Examination of cognitive function in Parkinson's disease

Ph.D Thesis

Tivadar Lucza

Theoretical Medical Sciences
Leader of the Doctoral School: Dr. Júlia Szekeres
Tutors: Dr. Kázmér Karádi and Dr. Norbert Kovács

University of Pécs
Medical School
2015

1. Study

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by both motor and non-motor symptoms including depression, fatigue, and autonomic problems. Among non-motor features, cognitive impairment has one of the most serious consequences by diminishing the quality of life and requiring an increase in caregiver's burden. Based on the findings of long-term follow-up studies, neurocognitive impairment unavoidably evolves by disease progression. According to some recent studies, the prevalence of dementia in PD is approximately 20–40%, furthermore, patients with PD have a six fold risk to develop dementia compared to healthy controls.

Although detection of neurocognitive impairment is of the utmost clinical importance, this task is difficult to accurately perform. One of the problems is the heterogeneity of definitions. Previously, the Movement Disorders Society (MDS) Task Force created definitions for dementia in PD (PDD) and mild cognitive impairment in PD (PD-MCI). Moreover, the PD-MCI diagnosis can also be based on two assessment levels: abbreviated (Level I) and comprehensive (Level II).

Until the publication of the most recent version of Diagnostic and Statistical Manual of Mental Disorders (5th edition, DSM-5) in 2013, the diagnosis of PD MCI was impossible from psychiatric point of view due to the lack of appropriate definitions.

According to DSM-5, minor and major neurocognitive disorders (NCD) in PD may be diagnosed which can be considered as the equivalent versions for PD-MCI and PDD, respectively. Comparing to the previous version (DSM 4th edition text revision, DSM-IVTR), the establishment of mild and major NCD in PD is an important and new enhancement, because previously only the dementia in PD was defined. Therefore, a less severe level of cognitive impairment could not be coded and diagnosed by DSM-4TR.

The newly recognized term of mild NCD due to PD may facilitate research and change clinical practice (e.g., patient selection for deep brain stimulation surgery).

According to DSM-5 mild and major NCD may be diagnosed if evidence of significant or modest cognitive decline from a previous level of performance in one or more cognitive domains can be established, respectively.

This evidence must be supported by both the concern of the individual, a knowledgeable informant, or the examining clinician noting a significant decline in cognitive function, and a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

In the case of major NCD the cognitive deficits interfere with independence in everyday activities, whereas in minor NCD the cognitive deficits do not interfere with capacity for independence in everyday activities, but greater effort, compensatory strategies, or accommodation may be required.

The problem with the establishment of diagnosis is the lack of appropriate clinical screening testing. An ideal screening test should be brief, fast, and appropriately sensitive

and specific for detecting subjects possessing characteristics of cognitive impairment. Detection of minor and major NCD in Parkinson's disease is an important task, because cognitive decline is a frequent and important exclusion criteria for deep brain stimulator (DBS) implantation. Therefore, the necessity of proper screening for cognitive impairment in PD is highly encouraged in clinical practice.

Currently, Mini Mental State Examination (MMSE) is the most commonly used tool for screening cognitive abilities in Hungary. Although it can evaluate orientation, memory, visual abilities, attention and calculation, language, writing, reading, and constructive capabilities, it is not sensitive enough for identifying frontal and executive deficits, and visuospatial dysfunctions. Moreover, it has a limited and poor sensitivity for detecting dementia in early stages and it is also unable to differentiate between major types of dementia if applied alone. Although MMSE has been translated and validated into many languages and used in many countries, it remains unsuitable for judging eligibility for deep brain stimulation of the subthalamic nuclei (STN DBS). Best cut-off value for MMSE is 26 points with the sensitivity of 79.9% and specificity of 74.0% for detecting PDD, but for PD-MCI it remains unsuitable for screening.

Therefore, other dementia screening tests are needed in clinical practice. Although Addenbrooke's Cognitive Examination (ACE) is able to detect early stages of dementia and differentiate some subtypes, its applicability is limited in PD by the lack of widely applicable normative data.

ACE also evaluates the major domains of PDD such as orientation, attention and mental flexibility, episodic and semantic memory, verbal fluency, phonemic and semantic category, aphasia tasks, and visuospatial and constructional ability.

However, ACE was initially developed for differentiating between Alzheimer's disease (AD) and frontotemporal dementia (FTD). The maximum score on ACE is 100 points. ACE was translated into many languages including Hungarian.

ACE was validated in PD in some countries. It has limited (<80%) specificity for detecting PDD (the best cut-off score identifying PDD was 80 points, sensitivity = 74.0%, specificity = 78.1%, positive predictive value = 67.42%, negative predictive value = 83.42%). Therefore, both the original and the revised version of ACE (ACE-R) must be used cautiously as a screening tool for PD-MCI, with results largely influenced by its fluency subdomain score and patient education levels.

Mattis Dementia Rating Scale (MDRS) is also a widely used screening instrument for evaluating dementia. It can measure the domains of attention, initiation and perseveration, construction, conceptualization, and memory. MDRS seems to be sensitive for mediotemporal and frontal pathology, and it is one of the most frequently used screening tools for judging cognitive impairment in European DBS centers. Its maximum obtainable score is 144 points, whereas the cut-off scores for dementia in French and Spanish PD population was 130 and 123 points, respectively. For the Hungarian version, MDRS had a good sensitivity and specificity for detecting PDD (sensitivity = 89.8%, specificity = 98.3%) using the cut-off score of 125 point. Because the administration of MDRS requires a lengthy period (approximately 30–45 minutes) in clinical setting, MDRS is not an appropriate tool to identify dementia in PD in all occasions.

Montreal Cognitive Assessment (MoCA) was developed as a brief, 10-minute bedside assessment tool for detection of mild cognitive impairment and dementia in AD. It measures 7 domains of cognitive functioning, including visuospatial/executive functions, naming, memory, attention, language, abstraction, and orientation. Comparing to MMSE, MoCA is a more sensitive tool for testing executive, visuospatial functions and attention, which areas are most often impaired in PD. MoCA also has high inter rater, test retest reliability, and good discriminant validity for assessing dementia in PD. Further studies demonstrated that MoCA was able to assess broader cognitive domains, and it had higher sensitivity for detecting mild cognitive impairment and dementia in PD. Larner demonstrated better sensitivity and specificity of ACE-R and MoCA over MMSE by comparison. MoCA has been translated and validated into several languages and has several alternative forms to overcome the potential practice effects.

