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Fist-Edge-Palm (FEP) test has a high sensitivity in differentiating dementia from normal cognition in Parkinson's disease

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ABSTRACT

Background: The Fist-Edge-Palm (FEP) test takes 0.5–3 min to complete and is highly sensitive in differentiating Alzheimer's disease and frontotemporal dementia from normal cognition, but it has not yet been studied in Parkinson's disease (PD).
Objective: To determine the sensitivity and specificity of the FEP test in screening patients with PD for cognitive impairment and dementia.
Methods: PD patients were recruited and divided into three groups based on cognitive status: normal cognition, mild cognitive impairment (MCI) and dementia according to 2015 MDS clinical diagnostic criteria for PD and clinical dementia rating scale (CDR) assessment for cognitive status. MMSE, FEP and clock drawing test (CDT) were tested in all recruited PD patients. Chi-square test was used to compare the sensitivity of FEP and CDT in detecting PDD and PD-MCI.
Results: A total of 108 PD patients were included: 52 normal cognition, 28 MCI, and 28 dementia. The sensitivity of FEP in differentiating PDD from PD-NC was 96.4% and the sensitivity for PD-MCI from PD-NC was 71.4%. The sensitivity of CDT in differentiating PDD from PD-NC was 71.4% and PD-MCI from PD-NC was 53.6%. The sensitivities of FEP and CDT were 83.9% and 62.5%, respectively, in identifying cognitive impairment (CDR $\geq$ 0.5) in PD patients.
Conclusion: FEP is a sensitive screening tool in differentiating PDD or PD-MCI from PD-NC, and it is much faster than MMSE and more sensitive than CDT. FEP may be a practical screening tool for daily clinical practice.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease, affecting about 1–2% of people older than 60 years of age [1]. Dementia affects approximately 40% of PD patients during the disease course, and PD patients have approximately at 6 times higher risk of developing dementia than age matched controls [2]. Dementia can significantly increase the morbidity and mortality of PD patients [3,4]. Early and active intervention including drug treatment benefits improving Parkinson's disease dementia (PDD) [5]. It is important to diagnose PDD

Abbreviations: AD, (Alzheimer's disease); CDR, (Clinical Dementia Rating scale); CDT, (Clock drawing test); DLB, (Dementia with Lewy bodies); DSM, (Diagnostic manual of mental disorders); FAB, (Frontal assessment battery); FEP, (Fist-Edge-Palm (FEP) task); FTD, (Frontotemporal dementia); GDS-15, (Geriatric depression scale in 15 items); HAMA-24, (Hamilton anxiety rating scale in 24 items); HY, (Hoehn & Yahr staging scale); LEDD, (levodopa equivalent daily dose); MCI, (mild cognitive impairment); MMSE, (Mini-Mental State Examination); MDS, (Movement Disorder Society); MoCA, (Montreal Cognitive Assessment); NC, (normal cognition subjects); NINDS-AIREN, (National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l' Enseignement en Neurosciences); PD, (Parkinson's disease); PDD, (Parkinson's disease dementia); PD-MCI, (mild cognitive impairment in Parkinson's disease); PD-NC, (Parkinson's disease with normal cognition); PFC, (prefrontal cortex); PSP, (progressive supranuclear palsy); UPDRS III, (Unified Parkinson's Disease Rating Scale III); VD, (Vascular dementia).

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and mild cognitive impairment in Parkinson's disease (PD-MCI) for earlier therapeutic intervention.

The most widely used tools for assessing global cognitive impairment are the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) [6]. It takes about 10–20 min to complete each brief global cognitive tool. A faster and sensitive cognitive tool is needed for screening cognitive impairment in busy clinical practice.

The dementia associated with PD is characterized by a dysexecutive syndrome affecting mainly executive and visuospatial functions while preserving memory [7]. The Luria sequential motor test, also referred to as the Fist-Edge-Palm (FEP) task or Luria's three-step test, is a motor sequencing task in neurological examination that is related to executive function, reflecting the function of prefrontal cortex and frontostriatal pathways in PD [8]. Despite Luria's initial 20 cycles protocol, several studies have used fewer cycles (three cycles [9], six cycles [10,11] or 15 cycles [12]), and the optimal number of cycles has yet to be established. In a Chinese edition of Frontal Assessment Battery (FAB), six cycles of FEP are used [13] because this balances sensitivity and convenience compared with the 3-cycle and 15-cycle versions. Fama et al. demonstrated that motor sequencing performance was more closely correlated with executive function than MMSE and influenced by age and motor rigidity [8]. To our knowledge, there are limited studies that examine the sensitivity and specificity of FEP in detecting cognitive impairment in PD.

