EXAMINATION OF COGNITIVE FUNCTIONS IN PATIENTS WITH PARKINSON'S DISEASE

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Summary. Parkinson's disease is a neurodegenerative disorder whose main clinical features are rigidity, tremor, akinesia and postural instability. While Parkinson's disease primarily impairs the motor function, numerous studies have shown that it also affects cognition. Mental changes are often the inevitable follower of Parkinson's disease motor symptoms. The cognitive dysfunction of the subcortical-frontal type sometimes leading to dementia. Results of neuropsychological testing of 25 patients in I and II stages of the disease are shown. Tests for the frontal functions, visuomotor skills, visual organization and memory were administered. Results of this investigation showed that nondemented patients in early stages of the disease have low achievements on tests of frontal functions and memory. Patients exhibited the specific deficit in executive functioning, spatial behaviour, verbal and visual memory. Used neuropsychological tests have the diagnostic value in cognitive dysfunction detection, in an early phase of Parkinson's disease. We may conclude that neuropsychological tests are important for identification of early cognitive disturbances in Parkinson's disease. By neuropsychological testing we can get data on cerebral dysfunction that can be used for diagnostic, therapeutic, rehabilitational and research purposes.

Key words: Cognitive disturbances, Parkinson's disease, neuropsychological testing

Introduction

Parkinson's disease is characterised by rigidity, bradykinesia, tremor and gait disorders. The primary pathology involves loss of dopaminergic cells in the substantia nigra and the ventral tegmental area. These two subcortical dopaminergic sites give rise to two projection systems important for motor, cognitive and affective functioning. The nigrostriatal system, primarily implicated in motor functions, originates in the pars compacta of the substantia nigra and terminates in the striatum. The meso-limbic-cortical system contributes to cognitive and affective functioning. It originates in the ventral tegmental area and terminates in the ventral striatum, frontal lobes, amygdala and some other basal forebrain areas.

In Parkinson's disease, dopamine levels in the frontal lobes, ventral striatum and hippocampus are lower than normal values. The degree of nigro-striatal impairment correlates with the degree of motor impairment in parkinsonian patients. The degree of ventral tegmental area - mesocortical dopaminergic impairment correlates with the degree of intellectual and affective impairment. The mesocortical dopaminergic dysfunction has a negative impact on prefrontal lobe functions.

Past research show that dementia appears with Parkinson's disease in 14-40% of ill subjects. Dementia is of the "subcortical-frontal" type and lesions of subcortical structures take part in its genesis leading to cognitive programmes "desactivation" in cerebral cor-tex. Dementia is represented with disexecutive syndrome marked by: slowness of mental processes, memory disorders, changes in personality as well as damaged usage of accomplishments.

Parkinson's disease, associated with nigrostriatal dopamine depletion and mesocorticolimbic dopamine depletion, is accompanied by cognitive impairments even in its early stages. Studies of patients with Parkinson's disease suggest that the characteristic motor symptoms are accompanied by impairments in cognition that are most profound in tasks of executive function. Every form of psychic and intellectual effort significantly worsens motor disorders which is a proof of integrative role of the basal ganglia. Still, even where there is no mental deterioration in patients with Parkinson's disease, selective cognition deficits can be found. Cognition disorders and disorders in new manual skills as well as concentration deficit are evident. Patients with the basal ganglia dysfunction are characterized by central programming deficit manifested in verbal, figural and motor modality. It is possible for the deficit of central executive mechanisms not to be inevitable Parkinson's disease eminence but its expression depends on the nature of the task (visuomotor, cognitive) and on the usage of dopaminergic medication.

The aim of this paper is an examination of frontal functions, attention, concentration and memory by neuropsychological tests in an early stage of Parkinson's disease.
Patients and methods

We analysed a group of 25 patients (15 men and 10 women) with idiopathic Parkinson’s disease, without manifested clinical signs of dementia and depression. They fulfilled the diagnostic criteria of idiopathic Parkinson’s disease. Tested subjects didn’t get substitution therapy. By other clinical methods we had preliminary excluded other etiological possibilities for parkinsonian syndrome genesis.