With reference to the authors' awareness none of the above mentioned screening tools were validated against the diagnostic criteria of DSM-5. Therefore, the aim of our study was to establish the diagnostic accuracy of Montreal Cognitive Assessment (version 7.2) as compared to other widely used screening tests for detecting mild and major neurocognitive disorder in a large sample of Hungarian PD patients.

Methods

Participants.
Four hundred and seventy-two consecutive PD patients treated at Department of Neurology, University of Pécs, were recruited for this study. Each patient fulfilled the clinical diagnostic criteria for idiopathic PD. All of the subjects provided a written informed consent according to the approval of the Regional Ethical Board of University of Pécs. History of cerebrovascular disease, alcoholism, or other conditions known to impair mental status besides PD served as exclusion criteria for participation. Each patient had a routine brain MRI (or brain CT if MRI was contraindicated). Patients with focal abnormalities on neuroimaging studies, abnormalities in thyroid hormone levels, or non-compensated systemic diseases (i.e., diabetes, hypertension, heart failure) were also excluded.

Patient Evaluation.
Patients were evaluated using Hungarian versions of Lille Apathy Scale (LARS), Montgomery-Asberg Depression Rating Scale (MADRS), MMSE, ACE, MDRS, and MoCA. Severity of the Parkinsonian symptoms was assessed by the Hoehn & Yahr Scale (HYS) and the Hungarian validated version of Movement Disorders Society Unified Parkinson's Disease Rating Scales (MDS-UPDRS). Patients suffering from depression were excluded from clinical investigation (score > 18 on MADRS and/or fulfilling the criteria of DSM-5 for depression) to minimize the impact of affective syndromes on cognitive performance. Subsequently, the non-depressed PD patients were divided into three groups based on the fulfillment of the clinical diagnostic criteria for minor and major NCD in PD: patients with major neurocognitive disorder (major NCD group), patients with minor neurocognitive disorder (minor NCD group), and patients without either minor or major neurocognitive disorder (normal PD group). To increase reliability, a single experienced investigator categorized each patient into normal, minor NCD, and major NCD groups.

Data Analysis.
Statistical analyses were performed by The R Project for Statistical Computing (Windows version 3.1.2). Because most data did not follow the normal distribution, nonparametric tests (Kruskal-Wallis tests) were applied. Since HYS represents an ordinal scale, Chi-square test was applied for analyses involving HYS. The level of significance was set at 0.05. To measure diagnostic accuracy for neurocognitive batteries, Receiver Operating Characteristic (ROC) curve analysis was obtained to measure sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value, and diagnostic accuracy. Because the ideal cut-off is one which selects an immense amount of disease (high sensitivity) but has very few false positives (high specificity), we chose the best cut-off point for balancing the sensitivity and specificity by identifying the point on the curve closest to the (0, 1) point.

Results

One hundred and two patients expressed a coexistent depression and they were excluded from further analyses. Therefore, the data of 370 patients were analyzed subsequently. Out of the 370 evaluated subjects, 257 had normal cognitive profile, 60 had mild neurocognitive disorder, and 53 had major neurocognitive disorder in PD according to DSM-5 classification. The comparison of the demographic and clinical characteristics between normal, mild NC, and major NC groups is presented in Table 1. Fulfilling our expectations, all the examined dementia screening scales (MDRS, MoCA, MMSE, and ACE) demonstrated significant differences between the normal, mild NC, and major NC groups (Table 1). Based on ROC analysis, MoCA and ACE had the best diagnostic accuracy for detecting mild NCD in PD at the cut-off scores of 23.5 and 83.5 points, respectively (Table 2, Figure 1). The diagnostic accuracy of these tests was 0.859 (95% confidence interval—CI: 0.818–0.894, MoCA) and 0.820 (95% CI: 0.774–0.859, ACE) meaning 85.9% and 82.0% of true positive and true negative cases are identified. The other variables describing the diagnostic accuracy (specificity, sensitivity, positive and negative predictive values, and positive and negative likelihood ratios) are presented in Table 2 with their 95% CI values. Area under the curve (AUC) values are demonstrated in Figure 1. For detecting major NCD, MoCA and MDRS tests exhibited the highest diagnostic accuracy at the cut-off scores of 20.5 and 132.5 points, respectively (Table 3 and Figure 2). The diagnostic accuracy of these tests was 0.863 (95% CI: 0.823–0.897, MoCA) and 0.830 (95%CI: 0.785–0.869, MDRS) meaning 86.3% and 83.0% of true positive and true negative cases are identified. The other variables describing the diagnostic accuracy (specificity, sensitivity, positive and negative predictive values, and positive and negative likelihood ratios) are presented in Table 3 with their 95% CI values. AUC values are demonstrated in Figure 2.

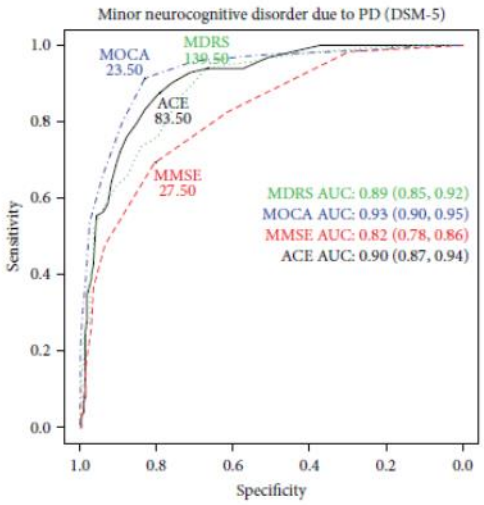

FIGURE 1: Receiver Operating Characteristic analysis of Addenbrooke's Cognitive Examination (ACE), Mattis Dementia Rating Scale (MDRS), Mini Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA) for detecting mild neurocognitive disorder due to Parkinson's disease (PD) in accordance with the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria. Area under the curve (AUC) values are also represented with the 95% confidence interval values.