2. Methods

2.1. Inclusion and exclusion criteria of patients

The present study includes consecutive cases of probable or clinical definite PD for 1 year or longer from Oct. 2017 to Oct. 2020 and diagnosed by movement disorder specialists in Shanghai General Hospital, which is a tertiary care center. PD was diagnosed according to 2015 Movement Disorder Society (MDS) Clinical Diagnostic Criteria for Parkinson's disease (PD) [14].

We excluded: Alzheimer's disease (DSM-5 criteria) [15], frontotemporal dementia (2014 Chinese FTD diagnosis experts' consensus) [16], dementia with Lewy bodies (DLB) (2015 Chinese DLB diagnosis experts' consensus) [17], vascular dementia (NINDS-AIREN criteria) [18], progressive supranuclear palsy (2016 Chinese PSP diagnosis experts' consensus) [19], patients with history of drug or alcohol abuse, stroke, major depression (GDS-15 $\geq$ 12 score) and major anxiety (HAMA-14 $\geq$ 29 score), (8) cardiovascular disease and head trauma, patients who declined the assessments, patients with severe visual, hearing or movement disability that significant influence cognitive testing, (11) PD patients who lived alone without relatives.

2.2. Patient evaluation

The patients' drug dosages (anti-parkinsonian and/or cognition enhancing) were stable for 1 month prior to the study. Patients were evaluated during the “on” state at 30 min after taking the anti-parkinsonian medication. Newly-diagnosed cognitive impairment PD patients were naive to cognition enhancing drugs at the evaluation. Part III of the Unified Parkinson's Disease Rating Scale (UPDRS III) and the Hoehn & Yahr staging scale were used to assess the motor symptoms of PD. A 6-cycle Fist-Edge-Palm (FEP) task was performed by the patient's preferred hand. The investigator demonstrated Luria test tasks with the fist-edge-palm sequence three times before asking the patient to perform the task synchronously. Patients completed the motion six times by themselves and when the patient needed to think or take a rest, hesitations were acceptable. Luria test performance was scored from 0 to 3 (0 = Subject can't follow investigator correctly; 1 = Subject can follow correctly but can't complete independently; 2 = Subject can correctly complete 3 to 5 cycles independently; 3 = Subject can correctly complete all 6 cycles independently). MMSE [20] was used to assess the global cognitive state of PD patients. A score of 3 points on the FEP was regarded as normal cognitive status while 0–2 points was regarded as abnormal status, which in the present study, led to screening for cognitive impairment.

Patients were also assessed for cognitive impairment using the Clock Drawing Test (CDT) [21]. In the CDT, a score of 3 points was regarded as normal cognition. In the CDT, the patient receives 1 point for the closed round, 1 point for correct arrangement of the 12 Arabic numeric numbers and 1 point for correct arrangement of the position and length of the hour and minute hands [21] .

Patient cognitive status was assessed by the Clinical Dementia Rating scale (CDR) [22]. After a short communication with the PD patient and his/her cohabitant/care giver, the Clinical Dementia Rating Scale [21] was firstly administered to cohabitant/care giver who lived with the PD patient in a quiet clinic room. While PD patient was waiting at outside. Next, PD patient was administered the CDR, and then the MMSE, CDT and FEP in the clinic room. If the PD patient came alone, he/she would be asked to be accompanied by his/her cohabitant next time. After the two parts of interview were finished, the six sections of CDR including memory, orientation, judgment, and problem solving, community affairs, home and hobbies, personal care were evaluated [21]. Then the 6 parts' scores were imported to online CDR calculator (by University of Washington School of Public Health) to calculate the global CDR score. CDR = 0.5 is regarded as MCI and CDR $\geq$ 1 is regarded as dementia. PDD was diagnosed according to DSM-5 PDD [15] criteria and PD-MCI was diagnosed according to Petersen's MCI criteria [23].

2.3. Statistics

The sensitivity and specificity of the FEP and CDT for detecting cognitive impairment were compared with that of the CDR by Chi-square testing. The Pearson correlation analysis was used to describe the association between FEP and other clinical characteristics. ANOVA was done to compare multiple subgroups. The data were analyzed using the Statistical Package for Social Sciences (SPSS) 19(IBM Co., USA). A p value <0.05 was significant. A sensitivity or specificity higher than 90% is good, higher than 75% is moderate.

