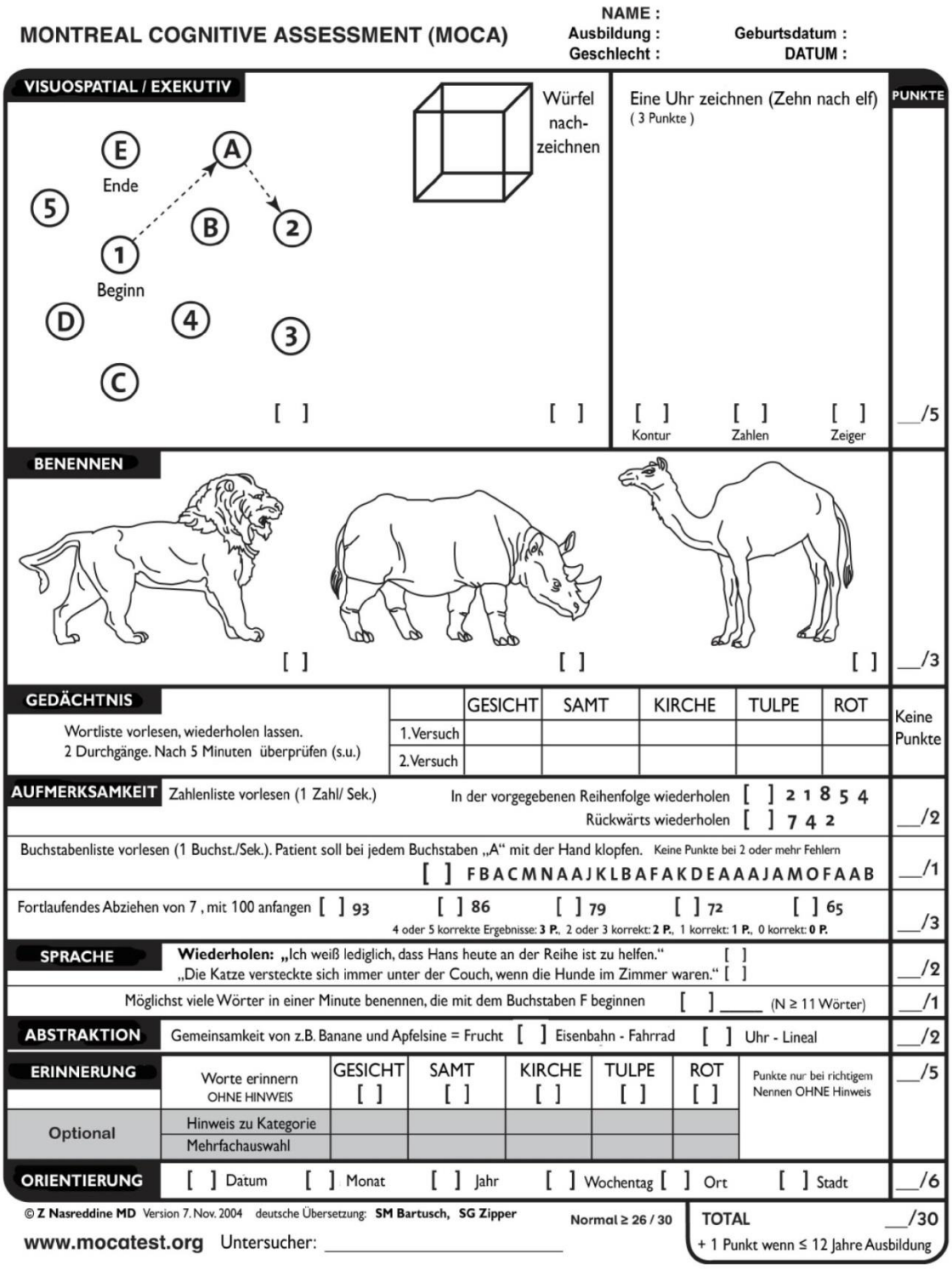
6. Appendix

6.1 German version of the MoCA test



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Ausbildung : Geburtsdatum :
Geschlecht : DATUM :

VISUOSPATIAL / EXEKUTIV — PUNKTE

Würfel nachzeichnen

Eine Uhr zeichnen (Zehn nach elf) (3 Punkte)

[ ] Kontur [ ] Zahlen [ ] Zeiger __/5

BENENNEN

[ ] [ ] [ ] __/3

GEDÄCHTNIS — Keine Punkte

Wortliste vorlesen, wiederholen lassen. 2 Durchgänge. Nach 5 Minuten überprüfen (s.u.)