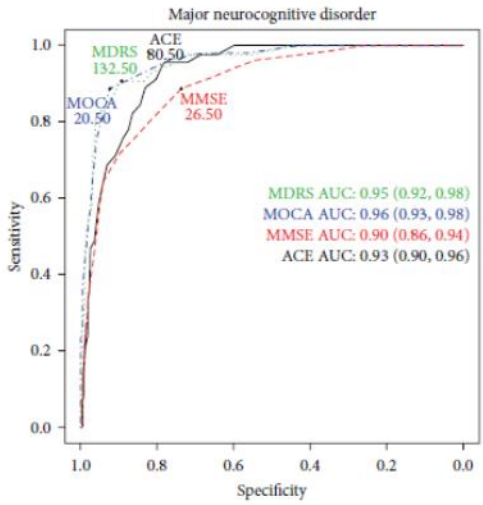

FIGURE 2: Receiver Operating Characteristic analysis of Addenbrooke's Cognitive Examination (ACE), Mattis Dementia Rating Scale (MDRS), Mini Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA) for detecting major neurocognitive disorder due to Parkinson's disease (PD) in accordance with the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria. Area under the curve (AUC) values are also represented with the 95% confidence interval values.

Table 1: Demographic, Parkinson's disease- (PD-) related and neurocognitive data of the study population.

	Normal cognition (n = 257)					Mild neurocognitive disorder due to PD (n = 60)					Major neurocognitive disorder due to PD (n = 53)					p value
	Median	Percentile 25	Percentile 75	Mean	SD	Median	Percentile 25	Percentile 75	Mean	SD	Median	Percentile 25	Percentile 75	Mean	SD	
Age (years)	65	59	70	63.73	10.13	71	65	76	70.35	7.33	74	70	79	74.28	7.03	0.000
Age at onset (years)	57	49	65	56.00	11.69	64	54	68	61.97	10.27	67	56	75	65.25	12.47	0.000
Education (years)	12	11	16	13.04	3.08	12	11	15	12.28	3.00	12	11	15	12.00	2.97	0.124
Sex (male/female)	201 M/56 F					47 M/13 F					42 M/11 F					0.986
Disease duration (years)	6	2	11	7.58	6.74	7	3	12	8.38	6.68	7	3	15	9.08	7.56	0.328
LED (mg)	400	14	885	559.30	544.13	330	14	765	506.80	614.24	334	14	780	490.94	558.59	0.642
MDS-UPDRS Part 1	12	9	17	12.63	5.96	13	10	18	14.13	6.88	13	11	20	13.44	6.64	0.077
MDS-UPDRS Part 2	13	7	19	13.93	8.65	13	9	19	13.35	7.83	16	9	22	15.92	7.83	0.137
MDS-UPDRS Part 3	37	28	46	38.22	14.73	40	34	51	42.07	14.56	50	41	58	48.72	13.55	0.000
MDS-UPDRS Part 4	4	2	6	4.77	3.50	4	2	6	4.12	3.06	4	2	6	4.57	3.21	0.423
Hoehn & Yahr Stage (1/2/3/4/5)	5/157/67/24/4					0/30/20/9/1					0/15/24/11/3					0.001
MADRS	8	5	13	9.48	5.79	10	5	15	10.08	5.97	10	6	15	10.68	5.48	0.092
LARS	−25	−30	−21	−24.01	7.61	−22	−28	−17	−21.91	7.02	−19	−26	−11	−17.79	10.97	0.000
ACE orientation	10	10	10	9.93	0.48	10	10	10	9.81	0.50	10	9	10	9.16	1.30	0.000
ACE attention	8	8	8	7.92	0.40	8	7	8	7.68	0.59	7	6	8	6.78	1.47	0.000
ACE memory	29	26	32	28.41	4.97	23	19	26	22.26	5.73	19	14	24	18.86	6.44	0.000
ACE verbal fluency	10	9	12	10.01	2.48	8	6	9	7.53	2.22	6	4	7	6.05	2.41	0.000
ACE language	28	27	28	27.53	0.97	27	27	28	27.06	0.94	26	26	28	25.89	2.60	0.000
ACE visuospatial	5	4	5	4.23	1.00	4	3	4	3.38	1.21	2	2	3	2.59	1.19	0.000
ACE total score	89	85	93	88.02	7.58	79	73	82	77.72	6.79	70	63	76	69.35	8.88	0.000
MMSE orientation	10	10	10	9.89	0.75	10	10	10	9.85	0.45	10	8	10	9.08	1.25	0.000
MMSE attention	8	8	8	7.90	0.46	8	8	8	7.66	0.82	7	5	8	6.51	1.67	0.000
MMSE memory	2	1	3	2.07	0.91	2	1	2	1.49	0.84	1	0	2	1.02	0.95	0.000
MMSE language	8	8	8	7.71	0.64	8	7	8	7.53	0.82	7	7	8	7.04	1.14	0.000
MMSE visuospatial	1	1	1	0.93	0.25	1	1	1	0.81	0.39	0	0	1	0.49	0.50	0.000
MMSE total score	29	28	30	28.51	1.98	28	26	29	27.34	1.71	25	22	27	24.13	3.09	0.000
MoCA Executive/visuospatial	4	4	5	4.13	0.86	3	3	4	3.14	1.09	2	2	3	2.49	1.10	0.000
MoCA naming	3	3	3	2.99	0.12	3	3	3	2.90	0.36	3	3	3	2.79	0.41	0.000
MoCA attention	6	5	6	5.45	0.84	5	4	6	4.75	1.04	3	3	4	3.49	1.42	0.000
MoCA language	2	2	3	2.35	0.72	2	1	2	1.63	0.91	1	1	2	1.34	0.81	0.000
MoCA abstraction	2	2	2	1.90	0.31	2	2	2	1.66	0.66	2	1	2	1.57	0.67	0.000
MoCA delayed recall	3	1	4	2.44	1.48	1	0	2	1.14	1.20	0	0	1	0.49	0.93	0.000
MoCA orientation	6	6	6	5.97	0.17	6	6	6	5.92	0.28	5	5	6	5.17	1.01	0.000
MoCA total score	26	24	27	25.70	2.28	22	20	23	21.71	2.18	18	17	20	18.08	3.02	0.000
Mattis attention	36	36	37	36.09	1.02	35	35	36	35.36	1.01	35	34	36	34.25	2.25	0.000
Mattis initiation/perseveration	37	34	37	35.23	2.72	34	31	37	33.36	3.23	29	26	31	28.39	4.16	0.000
Mattis construction	6	6	6	5.98	0.23	6	6	6	5.94	0.32	6	6	6	5.58	1.42	0.030
Mattis conceptualization	39	39	39	38.74	1.42	39	38	39	38.45	1.08	38	37	39	37.97	1.18	0.000
Mattis memory	24	23	25	23.52	1.84	22	20	24	21.38	3.96	19	17	21	18.56	3.80	0.000
Mattis total score	141	138	143	139.56	4.72	136	131	138	134.94	4.62	125	123	128	124.75	7.03	0.000

