Original Article

Comparison of Design Fluency Test Results among Patients with Parkinson's Disease, Frontotemporal Dementia, and the Control Group

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Abstract

Background: Design Fluency Test (DFT) is a nonverbal frame-free, nonstructured assessment of executive function (EF). Since previous studies evaluating EF in Parkinson's disease (PD) have mainly used verbal assessments for EF, this study aims to evaluate the pattern of executive domains in PD using DFT and to compare it with behavioral variant frontotemporal dementia (FTD) as a prototype for executive dysfunction and also with normal controls (NCs). **Materials and Methods:** Twenty-eight patients with PD, 27 with FTD, and 27 NCs were included in the study in Ayatollah Kashani Neuropsychiatry Clinic affiliated to Isfahan University of Medical Sciences from September 2019 to February 2020. All participants were assessed via semi-structured neuropsychiatric interview, questionnaire for demographic profile (age, handedness, gender, education, and marital status), duration of illness, comorbid medical condition, comorbid psychiatric illnesses and medications, DFT, Short Parkinson's Evaluation Scale, Frontal Assessment Battery, Judgment of Line Orientation, and Neuropsychiatry Unit Cognitive Assessment Tool. **Results:** Fixed condition novelty score was significantly different between FTD and PD ($P < 0.001$), FTD and control ($P < 0.001$), and also between PD and control ($P = 0.001$). When free and fixed condition novelty scores were considered to predict diagnostic attribution, multinomial logistic regression revealed that odds ratio for free condition novelty score was 0.705 ($P = 0.005$, 95% confidence interval [CI] = 0.553–0.899) and 0.494 ($P = 0.001$, 95% CI = 0.328–0.744) in PD and FTD, respectively. The odds ratio for fixed condition novelty score was 0.772 ($P = 0.011$, 95% CI = 0.632–0.942) and 0.449 ($P = 0.00$, 95% CI = 0.292–0.691). **Conclusion:** DFT subscores can be helpful in diagnosis and differentiation between FTD and PD.

Keywords: *Cognition, dementia, executive function, Parkinson disease*

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative illness. Nearly 1–2/1000 of the population is affected by the disease at any time.[1] PD is the most prevalent disease in the primary α-synucleinopathy spectrum.[2] In addition to motor symptoms, PD is now known to have various nonmotor features.[3,4]

Impairment of cognitive state is a cardinal, determining element of the clinical presentation of α-synucleinopathy spectrum. Among the cognitive domains, impairment of executive function (EF) has been the first and most problematic aspect in α-synucleinopathies. EF includes higher-order processes including working memory, reasoning, task flexibility, and problem-solving as well as planning and execution.[5] In patients with PD, EF decline may even occur in those with premotor syndromes such as rapid eye movement REM sleep behavior disorder and hyposmia. The most prevalent findings in patients with PD are deficits in working memory, attention, and verbal fluency tasks. Some studies revealed that EF impairment may be a herald symptom of dementia even in the absence of clinical dementia of PD.[6]

Another common type of neurocognitive disorder is frontotemporal dementia (FTD). FTD has three main variants: behavioral variant FTD (bv-FTD), semantic dementia (SD), and progressive nonfluent aphasia. bv-FTD is a neurodegenerative disorder mostly related to TAR DNA-binding protein (TDP), tau, and/or FUS proteins. It is associated with behavioral disturbances and significant executive dysfunction including impaired fluency. The point prevalence of bv-FTD is 15–22/100,000. Neuropsychological

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assessments in patients with bv-FTD indicate impaired attention, working memory and EF, decreased social cognition, delayed recall, and some degrees of apraxia.[7]

EF incorporates three different functions: initiation, shifting, and inhibition.[8-10] Initiation is defined as the ability to start to generate new content as an intentional self-motivated action. Initiation is often assessed through fluency tests. Common, current assessments of fluency are verbal fluency tests. Verbal fluency evaluation consists of lexical (phonemic) or semantic (category) fluency tests.[8,9] Inhibition is defined as the capacity to suppress action or content generation in order to facilitate goal achievement. It is usually examined with Go-No-Go and Stroop Test.[9] Shifting is the ability to refocus attention on a different target based on task or environmental requirements. It is assessed by tasks of mental flexibility including Wisconsin Card Sorting Test and Trail Making Test. Repeated studies showed that although patients with PD may perform normally in screening tests of cognition (like Mini-Mental State Examination), most of them have abnormal results in specific tests of EF.[8-10]

