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The deficit of executive functions in early stages of Parkinson's disease

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Abstract. Objective: Our study evaluates the presence of cognitive impairments in early stages of Parkinson's disease, focusing in the first place on executive function and attention deficits, which, according to current studies, might be affected. Material and Methods: The study included 30 patients previously diagnosed with Parkinson's disease stage I and II. Every participant was evaluated with the following tests: GoNoGo, Word List Memory, Spatial Target Detection Test and PEAT, all from COGTEST program. The results showed the presence of executive function deficit, impairment of working memory and social cognition in patients group, as compared with the control group. One of the significant results in the case group was prolongation of reaction time at test completion.
Key Words: Parkinson's disease, executive functions, working memory, neurocognitive evaluation.

Rezumat. Obiectiv: Studiul nostru şi-a propus să evalueze în ce măsură sunt prezente tulburări cognitive în stadiile de început al bolii Parkinson, cu focalizare în primul rând asupra deficitelor funcţiilor executive şi atenţiei, care, conform studiilor făcute până în prezent, par să fie afectate. Material şi metodă: Studiul a inclus 30 pacienţi diagnosticaţi cu boală Parkinson stadiul I şi II. Toţi participanţii la studiu au fost evaluaţi cu ajutorul testelor GoNoGo, Word List Memory, Spatial Target Detection Test şi PEAT, din cadrul programului COGTEST. Rezultatele au arătat prezenţa deficitului funcţiilor executive, afectarea memoriei de lucru şi afectarea cogniţiei sociale la lotul de pacienţi, comparativ cu lotul martor. Unul din rezultatele semnificative a fost prelungirea timpului de reacţie la efectuarea testelor la lotul de pacienţi.
Cuvinte cheie: boală Parkinson, funcţii executive, memorie de lucru, evaluare neurocognitivă.

Introduction. In the shadow of motor disorders that define Parkinson's disease (PD), lie a multitude of non-motor disorders, which, although less known and rarely associated by doctors with PD, significantly affect patient's life quality. Among these, an important place is occupied by cognitive impairment.

The most prominent cognitive deficit in PD consists in alteration of executive functions. Executive functions represent a set of cognitive abilities which control goal-oriented behavior. The following are included: ability of initiation or blocking of an action, monitoring and adjusting the behavior in any given context, as response to certain demands and situations, that allow the subject to anticipate the consequences of his actions and to adapt to situation (Bhatia et al 2009). Executive function deficits, in context of PD, were described regarding the capacity of planning, problem solving, establishing and maintaining rules, as well as the capacity of changing those rules as events dictate. Disexecutive syndrome is a term often used in relation with PD (Dubois & Pillon 1997; Emre 2003). The cognitive deficit is one of the most debilitating non-motor symptoms associated with PD.

As frontal lobes represent the main area responsible for most of these executive functions, frontal dysfunction is, largely, the underlying motive for cognitive modifications that take place in PD. However, as patients with frontal affection have the tendency to have repetitive behaviors (for example: loss of mental flexibility, inability of adapting the response to environmental changes), in PD the disorder is characterized by difficulty in ignoring or suppressing irrelevant stimuli during the course of cognition (for example:

difficulty in maintaining an adaptative response despite presence of competitive alternatives (Dubois & Pillon 1997; Emre 2003). The striate nucleus, through cortico-striate circuit, sends and receives projections from many cortical areas, including prefrontal cortex. Dysfunction of this circuit could be responsible for some of cognitive deficits encountered in PD (Olanow et al 2011).

Attention deficit in non-demented patients with PD was particularly described in situations that necessitate selective attention. During solicitations that needed attention directed at several concomitant activities, patients with PD presented difficulties in ignoring distracting factors. They were predisposed to let the distracting factors to interfere with activities that involve active response suppression or attention redirection (Zgaljardic et al 2006; Verleden et al 2007).

Non-demented PD patients present a specific alteration of working memory, with relative conservation of recognizing capacity, learning and long term keeping of the information, which suggests that storage and consolidation memory is intact, but the recuperation processes are, in some degree, affected. Paradigms of memory require manipulation of some elements, which are conditional-associative learning or spatial-temporal commands that are also deficient in PD (Dubois & Pillon 1997; Emre 2003; Zgaljardic et al 2006).

Visual-spatial and visual-perception functions in non-demented PD patients are seriously affected, including visual-spatial orientation, attention and constructive memory, linear orientation and object recognition (Uc et al 2005).

Some theories had been proposed in order to explain the mechanisms which stand at the base of PD cognitive decline. They are not mutually exclusive, but indicate a combined impact of neurochemical changes and neuropathologic processes that leads to the extension and rapidity of cognitive decline.

The evaluation of cognitive impairments in early stages of PD is the main objective of this paper. Our study is focused on attention and executive function deficits that might appear in early stages of PD.