3. Results

There were 108 PD patients fulfilling the inclusion criteria. Among them, 52 patients were PD with normal cognition (PD-NC), 28 patients were PD-MCI, and 28 patients were PDD. There were no statistical differences among the PD-NC, PD-MCI and PDD groups in age ($p = 0.052$), gender ($p = 0.121$), HY staging ($p = 0.089$), UPDRS III ($p = 0.071$), levodopa equivalent daily dose (LEDD) ($p = 0.676$) or disease duration ($p = 0.078$). PDD patients were significantly older than PD-NC ($p = 0.015$) but age had no significant difference between the PDD and PD-MCI groups ($p = 0.141$). No significant difference in age was noted between the PD-MCI and PD-NC groups ($p = 0.443$) . However, there was a trend toward cognitive impairment in older PD patients and those with greater HY staging scores. There were statistically significant differences among the PD-NC, PD-MCI and PDD groups in MMSE, FEP and CDT ($p < 0.001$) (Table 1).

MMSE, FEP and CDT scores were correlated with age (Table 2). In the 52 PD-NC patients, we compared the Pearson correlation between age and MMSE ($r = -0.298$, $p = 0.032$), FEP ($r = -0.146$, $p = 0.303$) and CDT ($r = -0.242$, $p = 0.084$), the influence of age at FEP is least in present study. MMSE, FEP and CDT scores were not correlated with education years, UPDRS III, HY staging or LEDD (Table 2). FEP and CDT were both significantly correlated with MMSE ($r \geq 0.6$, $p < 0.001$) (Table 2). FEP was completed in 30 s to 3 min according to patients' audition, comprehension and reaction speed. Most subjects completed the FEP less than 1 min.

FEP and CDT scores decreased as cognitive impairment worsened (Table 3). FEP had a sensitivity of 83.9% and specificity of 51.9% for

Table 1
Clinical characteristics of PD patients.

Group	Patients' Number	Age (y)	Education years	Male (%)	UPDRS III(score)	LEDD (mg)	HY	MMSE(score)	FEP(score)	CDT(score)
PD-NC	52	69.3 ± 8.4	10.5 ± 3.2	44.2	24.5 ± 13.7	504.8 ± 174	2.0 ± 0.8	28.4 ± 1.7	2.4 ± 0.8	2.9 ± 0.4
PD-MCI	28	70.8 ± 8.2	9.6 ± 2.5	67.9	32.1 ± 14.4	522.6 ± 146	2.4 ± 0.8	25.6 ± 2.2	1.9 ± 0.9	2.4 ± 0.7
PDD	28	74.1 ± 1.4	11.0 ± 3.7	57.1	27.4 ± 13.9	533.8 ± 127	2.5 ± 1.2	18.9 ± 6.0	1.0 ± 0.6	1.9 ± 0.9
Total PD	108	70.9 ± 8.4	10.4 ± 3.2	53.7	27.2 ± 14.1	516.9 ± 143.8	2.2 ± 0.9	25.2 ± 5.2	1.9 ± 0.9	2.5 ± 0.8

CDT: clock drawing test.
FEP: fist-edge-palm (FEP) task.
HY: Hoehn & Yahr staging scale.
LEDD: levodopa equivalent daily dose.
MMSE: mini-mental state examination.
PD: Parkinson's disease.
UPDRS III: Unified Parkinson's Disease Rating Scale III.

Table 2
The relationship between cognitive test and PD clinical characteristics.

	MMSE		FEP		CDT	
	Pearson correlation	*p* value	Pearson correlation	*p* value	Pearson correlation	*p* value
Age	**−0.269**	0.005	**−0.224**	0.02	**−0.251**	0.009
Education years	0.051	0.604	0.047	0.630	−0.070	0.473
UPDRS III	0.037	0.707	−0.069	0.480	−0.010	0.915
HY	−0.073	0.453	−0.112	0.247	−0.085	0.382
LEDD	−0.05	0.609	−0.001	0.996	−0.094	0.332
MMSE	–	–	**0.602**	< 0.001	**0.656**	< 0.001
FEP	**0.602**	< 0.001	–	–	**0.495**	< 0.001
CDT	**0.656**	< 0.001	**0.495**	< 0.001	–	–

CDT: clock drawing test.
FEP: fist-edge-palm (FEP) task.
MMSE: mini-mental state examination.
LEDD: levodopa equivalent daily dose.
PD: Parkinson's disease.
UPDRS III: unified Parkinson's disease rating scale III.
HY: Hoehn & Yahr staging scale.
The numbers of pearson correlation with Bold and underline are statistic significant by $p < 0.05$.

Table 3
The appearance of FEP and CDT in different PD subgroups.