	GESICHT	SAMT	KIRCHE	TULPE	ROT
1.Versuch					
2.Versuch					

AUFMERKSAMKEIT

Zahlenliste vorlesen (1 Zahl/ Sek.) In der vorgegebenen Reihenfolge wiederholen [ ] 2 1 8 5 4
Rückwärts wiederholen [ ] 7 4 2 __/2

Buchstabenliste vorlesen (1 Buchst./Sek.). Patient soll bei jedem Buchstaben „A" mit der Hand klopfen. Keine Punkte bei 2 oder mehr Fehlern
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Fortlaufendes Abziehen von 7 , mit 100 anfangen [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 oder 5 korrekte Ergebnisse: **3 P.**, 2 oder 3 korrekt: **2 P.**, 1 korrekt: **1 P.**, 0 korrekt: **0 P.** __/3

SPRACHE

Wiederholen: „Ich weiß lediglich, dass Hans heute an der Reihe ist zu helfen." [ ]
„Die Katze versteckte sich immer unter der Couch, wenn die Hunde im Zimmer waren." [ ] __/2

Möglichst viele Wörter in einer Minute benennen, die mit dem Buchstaben F beginnen [ ] _____ (N ≥ 11 Wörter) __/1

ABSTRAKTION

Gemeinsamkeit von z.B. Banane und Apfelsine = Frucht [ ] Eisenbahn - Fahrrad [ ] Uhr - Lineal __/2

ERINNERUNG

	Worte erinnern OHNE HINWEIS	GESICHT [ ]	SAMT [ ]	KIRCHE [ ]	TULPE [ ]	ROT [ ]
Optional	Hinweis zu Kategorie					
	Mehrfachauswahl					

Punkte nur bei richtigem Nennen OHNE Hinweis __/5

ORIENTIERUNG

[ ] Datum [ ] Monat [ ] Jahr [ ] Wochentag [ ] Ort [ ] Stadt __/6

© **Z Nasreddine MD** Version 7. Nov. 2004 deutsche Übersetzung: **SM Bartusch, SG Zipper**

Normal ≥ 26 / 30

TOTAL __/30
+ 1 Punkt wenn ≤ 12 Jahre Ausbildung

www.mocatest.org Untersucher: _____

6.2 Conversion table for scoring of the MoCA subtests

	MoCA Subtest	Original Points	New Points
Visuospatial and executive functions	Alternating Trail Making	0	0
		1	4
	Cube copy	0	0
		1	3
	Clock-drawing	0	0
		1	2
		2	3
		3	5
Naming	Animal Naming	0	0
		1	0
		2	1
		3	1
Attention	Digit Span	0	0
		1	0
		2	1
	Target tapping	0	0
		1	1
	Serial subtraction	0	0
		1	0
		2	0
		3	1
Language	Repetition	0	0
		1	2
		2	3
	Verbal fluency	0	0 to 3 words: 0
		1	4 to 7 words: 1
			8 to 10 words: 2
			> 10 words: 3
Abstraction	Abstraction	0	0
		1	0
		2	1
Memory	Learning	0	3 to 5 words: 1
			6 to 8 words: 2
			9 to 10 words: 3
	Memory	0	0
		1	1
		2	1
		3	2
		4	2
		5	3
Orientation	Orientation	0	0
		1	0
		2	0
		3	0
		4	1
		5	1
		6	1

7. Eigenständigkeitserklärung

Hiermit erkläre ich, dass ich die vorliegende kumulative Dissertation eigenständig und ohne unzulässige Hilfe Dritter sowie ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus fremden Quellen direkt oder indirekt übernommenen Gedanken und Inhalte sind unter Angabe der Quelle als solche kenntlich gemacht. Für die drei wissenschaftlichen Publikationen, die Teil dieser kumulativen Dissertation sind, ist angegeben, welchen Publikationsstatus die Manuskripte haben und welchen Anteil die jeweiligen Autoren an der Erstellung der Publikationen hatten. Diese kumulative Dissertation wurde von mir bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Köln, den 26. Juli 2016

_____

Sophie Fengler

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