Material and Method. Participants: 30 patients previously diagnosed with PD stage I and II (17 women, 13 men) (Hoehn & Yahr 1967). All participants are Caucasians. Mean age was 64.1 years. They were recruited from people that were examined at Integrated Ambulatory of Infectious Disease Clinical Hospital of Cluj-Napoca. The subjects were required to obtain a score of 27 out of 30 at MMSE (mini–mental state examination) test. Patients with dementia or PD stage III-IV were excluded (Hoehn & Yahr 1967). A control group was formed and it included 30 persons without PD.

Previous to the inclusion in study the subjects signed an informed consent form, in accordance with the protocol of "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca.

The most important coordinate of the study was the examination of cases and controls using the test COGTEST. COGTEST is an extremely reliable program, completely automated, which helps for a precise cognitive evaluation. It offers a grading instrument and storage of information on a computer, similarly to an electronic notebook. COGTEST has a wide variety of indications and can be personalized to the requirements and selected domains. Testing characteristics allow increase of working efficiency, cost cuts and complex manipulations, which allow modification of difficulty of the test at any given moment. All these characteristics minimize the duration of the test, allowing a sensitive and fast evaluation.

Go-No-Go, part of COGTEST, is a test that was created in order to evaluate response inhibition, using a fast computerized evaluation formula (language and motor function). The subjects learn to differentiate between two types of answers. Subject is required to make the correct choice depending of what kind of stimulus he sees: green stimulus is the "go" stimulus, while the red one is the "no-go" stimulus. The frequency of "go" and "no-go" stimuli is 80%. Key variables in this test include reaction times for "go" response and "false alarm" errors represented by "no-go".

Spatial Working Memory (SWM), part of COGTEST, is destined to evaluate working memory. The most important objective is to determine accuracy of location recalling of

some visual targets previously shown to subjects for a short time. All the answers are given by touching a sensitive screen. During the gap that exists between showing of targets and the moment when subject must respond (between 2 and 12 seconds), a series of distractors appear in different locations. These distracting factors help in preventing the subject to fixate the target. Also, the answers to these factors are recorded, thus assuring test adherence.

Strategic Target Detection (STD). In this test subjects touch different shaped targets stimuli on a sensitive monitor. A particular characteristic of this test is the fact that the subject is not informed what shape is the target stimulus. He must discover which the correct targets stimuli are by choosing one of them, observing computer response, which indicates if the choice is correct or wrong. After that the subject must: 1) choose the correct stimulus; 2) select all the target stimuli, after which the target stimulus is automatically; 3) stop selecting previous stimulus and detect as fast as he can the new target stimulus; 4) continue these cycles until the test finishes. The variables which must be analyzed by the end of the test are: the 4 forms of stimuli; total time of experiment (in msec) total number of correct answers; total number of preservative errors; strategic efficiency.

Word List Memory Test (WLM) is a test for verbal-hear recognition, adapted for a wide use. Subjects must recall as much as they can from 16 words, which the computer produces. In second round the computer repeats only those words that subject did not remember previously, but the subject must reproduce all 16 words. The cycle repeats itself 5 times, and the examiner records all responses. The recorded variables are: total number of words which the subject remembered first time; total learning capacity; the process of information transfer accumulated from a trial to another; correct late recalling; late recalling of differences.

PEAT test evaluates subject's emotional processing and it is a part from emotional and social cognition, being a test destined to evaluate emotion discriminating capacity. During the test random faces are presented to the subject with variable emotion expressions. The participant must differentiate facial expressions. Evaluated variables are accuracy by which subject identify correct emotional expression and the time that was needed for that action (reaction time).

Results. All obtained data were processed using Statistical Pack for Social Sciences v. 15.0 software. Normality was assessed using Kolmogorov-Smirnov test and equality of variances was assessed using Levene test. T test for independent variables and Mann-Whitney test were used when appropriate. Also Spearman's correlations were used. A P-value lower than 0.05 was considered to be statistically significant.

As it can be seen in table 1, at WLM test, the results did not show a statistically significant difference between patients and controls for total learning capacity ($p>0.05$), but there were significant differences for information accumulating capacity ($p<0.01$). Patients with PD showed a significantly greater rate for reproducing words which were not on the list ($p=0.044$), fact indicating that work memory is deficitary in PD patients.

When we used Spearman's correlation we determined that there is a low positive correlation between presence of PD and "total number of Non-List" variable ($r=0.270$) and a strong negative correlation between PD and "trial to trial transfer" (capacity of word memorization from a cycle to another) ($r=-0.776$).