Patients(number)	FEP				CDT			
	0 score	1 score	2 score	3 score	0 score	1 score	2 score	3 score
PD-NC(52)	1	7	17	27	0	1	3	48
PD-MCI(28)	2	8	10	8	1	1	13	13
PDD(28)	4	20	3	1	2	8	10	8

CDT: clock drawing test.
FEP: fist-edge-palm (FEP) task.
PD: Parkinson's disease.
PDD: Parkinson's disease dementia.
PD-MCI: mild cognitive impairment in Parkinson's disease.
PD-NC: Parkinson's disease with normal cognition.

screening cognitive impairment (CDR $\geq$ 0.5), and a sensitivity of 96.4% and specificity of 51.9% for differentiating PDD (CDR $\geq$ 1) from PD-NC, and a sensitivity of 71.4% and specificity of 51.9% for differentiating PD-MCI (CDR = 0.5) from PD-NC (CDR = 0) (Table 4). CDT had a sensitivity of 62.5% and specificity of 92.3% for screening cognitive impairment, and a sensitivity of 71.4% and specificity of 92.3% for differentiating PDD from PD-NC, and a sensitivity of 53.6% and specificity of 92.3% for differentiating PD-MCI from PD-NC (Table 5).

4. Discussion

The prevalence of dementia in PD has been estimated to be about 26% after 3 years and 48% after 15 years, and our study indicated that 8-year cumulative prevalence of dementia in PD is estimated at 78% [24]. MCI affects 19–38% of non-demented PD patients, depending on study method and subjects [25] . PD-MCI is correlated with increasing age, gender, lower levels of education and greater PD severity [26]. The formal assessment of MCI and dementia, alone or in the context of PD with established criteria [24,27], requires at least 30 to 90 min.

A fast and sensitive tool to screen for cognitive impairment in PD would be valuable because an initial positive screen followed by complete neuropsychological assessment would be more cost effective. A fast and sensitive tool to screen for cognitive impairment in PD would be valuable because the performing neuropsychological assessments based on a sensitive screening instrument would be more cost effective.

In our study, we showed that the FEP of 1 or 2, took about 1 min to complete, and it has a sensitivity of 96.4% and Specificity of 51.9% in differentiating PDD from PD-NC and a sensitivity of 71.4% and Specificity of 51.9% in differentiating PD-MCI from PD-NC. FEP tests the hand movement pattern but not the hand movement speed or rhythm. PD

Table 4
Sensitivity and specificity of FEP in PD cognitive impairment screening.

	PD: MCI + dementia	PD-NC
FEP+	47	25
–	9	27
Sensitivity		**Specificity**
0.839		0.519
PPV		**NPV**
0.653		0.750

	PDD	PD-NC
FEP+	27	25
–	1	27
Sensitivity		**Specificity**
0.964		0.519
PPV		**NPV**
0.519		0.964

	PD-MCI	PD-NC
FEP +	20	25
–	8	27
Sensitivity		**Specificity**
0.714		0.519
PPV		**NPV**
0.444		0.771

	PDD	PD-MCI
FEP+	27	20
–	1	8
Sensitivity		**Specificity**
0.964		0.286
PPV		**NPV**
0.574		0.889

FEP: fist-edge-palm (FEP) task.
NPV: negative predictive value.
PDD: Parkinson's disease dementia.
PD-MCI: mild cognitive impairment in Parkinson's disease.
PD-NC: Parkinson's disease with normal cognition.
PPV: positive predictive value.

Table 5
Sensitivity and specificity of CDT in PD cognitive impairment screening.

	PD-MCI + dementia	PD-NC
CDT+	35	4
–	21	48
Sensitivity		**Specificity**
0.625		0.923
PPV		**NPV**
0.897		0.696

	PD-MCI	PD-NC
CDT+	15	4
–	13	48
Sensitivity		**Specificity**
0.536		0.923
PPV		**NPV**
0.789		0.787

	PDD	PD-NC
CDT +	20	4
–	8	48
Sensitivity		**Specificity**
0.714		0.923
PPV		**NPV**
0.833		0.857

	PDD	PD-MCI
CDT +	20	15
–	8	13
Sensitivity		**Specificity**
0.714		0.464
PPV		**NPV**
0.571		0.619

CDT: clock drawing test.
NPV: negative predictive value.
PDD: Parkinson's disease dementia.
PD-MCI: mild cognitive impairment in Parkinson's disease.
PD-NC: Parkinson's disease with normal cognition.
PPV: positive predictive value.

patients with severe motor disability for example who cannot move their hands or speak, draw or write could not perform cognitive tests such as the FEP, so these patients were excluded from this study. PD patients with hand tremor and/or bradykinesia were included and completed the FEP without limitations.