The most commonly used tasks for evaluation of EF in PD and bv-FTD are the tasks of fluency. Current fluency tasks are mainly based on language lexical (phonemic) or semantic (category) concepts.[9,10] However, verbal fluency tasks are not considered as pure EF tasks because they assess both language capacity and EF.[8,10,11] To overcome the issue of limited specificity and low distinguishing ability of these tests, neuropsychologists introduced nonverbal fluency assessment. An equivalent for verbal fluency is known as nonverbal fluency, which comprises the fluency of drawing, voluntary gestures, and everyday activities.[8,10,11] Drawing fluency, known also as design fluency (DF), can be subdivided into free/unstructured and fixed/structured fluency tests.[12] There are several nonverbal drawing fluency tests including Jones-Gotman and Milner's Design Fluency Test (DFT), the Five-Point Test, Ruff Figural Fluency Test (RFFT), and Delis–Kaplan EF System-DF. Among the aforementioned fluency tasks, DFT, introduced by Jones-Gotman and Milner, is the sole unstructured nonverbal fluency assessment, as other tasks have structured frameworks.[12,13]

Although previous studies have shown that patients with PD may have impairments in verbal cognitive domains, to our knowledge, very few studies have focused on nonverbal fluency assessment for evaluation of EF in PD.[12] Now, it has been repeatedly reported that unstructured, frame-free nonverbal fluency assessment gives a more real perspective on the patients' ability to initiate and generate new content. However, none of the previous studies have used unstructured fluency tests in assessment of PD patients.[13] The goal of the present study is to compare the results of DFT scores among patients with PD, patients with bv-FTD, and the control group. This study firstly aims to assess the differences in the elements of EF (including novelty score, perseveration, and rule violation) between FTD (as a group of patients with definite executive dysfunction) and PD and to compare PD with normal controls (NCs) (as a group presumably without executive dysfunction) in terms of initiation, shifting, and inhibition.

Materials and Methods

This was a case–control, descriptive-analytic study. The study was approved and registered in the Research and Ethics Committee of Isfahan University of Medical Sciences (registration number: IR.MUI.MED.REC.1398.686).

Cases were outpatients referring to Ayatollah Kashani Neuropsychiatry Clinic affiliated to Isfahan University of Medical Sciences from September 2019 to February 2020. All patients who were referred to the neuropsychiatry clinic with diagnosis of PD or FTD were included the primary evaluation to confirm the diagnosis. Inclusion criteria were the diagnosis of either PD or FTD. Convenience sampling method was used. A neurologist confirmed the diagnosis of PD and a neuropsychiatrist confirmed FTD. Exclusion criteria were diagnosis of a movement disorder other than PD, another already-established cognitive impairment, any severe mental disorders, history of head injury, and any medical condition that aggravates psychomotor speed or cognitive function, for example, hypothyroidism, multiple sclerosis, and malignancies. The NC group was selected among healthy family members of patients matched with age. They underwent a semi-structured interview and full neurological examination to confirm their healthy state. Among 37 patients referred with PD diagnosis, 28 were eligible to enter the study. Furthermore, out of 33 patients with possible FTD, 27 were included as probable FTD. Early assessment was composed of a semi-structured neuropsychiatric interview and filling up a questionnaire for demographic profile (age, handedness, gender, education, and marital status), duration of illness, comorbid medical condition, comorbid psychiatric illnesses, and medications. All participants were assessed using DFT to evaluate their nonverbal fluency, Short Parkinson's Evaluation Scale (SPES) for scoring movement impairment, Frontal Assessment Battery (FAB) for assessment of their overall executive ability, Judgment of Line Orientation (JLO) for evaluation of their visuospatial capacity, and Neuropsychiatry Unit Cognitive Assessment Tool (NUCOG) for assessment of their global cognitive profile. The neuropsychiatrist and neuropsychologist who performed the tests and calculated the scores were blinded to the examinee's diagnostic group.