Mild and major neurocognitive disorder because Parkinson's disease was defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria. p values are calculated by Kruskal-Wallis test with the exception of Hoehn & Yahr Scale and sex where Chi-square tests were utilized. ACE: Addenbrooke's Cognitive Examination; F: females; LARS: Lille's Apathy Scale; M: males; MADRS: Montgomery-Asberg Depression Rating Scale; MDRS: Mattis Dementia Rating Scale; MDS-UPDRS: Movement Disorders Society's Unified Parkinson's Disease Rating Scale; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment.

Table 2: Diagnostic accuracy of screening tests for detecting mild neurocognitive disorder due to Parkinson's disease.

	Diagnostic accuracy											
	MoCA			ACE			MMSE			MDRS		
	Estimation	Lower 95% CI	Upper 95% CI	Estimation	Lower 95% CI	Upper 95% CI	Estimation	Lower 95% CI	Upper 95% CI	Estimation	Lower 95% CI	Upper 95% CI
Best cut-off score	23.5			83.5			27.5			139.5		
Sensitivity	0.915	0.848	0.958	0.871	0.790	0.930	0.602	0.540	0.714	0.939	0.873	0.977
Specificity	0.831	0.777	0.877	0.797	0.741	0.847	0.706	0.652	0.723	0.670	0.605	0.730
Positive predictive value	0.733	0.653	0.803	0.647	0.561	0.727	0.623	0.534	0.707	0.550	0.472	0.627
Negative predictive value	0.950	0.911	0.976	0.936	0.892	0.965	0.650	0.598	0.793	0.962	0.920	0.986
Diagnostic accuracy	0.859	0.818	0.894	0.820	0.774	0.859	0.671	0.624	0.712	0.751	0.700	0.797
Likelihood ratio of a positive test	5.417	4.047	7.250	4.302	3.305	5.599	2.575	1.804	3.125	2.843	2.349	3.440
Likelihood ratio of a negative test	0.103	0.057	0.187	0.161	0.097	0.269	0.312	0.259	0.484	0.091	0.041	0.198

Mild neurocognitive disorder because Parkinson's disease was defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria.
ACE: Addenbrooke's Cognitive Examination; CI: confidence interval; MDRS: Mattis Dementia Rating Scale; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment.

Table 3: Diagnostic accuracy of screening tests for detecting major neurocognitive disorder due to Parkinson's disease.

	Diagnostic accuracy											
	MoCA			ACE			MMSE			MDRS		
	Estimation	Lower 95% CI	Upper 95% CI	Estimation	Lower 95% CI	Upper 95% CI	Estimation	Lower 95% CI	Upper 95% CI	Estimation	Lower 95% CI	Upper 95% CI
Best cut-off score	20.5			80.5			26.5			132.5		
Sensitivity	0.921	0.860	0.962	0.869	0.784	0.927	0.692	0.600	0.774	0.566	0.462	0.665
Specificity	0.801	0.738	0.859	0.790	0.737	0.841	0.806	0.752	0.853	0.943	0.905	0.970
Positive predictive value	0.750	0.674	0.816	0.640	0.550	0.714	0.623	0.534	0.707	0.812	0.699	0.896
Negative predictive value	0.953	0.917	0.980	0.921	0.874	0.945	0.850	0.798	0.893	0.835	0.784	0.878
Diagnostic accuracy	0.863	0.823	0.897	0.814	0.764	0.879	0.770	0.724	0.812	0.830	0.785	0.869
Likelihood ratio of a positive test	5.457	4.081	7.297	4.284	3.292	5.575	3.575	2.704	4.725	10.008	5.742	17.442
Likelihood ratio of a negative test	0.095	0.052	0.172	0.162	0.097	0.269	0.382	0.289	0.504	0.460	0.367	0.578

Major neurocognitive disorder because Parkinson's disease was defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria.
ACE: Addenbrooke's Cognitive Examination; CI: confidence interval; MDRS: Mattis Dementia Rating Scale; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment.

Discussion

Screening for NCD in PD is an important clinical necessity for establishing diagnosis and initiating effective and proper treatment. In differentiating between normal cognition from impaired cognitive abilities an easily applicable, reproducible, and validated test battery with high diagnostic accuracy is needed. The aim of our study was to establish the diagnostic accuracy of widely used screening tests for detecting mild and major neurocognitive disorder in PD.

Although some major demographic and PD-related properties (e.g., education, sex, disease duration, and anti-Parkinson medication expressed in levodopa equivalent dosage and severity of depressive symptom measured by MADRS) were comparable, patients with either minor or major neurocognitive disorder were older and had higher age at disease onset and more severe Parkinsonian symptoms (MDS-UPDRS and HYS). This is not a surprising factor, because age and age of disease onset are significant factors for developing major neurocognitive disorder, and the presence of cognitive impairment is associated with more severe gait and postural instability resulting in higher HYS and MDS-UPDRS Part 3 (Motor Examination) values.