SWM test implies that maintaining and manipulation of information may be considered as instrument of evaluation of work memory executive function. We found statistically significant differences between groups for all variables ($p<0.05$) (table 1). The application of Spearman's correlation indicated a low positive correlation ($r=0.284$) between PD and "short median distance" variable, medium positive correlations for PD and "short mean distance" ($r=0.470$), "long median distance" ($r=0.469$) and high positive correlation for PD and "overall median distance" ($r=0.560$), "long mean distance" ($p=0.547$).

Table 1

Work memory for patients vs. controls

Tests	Patients		Controls		p
	Mean	SD	Mean	SD	
Word List Memory Test (WLM)					
Total Number of Non-List Words	2.30	2.18	1.23	1.79	0.044[1]
Total Trial-to-Trial Transfer	61.85	14.83	87.21	8.99	<0.01[1]
Total Learning	47.89	8.67	51.80	14.31	>0.05[2]
Spatial Working Memory Test (SWM)					
Short Mean	56.20	25.21	38.86	15.19	<0.01[2]
Short Median	41.44	11.02	35.00	12.06	0.045[2]
Long Mean	95.50	38.77	59.81	23.74	<0.01[2]
Long Median	77.88	25.48	54.37	22.97	<0.01[2]
Overall Mean	75.85	24.87	49.37	16.57	<0.01[2]
Overall Median	54.28	11.78	39.80	13.13	<0.01[2]

[1] Mann-Whitney Test
[2] t Test

At GoNoGo test we identified significant medium negative correlation between PD and "correct Go" variable ($p=0.021$; $r=-0.311$). There were no significant differences for "correct NoGo" variable. "Mean reaction time" was significantly different in patients and controls ($p<0.01$). A high positive correlation was found between PD and "mean reaction time" ($r=0.526$). These results point towards a impairment of executive functions in PD patients.

Table 2

Executive functions changes in patients vs. controls

Tests	Patients		Controls		p
	Mean	SD	Mean	SD	
Go-No-Go Test					
Correct Go (%)	98.21	3.20	99.68	0.82	0.021[1]
Correct No Go (%)	99.25	1.90	99.82	0.95	>0.05[1]
Mean Go Reaction Time	576.45	114.81	477.63	61.13	<0.01[2]

[1] Mann-Whitney U Test
[2] t Test

In STD test we followed three parameters: errors that were present in problem solving, problem solving reaction time and strategic efficiency in patients vs. controls.

The results showed significant differences for "two shape proportion non-response" variable ($p<0.01$) and "four shape proportion non-responses" ($p<0.01$). High positive correlations were established between PD and "two shape proportion non-response" ($r=0.525$) and "four shape proportion non-responses" ($r=0.595$). Same results were recorded for evaluation of error percent, much higher in PD patients. The correct responses percent was lower in PD patients (table 3).

When we evaluated reaction time in STD test we found a medium positive correlation between PD and "two shape duration time" variable ($r=0.397$; $p<0.01$) and a high positive correlation between PD and "four shape mean reaction time" ($r=0.622$; $p<0.01$).

Table 3

Problem solving changes in patients vs. controls – errors

Tests	Patients		Controls		p
	Mean	SD	Mean	SD	
Strategic Target Detection Test (STDT)					
Two Shape Proportion of Non-Responses	0.1158	0.1524	0.0410	0.0766	<0.01[1]
Two Shape Proportion of Spatial Repeat Errors	0.0259	0.0578	0.0280	0.0990	>0.05[1]
Two Shape Proportion of Perseverative Errors	0.6948	0.2621	0.5514	0.2682	>0.05[1]
Two Shape Proportion of Non-Perseverative Errors	0.3608	0.3983	0.4486	0.2682	>0.05[1]
Two Shape Proportion of Errors	0.2744	0.1240	0.2079	0.1107	0.041[1]
Two Shape Proportion of Correct Responses	0.7256	0.1240	0.7921	0.1107	0.040[1]
Four Shape Proportion of Non-Responses	0.0246	0.0310	0.0044	0.0088	<0.01[1]
Four Shape Proportion of Spatial Repeat Errors	0.0405	0.0630	0.0471	0.0691	>0.05[1]
Four Shape Proportion of Perseverative Errors	0.4413	0.1169	0.4312	0.1088	>0.05[1]
Four Shape Proportion of Non-Perseverative Errors	0.5587	0.1169	0.5688	0.1088	>0.05[1]
Four Shape Proportion of Errors	0.2748	0.1018	0.1757	0.0577	<0.01[1]
Four Shape Proportion of Correct Responses	0.7252	0.1018	0.8243	0.0577	<0.01[1]

[1] Mann-Whitney Test

Table 4

Problem solving changes in patients vs. controls – reaction time

Tests	Patients		Controls		p
	Mean	SD	Mean	SD	
Strategic Target Detection Test (STDT)					
Two Shape Mean Reaction Time	1105.43	334.36	962.24	254.83	>0.05[1]
Two Shape Duration	61136.88	35136.29	39672.95	19221.83	<0.01[1]
Four Shape Mean Reaction Time	1084.14	158.09	837.48	176.65	<0.01[1]
Four Shape Duration	181557.78	40337.72	113089.88	38504.97	<0.01[1]

[1] t Test

At strategic efficiency evaluation, as it can be seen in table 5, we did not found any significant differences between the two groups (p>0.05).