There were 15 healthy persons of both sexes and certain age at our control group. We used following neuropsychological tests: Mini Mental State Examination, Rey Auditory Verbal Learning Test, Trail Making Test (form A and B), Hooper Visual Organisation Test, Wisconsin Card Sorting Test.

Mini Mental State Examination (Folstein and associates, 1975) is a test which evaluates the grade of cognition fall in patients with dementia. It is a screening test primary made for the evaluation of dementia stage because of its simplicity and easy usage it became widely used.

The Rey Auditory Verbal Learning Test (Rey, 1964) evaluates verbal learning and memory. The test is short and convenient for direct and postponed verbal memory evaluation. During these functions direct memory (attention span) is measured, learning strategy defined, curve of learning formed, proactive and retroactive interference found, tendentious to confabulation detected, recognition and retention evaluated.

The attention is defined as ability to focus on specific stimulus without distraction by other stimulus. It is tested first being prerequisite for cognitive functioning. Concentration refers to prolonged attention, which is ability to focus attention during long period of time. Trail Making Test consists of two parts – A and B, and each of them has specific assignment. Part A mostly evaluates attention that is concentration, visual perception, visuospatial orientation and visuomotor abilities. Part B evaluates, besides mentioned, complexes conceptual following as an executive ability.

Hooper Visual Organisation Test (Hooper, 1958) is a test of visual organisation, not in correlation to sex, education and age of tested person. Tasks require visuo-perceptive analysis and conceptual reorganization including mental rotation of fragmentary objects. Test is convenient for differentiation of visuospatial and visuomotor component at certain constructive tasks. Test is without localization value but is sensitive to brain pathology discover as well as to quality discover of fragmentary observation.

Wisconsin Card Sorting Test (Heaton, 1981) is the most known test for perseveration and mental rigidity detection (ability of set change and maintenance). Card sorting is good method of testing the way of problem solving. This test measures perseveration, conceptual ability, non perseverant aspects of mistake and learning improvement. It was at first used for abstraction evaluation in healthy people (Grant, Berg, 1948).

Results

Patients age structure in accordance with stage of Parkinson’s disease is shown at Table 1. According to examination results, average value was 60.2 years for male, and 64.3 years for female.

Table 1. Patients age structure in accordance with stage of PD

<table>
<thead>
<tr>
<th>Sex</th>
<th>Stage of PD</th>
<th>N</th>
<th>%</th>
<th>Average Age of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>I</td>
<td>10</td>
<td>40</td>
<td>56.0</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>5</td>
<td>20</td>
<td>64.4</td>
</tr>
<tr>
<td>Females</td>
<td>I</td>
<td>8</td>
<td>32</td>
<td>62.2</td>
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<tr>
<td></td>
<td>II</td>
<td>2</td>
<td>8</td>
<td>66.4</td>
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Table 2. Average values (X) and standard deviations (SD) of neuropsychological tests

<table>
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<th>Control group</th>
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<td>NPT</td>
<td>X1</td>
<td>X2</td>
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<tr>
<td>MMSE</td>
<td>26.5</td>
<td>29.5</td>
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<tr>
<td>TMT-A</td>
<td>110.4</td>
<td>70.5</td>
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<tr>
<td>TMT-B</td>
<td>261.6</td>
<td>145.6</td>
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<tr>
<td>RAVLT N</td>
<td>31.5</td>
<td>39.5</td>
</tr>
<tr>
<td>RAVLT E</td>
<td>4.5</td>
<td>8.6</td>
</tr>
<tr>
<td>RAVLT R</td>
<td>6.2</td>
<td>8.9</td>
</tr>
<tr>
<td>WCST categ.</td>
<td>1.1</td>
<td>3.2</td>
</tr>
<tr>
<td>HVOT</td>
<td>20.25</td>
<td>26.5</td>
</tr>
<tr>
<td>N - number of patients with PD</td>
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The period from the beginning of the disease to neuropsychological examination was 1 to 2 years. Patients were at I and II stadium, classified according to classic clinical scale of Hoehn and Yahr. At I stadium, where signs of disease are expressed only at one side of the body, there were 18 patients (72%), 10 men (40%) and 8 women (32%). At II stadium, where signs are present on both sides but without postural disorders, there were 7 patients (28%), 5 men (20%) and 2 women (8%).