Design fluency test

DFT assesses initiation, shifting, perseveration, and inhibition. The testee is asked to draw as many different nonsense figures as possible in a limited time. The figures should not be namable, repetitive, or similar, and they

should not resemble anything real. Hence, they should invent as many novel drawings as possible while limiting their inventions to those that neither represent real objects nor resemble any concrete objects. The test is divided into two parts: first, the free condition lasting for 5 min, and second, the fixed four-line condition lasting for 4 min. Three main indices are derived from each part, including "novelty score," "perseveration," and "rule violation." The minimum score in each index is zero; however, there is no maximum score. The inter-rater reliability is 90%, and "novelty score" is correlated to COWAT score ($r = 0.34$, $P < 0.05$).[14]

Short Parkinson Evaluation Scale

SPES is a brief assessment tool in PD, consisting of three sections: motor impairment (MI), activities of daily living (ADLs), and motor complications (MCs). There are 21 items, each having four response options ranging from 0 (normal) to 3 (severe). The score range is within 0–61. Inter-rater reliability for each item ranges from 0.27 to 0.83 in the MI section, from 0.58 to 0.82 in the ADL section, and from 0.65 to 0.92 in the motor complication section. Inter-rater reliability of the motor items ranged from 0.70 to 0.87, and intra-rater reliability ranged from 0.81 to 0.95. The correlation of MI, ADL, and MC scores with those of the Unified Parkinson's Disease Rating Scale is 0.88, 0.86, and 0.95 respectively.[15]

Neuropsychiatry Unit Cognitive Assessment Tool

NUCOG is a brief bedside cognitive screening tool with excellent face validity, assessing all principal cognitive domains, giving graded scores for each cognitive domain, and yielding multidimensional scoring and producing a cognitive "profile." The five major cognitive areas are attention, memory, executive functioning, language, and visuoconstructional function, utilizing a number of tests in each domain. Internal consistency, using Cronbach's alpha, was 0.924 in the whole sample. Regarding convergent validity, NUCOG and MMSE were strongly correlated in the whole sample ($r = 0.922$; $P < 0.0001$).[16]

Frontal Assessment Battery

FAB is a fast and efficient battery to evaluate frontal lobe function in various patients. FAB is composed of six subtests, each assessing an "executive" function domain attributed to prefrontal cortex. Internal consistencies of FAB scores in patients with PD and in the control group are 0.68 and 0.53, respectively. High Cronbach's alpha values were acquired in both groups. Intra-rater reliability rate was high ($r = 0.90$). Consistency was statistically significant ($r = 0.89$; 95% confidence interval [CI]: 0.72–0.95) in monthly retests.[17]

Judgment of Line Orientation

JLO is a common test of visuospatial capacity, comprising 30 pairs of lines; the patient is asked to link the orientation of two lines to a set of 11 lines on a distinct page. Reliability, using Cronbach's alpha, was 0.81 for both PD and control.[18]

Statistical analysis

Data were analyzed in SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Basic quantitative variables were analyzed between groups using ANOVA. Chi-square was used for analysis of basic qualitative variables. Outcome variables were analyzed and compared with analysis of covariance (ANCOVA) and Games–Howell *post hoc* multiple comparison tests when equal variance was not assumed. Prediction of probabilities of the different possible outcomes of categorically distributed diagnoses (given a set of the test results) was performed by multinomial logistic regression.

Table 1: Baseline qualitative variables based on comparison among the three groups