To the best of the author's knowledge, this study is the first validating the most popular screening tests against the recently developed mild and major NCD due to PD established by the DSM-5. Based on our results, MoCA had better diagnostic accuracy for detecting mild NCD in PD based on theDSM-5 criteria. Scores <139.5 on MDRS or <83.5 on ACE or <23.5 on MoCA can suggest the presence of mild NCD in PD (DSM-5). Recent studies revealed similar cutoff values for MDRS. Villeneuve et al. suggested a normality cut-off score of 138 points on the MDRS having the sensitivity of 72% and specificity of 86% with a correct classification of 80% for detecting PD-MCI (MDS Task Force criteria). One of the limitations of their study was, however, the relatively low number of PD patients involved (n = 40). Pirogovsky et al. published a different study on MDRS having the sample of 30 patients diagnosed with PD-MCI based on Level II MDS criteria and 68 PD patients with normal cognition. They suggested that a total score of ≤139 for screening purposes yielded a better balance between sensitivity (77%) and specificity (65%). Previously our team also validated MDRS against the PDD criteria (MDS Task Force criteria). In this former study we suggested the usage of 125 points as a cut-off score for diagnosing PDD. However, in the present study we recommended the cut-off of 132.5 points to diagnose major NCD in PD. This apparent difference might be due to the larger sample size (370 versus 73), the difference between the applied diagnostic criteria (major NCD according to DSM- 5 versus PDD established by MDS Task Force), and the discrepancies between the mean educational levels (11.9 +- 4.4 versus 13.0 +- 3.8 years).

Although MMSE is still one of the most frequently used screening tests, it is generally considered unsuitable for reliable NCD identification in PD. Despite the MoCA and MMSE scores which can be converted, MoCA, MDRS, and ACE tests appear to be generally superior for screening NCD in PD. PD subjects with normal range MMSE but abnormal MoCA scores had evidence of caudate nucleus dopaminergic denervation and mild cognitive changes, predominantly in executive function. PD patients with borderline cognitive impairment have impairments in their decisional capacity. The MoCA may be useful to identify the patients at risk of impaired capacity. The Parkinson Study Group Cognitive/Psychiatric Working Group recommended MoCA as a minimum cognitive screening measure in clinical trials of PD where cognitive performance is not the primary outcome measure. The commonly recommended cut-off screening score for dementia of 26 points on the MoCA is too high for PD patients and most studies suggest the utilization 23-24 points for cut-off. However, the application of MoCA in PD-MCI remained

controversial. A recent study demonstrated that MoCA is suitable for screening large population for Parkinson's disease dementia (PDD, according to MDS Task Force criteria). On the contrary, other studies showed that when decline from estimated premorbid levels was considered evidence of cognitive impairment (Level 2 criteria for PD-MCI), both MoCA and MMSE had poor diagnostic accuracy for PD-MCI (65.3%). At the lowest cut-off levels that provided at least 80% sensitivity, specificity was low (44%) for the Montreal Cognitive Assessment. Therefore the authors concluded that MoCA may be able to preferentially detect executive dysfunction compared to the MMSE, but the MoCA has limited diagnostic accuracy for PD-MCI and should not solely be used to substantiate this diagnosis. The MoCA may be more sensitive than the MMSE in detecting early baseline and longitudinal cognitive impairment in PD. Based on the analysis of 95 patients, a MoCA score of ≤26 provided a sensitivity of 93.1% for the diagnosis of PD-MCI. In the longitudinal cohort, baseline MoCA was useful in predicting cognitive decline over 2 years. A baseline MoCA ≤26 was highly predictive of progressive cognitive decline (HR 3.47, 95% CI: 2.38–5.07; $p < 0.01$) over 2 years. This finding was also confirmed by another study. The longitudinal data from 155 patients with PD over 18 months showed significant reductions in MoCA scores, but not in MMSE scores, with 21.3% of patients moving from normal cognition to MCI and 4.5% moving from MCI to dementia.

Conclusions

DSM-5 criteria for diagnosing mild and major NCD in PD are clinically feasible. Although most popular screening tests including MoCA, MDRS, and ACE are proven useful for screening patients, in the risk population the accurate diagnosis should be based on appropriate neuropsychological evaluation.

2. Study
Visuospatial impairment in Parkinson's disease: The role of laterality

Introduction

Asymmetry is a well-known, however, still mysterious phenomenon of PD. Motor symptoms including bradykinesia and rigidity required for establishing the clinical diagnosis of PD emerges unilaterally (Hoehn-Yahr Stage 1). As the disease progresses, the motor symptoms spread over the other side and the symptoms become consequently bilateral. However, the asymmetry is present throughout the whole disease course and the motor symptoms remain more severe on the side on which initially emerged.

Although the pathomechanism of asymmetric symptomology is still unknown, it is a clinical feature that clearly differentiates PD from several other forms of Parkinsonism. According to recent studies, laterality is caused by coincidence of genetic, environmental, structural and neurochemical determinants. Several studies and a recently published meta-analysis demonstrated that handedness and symptom dominance in PD are tightly related with each other in such a way that the PD symptoms appear more often on the dominant hand side with the odds ratio of 2.13. Moreover, handedness and side of disease onset also determine the disease course.

Among non-motor symptoms, cognitive impairment is one of the most troublesome problems in PD emerging inevitably. Several studies focused on the relationship between the asymmetry of PD and cognitive profile; however, their results are highly inconsistent.

Verreyt and coworkers reviewed several articles demonstrating cognitive difficulties in PD patients associated with the side of disease onset. According to their conclusions, PD patients with **right symptom dominance (RPD)** usually had worse performance in tasks of verbal expression, naming and vocabulary, whereas **left symptom dominance (LPD)** usually determined worse performance in spatial attention, orientation, mental imagery and visual memory. However, these differences in drawing, object recognition, visuospatial and verbal memory, executive functions were conflictingly reported. For example, Cooper et al. (2009) did not reveal any group differences between the side of disease onset and any specific cognitive domains.
The Rey-Osterrieth Complex Figure (ROCF) test is the standard and most commonly used tool to assess visuospatial construction and material specific memory in various neurological and psychiatric disorders (e.g. schizophrenia, obsessive–compulsive disorder, depression, Alzheimer' s disease, epilepsy and sleep disorders).
The objective of this study is to compare the visuospatial performance of RPD and LPD patients.