FEP has historically been considered as a tool for assessing frontal lobe function and has been used to identify patients with frontotemporal dementia (FTD). However, two recent functional brain imaging studies failed to demonstrate FEP-induced activation in the prefrontal cortex (PFC), but did showed changes in functional connectivity between bilateral sensorimotor cortex and the right inferior and middle frontal cortex instead during the task [28,29]. These findings suggest that PFC may regulate, rather than directly participate in the execution of complex motor sequence tasks [30]. It is now recognized that the FEP can detect cognitive impairment beyond FTD. FEP is rarely impaired in people with normal cognition, and impairment occurs in 21.3% of persons with MCI [9]. Weiner et al. demonstrated that 100% of patients with FTD and 72.2% of those with Alzheimer's disease (AD) showed cognitive deficits in the FEP task [9]. Herrera found 40% of mild AD patients and 84% of moderate AD patients were not able to perform the FEP test [31].

Both MoCA and MMSE, which take about 10 min to complete, are frequently used in clinical practice. Hoops et al. suggest that the optimal screening cutoff points for any cognitive impairment would be MoCA≤26 (sensitivity =0.90, specificity =0.53) and MMSE≤29 (sensitivity =0.90, specificity =0.38); the optimal screening cutoff points for PDD were MoCA≤24 (sensitivity =0.82, specificity =0.75) and MMSE≤28 (sensitivity = 0.82, specificity = 0.63); the optimal screening cutoff points for MCI detecting were MoCA≤26 (sensitivity =0.83, specificity =0.53) and MMSE≤29 (sensitivity =0.91, specificity = 0.38) [6]. The CDT assesses executive and visuospatial function. It is also widely used and can be completed in less than 3 min.

In a cross-sectional study, 1449 outpatients with PD with and without dementia were comprehensively assessed. As a screening tool for PDD, the CDT has a sensitivity of 70.7% and a specificity of 68.9% [32]. In the present study, we demonstrated a similar CDT sensitivity of 71.4% but a much higher specificity of 92.3%; the different result may be from different hints and scoring methods. In present study, the sensitivity and specificity of FEP for differentiating PDD from PD-NC were 96.4% and 51.9% respectively, while for differentiating PD-MCI from PD-NC were 71.4% and 51.9% respectively; the sensitivity of FEP is 83.9% for screening cognitive impairment (CDR ≥ 0.5) from PD patients.

Cognitive impairment in PD is characterized by prominent frontal lobe dysfunction in which dopamine depletion from frontal-striatal loop plays an important role [33]. We found that the FEP was sensitive in detecting cognitive impairment in PD patients. The difference in age was nonsignificant among PD-NC, PD-MCI and PDD groups.

Our study also has some weaknesses. First, our sample was relatively small (108 patients) which limits the generalizability of the study. Further studies with larger cohorts are needed. Second, most PD patients in the outpatient departments are in HY stages 1–3. Our findings may not apply to advanced PD. In the present study, PD patients with severe motor symptoms were excluded because they had difficulties in completing the whole motor and cognitive tests, but in those who were able to finish FEP test, we found that it would not be influenced by motor

disability. Third, this was a consecutive case study and the three groups were not age or gender matched, although age ($p = 0.052$) and gender ($p = 0.121$) were not statistically different . Age showed some differences among three PD sub-groups; specifically, PDD patients were significantly older than PD-NC ($p = 0.015$) but no significant difference was noted between the PDD and PD-MCI groups ($p = 0.141$). Previous studies have found that age is an important risk factor in PD cognitive impairment [2,3]. Normal aging has a slight influence on MMSE (0.25 score decline per year) [21], and FEP is abnormal in 2.3% of normal elderly people [9]. We proposed that aging raised the risk of cognitive impairment instead of directly influenced the FEP test appearance in the present study.

5. Conclusion

FEP has a sensitivity of 96.4% in differentiating PDD from PD-NC and a sensitivity of 71.4% in differentiating PD-MCI from PD-NC. The FEP takes less time than MMSE and is more sensitive than CDT, which had a sensitivity of 71.4% for differentiating dementia and 53.6% for MCI. However, the specificity of the cognitive impairment in PD detected by FEP is low. Further studies evaluating the cost effectiveness of FEP in larger cohorts will be useful.

Authors' contributions

Ye Liu and Yun-Cheng Wu designed the study, Ye Liu, Meng-Yao Qiu, Yu-Lei Zhang and Xiao-Jing Zhang followed up the patients and collected the data. Ye Liu analyzed the data and wrote the original draft. Yun-Cheng Wu, Eng-King Tan and Daniel Truong reviewed and edited the draft. All authors participated in the analysis of the literature, wrote, and reviewed the manuscript and approved the final version.

Conflicts of interest

The authors have no potential conflicts of interest to disclose.

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