Variables	FTD, *n* (%)	Parkinson, *n* (%)	Control, *n* (%)	*P* (χ^2)
Handedness				
Right	25 (33.3)	26 (34.7)	24 (32)	0.691
Left	3 (42.9)	1 (3.7)	3 (42.9)	
Movement symptoms				
Yes	20 (38.8)	27 (51.9)	5 (9.6)	<0.001
No	8 (26.7)	0	22 (73.3)	
Gender				
Male	17 (41.5)	3 (31.7)	11 (26.8)	0.356
Female	11 (26.8)	14 (34.1)	16 (39.0)	
Marital status				
Single	1 (20.0)	3 (60.0)	1 (20.0)	0.523
Married	27 (35.1)	24 (31.2)	26 (33.8)	
HTN				
Yes	15 (37.5)	15 (37.5)	10 (25.0)	0.342
No	13 (31.0)	12 (28.6)	17 (40.5)	
DM				
Yes	15 (42.9)	11 (31.4)	9 (25.7)	0.322
No	13 (27.7)	16 (34.0)	18 (38.3)	
Dopamine agonist				
Yes	6 (18.2)	27 (81.8)	0	<0.001
No	22 (44.9)	0	27 (55.1)	
Anticholinergic				
Yes	0	7 (77.8)	2 (22.2)	0.003
No	28 (38.4)	20 (27.4)	25 (34.2)	
Antipsychotic				
Yes	17 (77.3)	0	5 (22.7)	<0.001
No	11 (18.3)	27 (45.0)	22 (36.7)	
SSRI				
Yes	12 (56.5)	5 (21.7)	5 (21.7)	0.038
No	15 (25.4)	22 (37.3)	22 (37.3)	
TCA				
Yes	6 (42.9)	4 (28.6)	4 (28.6)	0.816
No	22 (32.4)	23 (33.8)	23 (33.8)	

HTN: Hypertension, DM: Diabetes mellitus, SSRI: Selective serotonin reuptake inhibitor, TCA: Tricyclic antidepressants

Results

A total of 82 subjects were included in the study and entered the final analysis. Baseline qualitative and quantitative variables are demonstrated in Tables 1 and 2, respectively. There are no significant differences among the three groups regarding age, gender, marital status, handedness, and medical comorbidities. Table 2 also indicates baseline cognitive and movement/motor assessment including the illness duration, NUCOG, JLO, FAB, and SPES scores.

Free and fixed condition novelty score, perseveration, and rule violation were compared among the three groups, while age, gender, handedness, years of illness, years of education, comorbid medical condition, medication use, movement symptoms, baseline NUCOG, JLO, and SPES scores were controlled, using ANCOVA; the results are depicted in Table 3. The values for free and fixed condition perseveration, novelty score, and perseverative percentage were significantly different among the three groups [Table 3].

Since these variables had significant differences in ANCOVA, they were then analyzed with Games–Howell *post hoc* multiple comparison test [Table 4]. Free and fixed condition perseveration and perseverative percentage were significantly different between PD and FTD and also between FTD and control ($P < 0.001$). However, the aforementioned variables were not significantly different between PD and control ($P > 0.05$). The free condition novelty score was significantly different PD and FTD ($P = 0.001$) and also between FTD and control ($P = 0.001$), while it was not significantly different between PD and control ($P = 0.984$). Fixed condition novelty score was significantly different between FTD and PD ($P < 0.001$), FTD and control ($P < 0.001$), and also between PD and control ($P = 0.001$) [Tables 4 and 5].

When free and fixed condition novelty scores were considered to predict diagnostic attribution, multinomial logistic regression revealed that odds ratio for free condition novelty score was 0.705 ($P = 0.005$, 95% CI = 0.553–0.899) and 0.494 ($P = 0.001$, 95% CI = 0.328–0.744) in PD

Table 2: Baseline quantitative variables and cognitive and motor assessments based on comparison among the three groups

Variables	Mean±SD			ANOVA
	FTD (*n*=28)	Parkinson's disease (*n*=27)	Control (*n*=27)	*P*
Age	65.14±10.80	69.03±10.82	65.44±7.43	0.273
Years of education	6.35±5.09	10.59±4.78	14.18±5.43	<0.001
Years of illness duration*	5.75±2.79	4.44±2.27	0	0.064
FAB score	6.50±2.95	13.66±3.39	16.59±1.33	<0.001
JLO	7.96±6.23	15.70±3.50	20.25±5.33	<0.001
NUCOG total score	49.80±11.47	77.16±10.32	88.96±6.61	<0.001
Attention	8.05±3.67	14.51±1.69	17.24±1.52	<0.001
Visuoconstruction	11.16±2.89	15.07±3.06	17.35±2.27	<0.001
Memory	8.75±2.69	14.29±3.21	17.11±1.92	<0.001
Executive function	7.16±3.55	14.22±3.65	17.55±1.78	<0.001
Language	14.78±3.05	18.94±1.54	19.70±0.48	<0.001
SPES	6.92±5.17	18.37±7.41	1.70±1.20	<0.001