Methods

Participants

Ninety idiopathic, right-handed PD patients treated at the Department of Neurology, University of Pécs, were recruited for this study. Each patient fulfilled the clinical diagnostic criteria for PD. History of cerebrovascular disease, substance abuse or other conditions known to impair mental status besides PD served as exclusion criteria for participation. Each patient underwent a routine brain MRI scan before the neuropsychological examinations (1 day to 3 months prior).

Patient evaluation

Patients were evaluated for depression and dementia by the Hungarian version of Mattis Dementia Rating Scale (MDRS), Addenbrooke's Cognitive Examination (ACE) and Frontal Assessment Batter. Severity of the Parkinsonian symptoms was assessed by the modified Hoehn-Yahr Scale and Unified Parkinson's Disease Rating Scales, whereas, levodopa equivalent dosage (LED) was calculated to describe medication usage.
Severity of right-sided symptoms (R-score) was calculated as the sum of the motor examination scores of UPDRS evaluating the Parkinsonian symptoms on the right extremities. Similarly, the severity of left-sided symptoms (L-score) was measured as the sum of respective scores for the left extremities. The side of onset was characterized as either right or left based on the concomitant and consistent (1) report of patients', (2) statements of their medical reports at the onset of the disease, and (3) at least two points higher scores for the indicated side compared to the other side. Asymmetry of motor symptoms was characterized by the asymmetry index (AI). Negative AI values represent more severe motor symptoms on the left side (left-dominant PD, LPD), whereas, the positive AI values mean right-sided dominant Parkinsonism (right-dominant PD, RPD). Higher absolute values of AI indicate more prominent the asymmetry between the two sides.

The Rey-Osterrieth Complex Figure (ROCF) test

The ROCF consists of copy and recall tasks (Ogino et al., 2009). In copy task, patients were told to draw a freehand complex figure without time limit as best as they could. There was no warning for memorizing of complex figure. Thirty minutes later, the patients were asked to reproduce the figure from their memory (recall phase).

Copied and recalled drawings were scored according to traditional **Taylor's scoring system.** Higher scores on the Taylor's scoring system represent better performance on the delayed recall and consequently better visual memory. The scores of ROCF1 refer to the copy phase and the ROCF2 to the recall phase of the exam.
Delayed recall of ROCF was evaluated by the **Loring's scoring system.** In Loring's system, 12 spatial errors of drawing were scored by qualitative error guidelines. Higher scores on the Loring's system (LOR2) mean more spatial errors on the recall phase of ROCF.

Data analysis
SPSS software package (IBM Inc, MN, version 21) was applied for statistical analyses. For categorical variables (e.g. HYS and sex), chi-square and Fisher's Exact tests were applied. Subsequently, we tested the data for normality by the application of Shapiro–Wilk test. Because the rest of the data did not follow the normal distribution, Mann–Whitney and Spearman's correlation tests were used. Because of the multiple group comparisons, Bonferroni correction was applied to reduce the Type 1 error. Level of statistical significance was set at 0.05 for the Bonferroni-adjusted p-values. In the first part of the study, we analyzed the whole group of the patients. To assess the role of disease duration, we also performed a subgroup analysis on subjects with a maximum of five years disease duration subsequently.

Results
Out of 90 enrolled patients, 71 fulfilled our criteria for participation (35 with LPD and 36 RPD). The clinical characteristics are included in Table 4. The basic demographic (age, education years and sex) and the most important PD-related factors (disease duration, UPDRS and HYS) were similar in the left- and right-side disease onset groups (Table 1). The standard analysis of ROCF according to Taylor's system did not reveal any differences in the visual memory between RPD and LPD groups. The utilization of the Loring's system demonstrated that LPD patients achieved significantly more spatial errors than the subjects with RPD (3 vs. 2 points, median values, $p = 0.006$; Table 1). Correlation between the number of spatial errors (LOR2) and the AI was mild, but highly significant (correlation coefficient = −0.437, $p = 0.003$; Figure 3A).
Subsequently, we evaluated the impact of disease duration. First, patients having short (the maximum disease duration of five years) were included (15 LPD and 15 RPD). However, in this subset of patients, the side of disease onset did not influence any of the variables measuring the visual cognition. Correlation analysis between the LOR2 and the AI also did not reveal any significant relationship either (correlation coefficient = −0.306, $p = 0.411$) (Figure 3B). Subsequently, we also compared the subgroup of patients with disease duration >5 years. The standard analysis of ROCF according to Taylor's system did not reveal any differences in the visual memory between RPD and LPD groups. The utilization of the Loring's system demonstrated that LPD patients achieved significantly more spatial errors than the subjects with RPD (3 vs. 2 points, median values, $p = 0.006$, Supplementary material). Correlation between the number of spatial errors (LOR2) and the AI was moderate, but highly significant (correlation coefficient = −0.624, $p = 0.001$, Figure 3C).

Table 4. Comparison of demographic and neuropsychological profile of PD patients in the respect of the side of disease onset.