Table 5

Problem solving changes in patients vs. controls – strategic efficiency

Tests	Patients		Controls		p
	Mean	SD	Mean	SD	
Strategic Target Detection Test (STDT)					
Two Shape Strategic Efficiency	3100.27	1006.83	2730.87	1196.77	>0.05[1]
Four Shape Strategic Efficiency	17203.07	3588.19	16422.71	3337.84	>0.05[1]

[1] t Test

In emotion discriminating test we did not found any significant differences between patients and controls for emotion differentiating ability (p>0.05) (table 6), but we found a high positive correlation between PD and reaction time (r=0.507; p<0.01).

Table 6

Emotion discrimination changes in patients vs. controls

Tests	*Patients*		*Controls*		*p*
	Mean	*SD*	*Mean*	*SD*	
Penn's Emotional Aquity Test (PEAT)					
Mean Response Rating	3.94	0.46	3.93	0.17	>0.05[1]
Mean Reaction Time	5874.29	1608.40	4541.53	1978.60	<0.01[1]

[1] t Test

Discussions. Neurocognitive evaluation of subjects in early stages of PD showed significant modifications of evaluated cognitive functions.

Evaluation of work memory through WLM and SWM tests showed significant differences between the two groups. At the first test, PD patients presented a higher rate for reproducing word that were not on the list and a reduced capacity of accumulating information from a cycle to another. These facts indicate that work memory is deficitary in PD patients. At the second test, SWM, we found significant differences for all variables, fact which indicates that work memory is affected as well in PD patients. This information is in concordance with data from literature (Higginson et al 2003).

Short working memory is, in fact, a particular part of working memory. Short and long work memory are different activation mods of the same declarative mnesic-memory system. The type of task and stimuli, that a subject is receiving, determines which knowledge is temporary activated and which one is temporary subactivated. There are not clear quantitative differences for work and long term memory level of activation. The intellectual performances seem to be determined by working memory, but not by long term memory. It does not matter how many information and what processing mechanisms are part of long term memory. It counts only how many are activated in order to perform a task in an efficient way. For that matter, one of the most stable recorded results, regarding cognitive development, are about working memory. The size of working memory is one of the essential differences between subjects with different intellectual levels (Miclea 1990).

In order to evaluate the executive functions we used GoNoGo and STDT tests. GoNoGo test identifies significant differences between patients and controls at "correct Go" variable. Medium reaction time is significantly longer in patients group.

In STDT test we followed three consecutive parameters which compare errors that were present during problem solving, reaction time for problem solving and strategic efficiency between patients and controls. Results showed a greater percent of errors and significantly higher lack of responses rate at test's demands in patients group as compared with control group. Medium reaction time was significantly longer for most of variables in PD patients. These results indicate towards an impairment of executive functions in patients with PD. These data are in concordance with medical literature (Pagonabarraga et al 2008).

Medical literature leaves a question mark about the fact if this matter is caused exclusively by executive function deficit or it may be determined by motor impairments which characterize the disease.

Problem solving ability it is a part of executive functions, which include planning processes, organizing and problem solving. Additionally, the capacity of learning from mistakes, initiating adequate actions and, respectively, inhibiting inadequate actions, represents a big area of this subject.

At PEAT test there were none significant differences between the two groups for the ability of emotion differentiation. The difference appeared in evaluation of time that was necessary for resolving the test, when PD patient's reaction time was significantly longer. These data correspond with those from other studies. In 2006 Kawamura and Koyama identified the impairment of social cognition, which consists in ability of reading between the lines, recognizing facial expression and making decisions. All those contribute to a correct interaction between individuals. In fact, this

symptomatology can appear before motor one. These modifications might be caused by dopaminergic mesolimbic system dysfunction (Kawamura & Koyama 2006).

No matter whether PD patients will develop or not dementia, even a mild cognitive deficit can represent a significant handicap for daily activities. The greatest difficulties are met by younger PD patients, often still employed, with a demanding cognitive activity. For this reason, this group of PD patients can be confronted with greater problems than elderly persons, which have less demanding activities. However, even a usual activity can suffer because of the presence of cognitive deficit and can produce significant personal suffering.

For PD patients mild cognitive difficulties may sometime seem unimportant when compared with the challenge of physical symptoms of the disease. This perception may be shared by medical personnel, which, although aware of dementia risk, does not pay attention to the presence and potentially significant in time cognition impairment. However, these kinds of changes continue to have an impact on the life of some patients and might have important implications regarding their medical care.

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