*Compared between FTD and PD groups. FTD: Frontotemporal dementia, PD: Parkinson's disease, JLO: Judgment of Line Orientation, SPES: Short Parkinson's Evaluation Scale, FAB: Frontal Assessment Battery, SD: Standard deviation, NUCOG: Neuropsychiatry Unit Cognitive Assessment Tool

Table 3: Comparison of Design Fluency Test subscores among the tree groups

Variable	FTD	Parkinson	Control	ANCOVA*, *P*
Free condition total	22.39±13.15	13.74±4.68	19.14±5.78	0.247
Free condition perseveration	15.17±13.16	1.48±1.04	1.92±1.63	0.047
Free condition rule violation	2.96±2.72	1.51±1.05	0.55±0.47	0.828
Free condition perseverative percentage	61.92±33.33	9.44±5.15	3.81±5.51	0.001
Free condition novelty score	5.25±4.23	11.92±4.76	17.66±4.69	0.027
Fixed condition total	13.75±8.84	10.25±3.83	14.81±3.93	0.265
Fixed condition perseveration	6.32±6.25	3.33±0.73	0.70±0.38	0.010
Fixed condition rule violation	4.07±3.79	1.55±1.45	0.85±0.71	0.321
Fixed condition perseverative percentage	43.82±32.71	8.38±3.40	4.75±2.48	<0.001
Fixed condition novelty	3.35±2.42	9.37±4.37	13.59±3.66	0.007

Controlled for age, gender, handedness, years of illness, years of education, comorbid medical condition, medication use, movement symptoms, baseline NUCOG, JLO, and SPES scores. JLO: Judgment of Line Orientation, SPES: Short Parkinson's Evaluation Scale, FTD: Frontotemporal dementia, NUCOG: Neuropsychiatry Unit Cognitive Assessment Tool

Table 4: Games-Howell *post hoc* multiple comparison test of free condition Design Fluency Test perseveration and novelty subscores

Variables	*P*
Free condition perseveration	
PD	
FTD	<0.001
CTL	0.518
FTD	
PD	<0.001
CTL	<0.001
Free condition perseverative percentage	
PD	
FTD	<0.001
CTL	0.181
FTD	
PD	<0.001
CTL	<0.001
Free condition novelty score	
PD	
FTD	0.001
CTL	0.984
FTD	
PD	0.001
CTL	0.001

FTD: Frontotemporal dementia, PD: Parkinson's disease, CTL: Control

Table 5: Games-Howell *post hoc* multiple comparison test of fixed condition Design Fluency Test perseveration and novelty subscores

Variables	*P*
Fixed condition perseveration	
PD	
FTD	0.001
CTL	0.984
FTD	
PD	0.001
CTL	0.001
Fixed condition perseverative percentage	
PD	
FTD	0.000
CTL	0.872
FTD	
PD	0.000
CTL	0.000
Fixed condition novelty score	
PD	
FTD	0.000
CTL	0.001
FTD	
PD	0.000
CTL	0.000

FTD: Frontotemporal dementia, PD: Parkinson's disease, CTL: Control

and FTD, respectively. Furthermore, the odds ratio for fixed condition novelty score was 0.772 (P = 0.011, 95% CI = 0.632–0.942) and 0.449 (P = 0.00, 95% CI = 0.292–0.691) [Table 6].

Discussion

DFT, introduced by Milner and Jones-Gotman, is an assessment tool for nonverbal domains of EF; it is designed to evaluate subdomains of EF, including initiation, inhibition, and shifting capacity. Due to its frame-free process, it is believed that it allows creativity and initiative in generating novel contents.[19]

In this study, we aimed to find the differences in the pattern of subdomains of EF; we explored whether DFT is able to discriminate PD, FTD, and NC through novelty, perseveration, and inhibition parameters.

Logistic regression analysis was therefore used to assess the power of DFT to predict the diagnostic attribution (group belonging). This means that, considering the concept of EF, DFT subdomain results may have the power to differentiate PD from FTD and PD from NC. That is to say, in addition to motor problems, executive dysfunction can also be considered as a discriminating feature of PD. In this study, multinomial logistic regression indicated that decreased initiation can predict the chance of both PD and FTD with different strengths.