For neuropsychological evaluation of patients and healthy persons in control group, we used following tests: Mini Mental State Examination, Trail Making Test (form A and B), Rey Auditory Verbal Learning Test, Wisconsin Card Sorting Test and Hooper Visual Organisation Test. Table 2. gives statistic parameters of

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NPT - neuropsychological tests, MMSE - Mini Mental State Examination, TMT - Trail Making Test (part A and B), RAVLT - Rey Auditory Verbal Learning Test, WCST categ. - Wisconsin Card Sorting Test categories, HVOT - Hooper Visual Organization Test, N - number of memorised words, E - evocation, R - recognition, X - average values, SD - standard deviations, CV - coefficient of variation, Te - empiric value of T-test
used tests as well as elements for evaluation of these groups difference.

Mini Mental State Examination is used for differentiation demented from nondemented patients with Parkinson's disease, that is for evaluation of every person's global cognitive functioning. Our results show statistically significant difference between Mini Mental State Examination score average values of patients and healthy individuals from control group, although all scores were above boarder values that indicates dementia (Table 2).

Evaluation of direct and postponed verbal memory is done by using Rey Auditory Verbal Learning Test. Attention is focused on total number of directly memorized words, evocation and recognition. There is statistically significant difference in total number of directly memorized words between a group of patients with Parkinson's disease and control group.

Results obtained show dysfunction of direct memory at nondemented patients. Statistically highly significant difference is evidenced in postponed verbal memory between patients and control subjects, indicating to dysfunction and those forms of memory at parkinsonian patients. By accomplishment evaluation in the part of test corresponding to recognition, statistically significant difference between control group and group of patients isn't detected (Table 2).

Trail Making Test is, at our work, used for evaluation of attention, concentration, visual observation, visuospatial orientation and visuomotor abilities (part A) as well as complexes conceptual following, belonging to executive abilities (part B). We noticed statistically highly significant difference of accomplishments on these test between a group of patients with Parkinson's disease and healthy subjects in control group, indicating presence of these functions disorders in nondemented patients (Table 2).

It is detected for parkinsonian patients on Wisconsin Card Sorting Test (used for evaluation of executive functions) to have more difficulty to form concept, have larger number of total and nonperseverative mistakes comparing to control group. By analyzing patient's behavior during this test, dissociation between thinking and action is detected behind strictly formulated verbal answer there is no adequate action.

Ability of visuoperceptive analysis and conceptual reorganization of tested subjects in both groups is evaluated by using Hooper Visual Organisation Test. There is statistically highly significant difference of score average values between control group and group of patients. These results confirm Hooper Visual Organisation Test, besides being sensitive test for dementia appearance and for duration of PD, indicate early dysfunctions of visual organization of nondemented patients (Table 2).

In this paper Wisconsin Card Sorting Test is used as method for evaluation of way to solve problems. This test evaluates perseveration, conceptual ability and learning improvement. Statistically highly significant difference is proved at number of accomplished categories between group of patients with Parkinson's disease and control group of healthy individuals. These results reflect presence of executive dysfunctions, even at nondemented patients at incipient stadiums of Parkinson's disease (Table 2).

From the table of t-test probability level of 0,05, theoretic fault for level of freedom is defined DF = 45 – 2 = 43 and measures t = 2.01. For risk level 0.01 theoretic t-test value is t = 2.69.

Statistically significant difference in used neuropsychological tests is evidenced between a group of parkinsonian patients and healthy subjects in control group.