	Side of disease onset						Statistical tests	
	Right (n=36)			Left (n=35)				
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75	Mann-Whitney	Fisher's test
Age	63.5	56.5	70.5	63.0	56.0	68.0	0.411	
Sex	23M/13F			26M/9F				0.443
Education years	13.0	11.5	15.5	13.0	12.0	15.0	0.710	
Disease-duration	8.0	4.5	10.5	7.0	4.0	13.0	0.968	
R-score	15.0	9.0	18.0	11.0	6.0	13.0	0.001	
L-score	10.0	7.0	13.0	18.0	14.0	22.0	0.000	
Asymmetry Index	0.286	0.167	0.519	-0.545	-0.800	-0.400	0.000	
LED	825.0	457.5	1200.0	780.0	320.0	1095.0	0.687	
UPDRS I	10.0	7.5	15.0	13.0	7.0	17.0	0.423	
UPDRS II	15.5	10.0	21.0	16.0	8.0	23.0	0.940	
UPDRS III	32.5	24.0	38.0	33.0	26.0	50.0	0.252	
UPDRS IV	5.0	2.0	7.0	4.0	1.0	7.0	0.231	
HYS (Stages 2/3)	25/11			21/14				0.462
MADRS	5.0	3.5	8.0	4.0	2.0	8.0	0.510	
MMSE	28.0	27.0	29.0	28.0	27.0	29.0	0.347	
ACE	85.0	81.0	88.5	87.0	82.0	91.0	0.289	
ACE Orientation	10.0	10.0	10.0	10.0	10.0	10.0	0.578	
ACE Attention	8.0	8.0	8.0	8.0	8.0	8.0	0.079	
ACE Memory	28.0	24.0	30.0	28.0	24.0	30.0	0.882	
ACE Fluency	10.0	8.0	12.0	10.0	8.0	12.0	0.346	
ACE Verbal	28.0	28.0	28.0	28.0	27.0	28.0	0.091	
ACE Visuospatial	4.0	4.0	4.0	4.0	3.0	4.0	0.663	
Mattis DRS	139.0	136.0	142.5	140.0	135.0	142.0	0.733	
Mattis Attention	36.5	35.0	37.0	36.0	36.0	37.0	0.867	
Mattis Initiation	37.0	33.5	37.0	37.0	32.0	37.0	0.879	
Mattis Construction	6.0	6.0	6.0	6.0	6.0	6.0	1.000	
Mattis Conceptualization	39.0	39.0	39.0	39.0	38.0	39.0	0.243	
Mattis Memory	24.0	22.0	25.0	23.0	21.0	25.0	0.082	
VLOM	3.0	2.1	3.0	3.0	2.0	3.0	0.871	
FAB	15.0	14.0	16.0	15.0	14.0	16.0	0.829	
ROC1	33.0	30.0	35.0	34.0	30.0	36.0	0.095	
ROC2	14.0	12.0	19.0	14.0	8.0	17.0	0.588	
LOR2	2.0	2.0	3.0	3.0	3.0	4.0	0.002	

Abbreviations: ACE = Addenbrooke's Cognitive Examination; FAB = Frontal Assessment Battery; HYS = Hoehn-Yahr Stages; LED = Levodopa equivalent dosage; LOR2 = Scores on the recall phase of Rey-Osterrieth Complex Figure Test according to Loring's system; L-score = severity of motor symptoms on the left extremities measured by UPDRS; MADRS = Montgomery-Asberg Depression Rating Scale; MDRS = Mattis Dementia Rating Scale; MMSE =Mini-Mental Status Examination; ROC1 = Copy phase of Rey-Osterrieth Complex Figure Test; ROC2 = Scores on the recall phase of Rey-Osterrieth Complex Figure Test according to Taylor's system; R-score= severity of motor symptoms on the right extremities measured by UPDRS; UPDRS = Unified Parkinson's Disease Rating Scale; VLOM = Verbal language/Orientation Memory ratio;

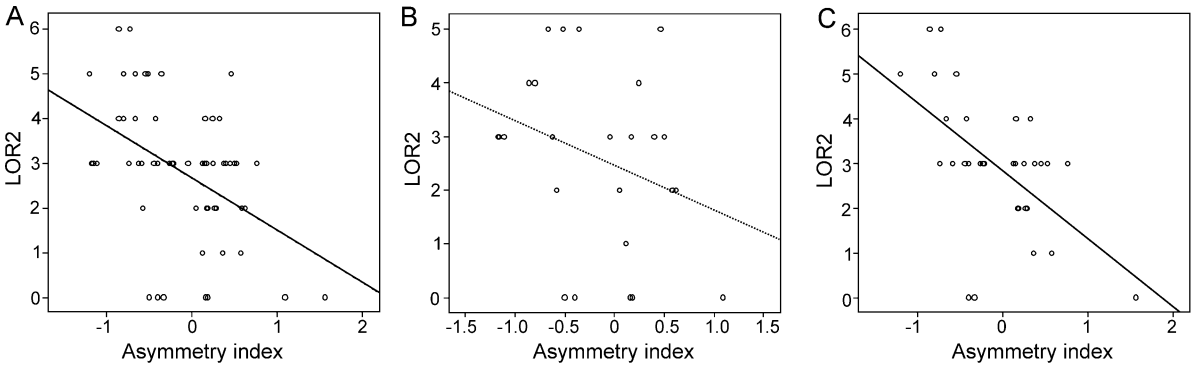

Figure 2. Spearman's correlation between the number of spatial errors in the recall phase of Rey-Osterrieth Complex Figure Test according to Loring's scoring system (LOR2) and the asymmetry of motor symptoms on the Motor Examination part of Unified Parkinson's Disease Scale (Asymmetry Index, for definition refer to text).
A. All patients (n = 71, correlation coefficient = −0.437, p = 0.003).
B. Patients with short (maximum 5 years) disease-duration (n = 30, correlation coefficient = −0.306, p = 0.411, not significant).
C. Patients with long disease duration (>5 years, n = 41, correlation coefficient = −0.624, p = 0.001).

Conclusion

Asymmetry is an intensively studied but still mysterious phenomenon of PD. Numerous studies aimed to evaluate the relationship between the side of onset and different cognitive functions leading up to inconsistent results. Our hypothesis was that the inconsistent conclusions of various studies targeting the relationship between the visual memory disturbances and side of disease onset in PD partly might also be due to methodological issues. The Taylor system awards points on the basis of the accuracy of both the figural elements themselves (perhaps it is more appropriate to call this "figural memory", instead of visual memory) and their proper placement in the overall complex design ("spatial memory"). It is certainly the case that scores based on the Loring system are more heavily loaded on spatial memory, but factors such as misplacement or absence of details, distortions, and major misallocations would certainly imply that figural memory also influences these scores.

Therefore, we compared the Taylor's and Loring's scoring systems in PD patients. To minimize the effects of other factors only non-depressed, non-demented and right-handed PD patients were recruited.