On the other hand, results of the ANCOVA revealed that fixed condition novelty, was a significant parameter in representation of executive dysfunction in PD. The results show that while both PD and FTD impaired executive profile, PD is associated with significantly impaired initiation under structured circumstances but not with significant perseveration and impaired shifting, while FTD is significantly associated with perseveration, impaired shifting, and decreased initiation in both free and fixed conditions.

Limited studies have administered DFT for cognitive/executive evaluation. DFT has previously been studied to differentiate different cortical lesions, for example, discriminate right cortical lesions from the left sided. However, DFT did not discriminate laterality, and it was influenced by the size of lesions. However, no diagnostic limits or cutoffs are available. Free condition novelty score has been used in assessment of closed head injury, especially in mild head trauma.[14,19,20]

On the other hand, FAB has been used to diagnose FTD- and PD-related cognitive deficits. Diagnostic cutoff points are provided for FTD and PD using FAB in different studies; however, these cutoff points are too near (FAB cutoff score = 12.8/18 for diagnosis of PD versus FAB cutoff score = 12/18 for diagnosis of FTD) and are not able to distinguish the two illnesses.[17]

Considering the necessity for early diagnosis of cognitive impairment in PD, Movement Disorder Society Task Force proposed diagnostic criteria for mild cognitive

Table 6: Multinomial logistic regression analysis of Design Fluency Test perseveration and novelty subscores in Parkinson's disease and frontotemporal dementia

Diagnostic group	Variables	OR	*P*	95% CI
PD	Free condition novelty score	0.705*	0.005	0.553-0.899
	Fixed condition novelty score	0.772	0.011	0.632-0.942
FTD	Free condition novelty score	0.494	0.001	0.328-0.744
	Fixed condition novelty score	0.449	0.000	0.292-0.691

*Adjusted for age, gender, and JLO sore. Other parameters are adjusted for age, gender, movement symptoms, years of education, years of illness duration, JLO, and SPES score. FTD: Frontotemporal dementia, PD: Parkinson's disease, OR: Odds ratio, CI: Confidence interval, JLO: Judgment of Line Orientation, SPES: Short Parkinson's Evaluation Scale

impairment (MCI) in PD (PD-MCI), comprising two operational levels: Level I and Level II. Montreal Cognitive Assessment, Mini-Mental State Examination, and Addenbrooke's Cognitive Evaluation-R have been proposed as screening tools for Level I assessment (sensitivity 80 and specificity <80). There is a lack of brief validated instruments for executive dysfunction in PD.[21] The FAB has shown discriminative validity for the differentiation of PD-MCI from PD-NC and controls (area under the curve >0.80). Furthermore, the voxel-based morphometry analysis revealed that lower FAB scores are specifically related to lower gray matter density in the right ventromedial prefrontal areas and precuneus. The FAB can be recommended as a valid instrument for PD-MCI Level I screening. FAB is sensitive to frontal lobe involvement in PD as reflected by lower gray matter density in prefrontal areas.[22]

In a study by Jaywant *et al*., both RFFT and verbal fluency tests were performed to evaluate verbal and nonverbal fluency as means of EF assessment and found that PD patients with left-sided nontremor symptoms had more perseveration, impaired inhibition, and self-monitoring.

Although the present study highlights the impairment of initiative in PD, another study by Koerts *et al*. indicated intact initiation but impaired sequencing and planning in patients with PD. This can be explained by the weakness of cognitive effort test in assessing initiation. Impaired initiation has challenging impacts on everyday life.[23,24]

It is noteworthy to highlight how the observed level of cognitive impairment is translated into everyday functioning and to consider executive dysfunctions in rehabilitation programs and to manage executive deficits.[23,24]

The limitations of the present study were the cross-sectional design, the limited sample size, lack of using biomarkers including imaging, and the rater-dependent testing process.

Conclusion

DFT subscores can be helpful in diagnosis and differentiation between FTD and PD.

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Conflicts of interest

There are no conflicts of interest.

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