In accordance with many published studies, our result did not demonstrate any differences in the numbers of recalled blocks of ROCF (Taylor's system) between the LPD and RPD groups. However, the Loring's scoring system revealed that PD patients with left disease onset had significantly higher number spatial errors in delayed recalled blocks of ROCF than RPD subjects made and the number of spatial errors significantly correlated with the AI (Figure 2).

The main conclusion of our study is that the asymmetry and laterality of PD do have an impact on visuospatial performance of PD patients and the severity of this influence is tightly correlated with the degree of the asymmetry and the disease-duration. However, we have to carefully select the test batteries and consider the influence of other clinical meaningful factors (e.g. handedness and disease-duration) in order to obtain consistent and reliable results.

LIST OF PUBLICATIONS

Publications related to the thesis

1. *Tivadar Lucza*, Kázmér Karádi*, János Kállai, József Janszky, Sámuel Komoly, Norbert Kovács* **(2015)** Screening mild and major neurocognitive disorders in Parkinson's disease. *Behavioral Neurology,* p. 983606.
IF: 1,642

2. *Lucza Tivadar, Karádi Kázmér, Komoly Sámuel, Janszky József, Kállai János, Makkos Attila, Kovács Márton, Weintraut Rita, Deli Gabriella, Aschermann Zsuzsanna, Kovács Norbert* **(2015)** Neurokognitív zavarok diagnosztizálási és kezelési lehetőségei Parkinson-kórban. Összefoglaló közlemény. *Orvosi Hetilap,* 156:(23) pp. 915-926.
IF: 0

3. *Kázmér Karádi, Tivadar Lucza, Zsuzsanna Aschermann, Sámuel Komoly, Gabriella Deli, Edit Bosnyák, Péter Ács, Réka Horváth, József Janszky, Norbert Kovács* **(2015)** Visuospatial impairment in Parkinson's disease: The role of laterality. *Laterality: Asymmetries of Body, Brain and Cognition,* 20 (1), 112-127.
IF: 1,312

Cummculative impact factor: 2,954 , Number of independent citations: 0

A tézisekhez nem kapcsolódó publikációk

1. Lucza Tivadar, Feldmann Ádám **(2013)** A memória és zavarai (procedurális). Neurológiai TÁMOP -4.1.2.A/11-0094 (könyvfejezet, oktatási segédanyag)

2. Tivadar Lucza, Ádám Feldmann **(2013)** Memory and its disorders (procedural). Neurológiai TÁMOP -4.1.2.A/11-0094 (könyvfejezet, oktatási segédanyag, angol nyelvű)

3. Tivadar Lucza, Ádám Feldmann **(2013)** Das Gedächtnis und seine Störungen (prozedurale). Neurológiai TÁMOP -4.1.2.A/11-0094 (könyvfejezet, oktatási segédanyag, német nyelvű)

4. Kázmér Karádi, József Janszky, Csilla Gyimesi, Zsolt Horváth, Tivadar Lucza, Tamás Dóczi, János Kállai, Hajnalka Ábrahám **(2012)** Correlation between calbindin expression in granule cells of the resected hippocampal dentate gyrus and verbal memory in temporal lobe epilepsy. *Epilepsy & Behavior* 25:(1) pp. 110-119.
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5. Beáta Kaszás, Norbert Kovács, Balás, I., János Kállai, Zsuzsanna Aschermann, Zsuzsanna Kerekes, Sámuel Komoly, Ferenc Nagy, József Janszky, Tivadar Lucza, Kázmér Karádi **(2012)** Sensitivity and specificity of Addenbrooke's Cognitive Examination, Mattis Dementia Rating Scale, Frontal Assessment Battery and Mini Mental State Examination for diagnosing dementia in Parkinson's disease. *Parkinsonism & Related Disorders*, 18(5), pp 553-556.
IF: 3,274, Independent citations: 5

6. Anna Altbäcker, Enikő Plózer, Gergely Darnai, Gábor Perlaki, Gergely Orsi, Szilvia Anett Nagy, Tivadar Lucza, Attila Schwarcz, Tamás Kőszegi, Norbert Kovács, Sámuel Komoly, József Janszky & Zsófia Clemens **(2014)** Alexithymia is associated with low level of vitamin D in young healthy adults. *Nutritional Neuroscience,* 17 (6), pp 284-288.
IF: 2,114; Independent citations: 2

7. Enikő Plózer, Anna Altbäcker, Gergely Darnai, Gábor Perlaki, Gergely Orsi, Szilvia Anett Nagy, Attila Schwarcz, Tamás Kőszegi, Gábor László Woth, Tivadar Lucza, Norbert Kovács, Sámuel Komoly, Zsófia Clemens & József Janszky **(2014)** Intracranial volume inversely correlates with serum 25(OH)D level in healthy young women. *Nutritional Neuroscience,* 18 (1), pp 37-40.
IF: 2,114; Independent citations: 1

8. Darnai Gergely, Plózer Enikő, Altbäcker Anna, Perlaki Gábor, Orsi Gergely, Kőszegi Tamás, Nagy Szilvia, Lucza Tivadar, Kovács Norbert, Janszky József, Clemens Zsófia **(2015)** The relationship between serum cholesterol and verbal memory may be influenced by body mass index (BMI) in young healthy women *Ideggyógyászati Szemle / Clinical Neuroscience*

Cummculative impact factor: 9,346, : Number of independent citations: 12

Acknowledgements

I would like to express my grateful thanks to my supervisors, dr. Kázmér Karádi and Dr. Norbert Kovács for their continuing support, which greatly contributed to the preparation of my dissertation and publications. Thank you for their constant support and for the possibility to use my knowledge in clinical practice, which greatly contributed to my professional development. I am also thankful to Prof. dr. János Kállai, for his teaching, guidance and maximum support. I would like to express my thanks to Rita Weintraut for her continuous support. I am also grateful to Gergely Darnai, who has accompanied my work as a colleague and friend. Special thanks to our Parkinson's Nurses Katalin Takács and Éva Balázs for the help. Also, I would like to express my thanks to the members of Institute of Behavioral Sciences and Department of Neurology in University of Pécs from whom I received so much support over the years. Finally, thank you to my family and friends for the constant support and for their continuous patience, which greatly helped me in achieving my goal.