Discussion

Parkinson's disease is a neurodegenerative disorder whose main clinical features are rigidity, tremor, akinesia and postural instability. Cognitive dysfunction of subcorticofrontal type sometimes leading to dementia. Cognitive deficits are common in Parkinson's disease, in particular in younger onset patients. The dysfunction of the striato-frontal circuits that occurs in this disorder, results in cognitive and behavioural problems as well as motor disturbances (1). However, even untreated, nondemented patients can show cognitive deficits. Girotti et al's neuropsychological investigations have indicated that non-demented patients with Parkinson's disease are impaired in several cognitive tasks (2). These mild cognitive dysfunctions do not progress to full dementia in all patients with Parkinson's disease. The premorbid personality profile of parkinsonian patients is characterized by a number of traits which figure prominently after the disease becomes manifest. Anxiety and depression have been shown to precede in some patients motor manifestations (3). Less novelty seeking is one premorbid trait providing an understanding of later cognitive deficits. Early detection of preclinical signs predictive of late dementia would have considerable clinical and therapeutic value.

In this paper, neuropsychological evaluation of patient with Parkinson's disease and healthy persons from control group, is done by using chosen series of tests. Evaluation of cognitive functions means establishing level and quality of their damage. Cognitive dysfunctions are manifested as measurable activity, skills, knowledge and intellectual capacity disorders so that their influence on subjects behavior can be followed. Evaluation of cognitive dysfunctions enables analysis of their neuroanatomical substrate. Impaired dopaminergic projections in the nigrostriatal pathway form the pathophysiological basis of Parkinson's disease.

Patients with Parkinson's disease show worst results at neuropsychological tests in memory and recognition of previously learned data after period of delay, comparing to normal values, but they are at the level of direct free memory. They have unable mechanism for calling information; they keep only the number of learned information got into the system of short – dated memory.
Past researches evidenced certain cognitive deficits insufficient for diagnosis of dementia at 93% of six persons at incipient stadium of Parkinson's disease. Changes in personality and temper are present, although mental status is relatively preserved. Memory disorders and disorders of visuospatial and executive functions are the most frequent. These isolated disorders of neuropsychological functions do not always evaluate to developed clinical picture of dementia and can be diagnostician in patients with Parkinson's disease who perform their professional activities successfully. Mohr et al. investigated the profile and extent of cognitive deficits in parkinsonian patients who continue to function successfully in leadership positions (4). While patients showed relative preservation of higher executive functions, they exhibited a significant reduction in episodic memory and visual-spatial function. The observation of these authors implicates cognitive and memory deficits as consistent features of Parkinson's disease.

Performance on the Wisconsin Card Sorting Test crucially depends on concept formation in addition to set shifting. In our study this test is used as method for evaluation of "way to solve problems". This test evaluates perseveration, conceptual ability, learning improvement. Our results reflect presence of executive dysfunctions, even at nondemented patients at incipient stadiums of Parkinson's disease, and are same as other authors results.

Cools et al. (5) showed a specific cognitive set shifting deficit in patients at the earliest stages of the Parkinson's disease, in a non-learning context. The impairment in task-set switching was only apparent when competing information was present. The data show that the shifting deficit is only present when stimuli activate the currently inappropriate task.

In Parkinson's disease, there is central programming deficit that manifests itself in verbal, figural and motor modalities. A diminished "shifting aptitude" is characteristic of patients with dysfunction of basal ganglia (6).

Flowers et al. described the effect of Parkinson's disease on the ability to maintain a mental set (7). The pattern of errors showed that the difficulty arises from instability of cognitive set rather than increased distractibility or loss of reasoning ability.

The basal ganglia play a crucial role in the selection and inhibition of competing cognitive and motor programs. Competing motor mechanisms are inhibited by subthalamic nucleus activation, leading to increased impact of tonically active inhibitory output of basal ganglia on thalamocortical areas and the brainstem. The striatum has been widely implicated in cognition, but a precise understanding of its role remains elusive. Context-dependent inhibitory output from the striatum selectively decreases activity in the globus pallidus, leading to disinhibition of the desired thalamocortical and brainstem programmes. The existence of large corticostral projections that subserved mainly cognitive functions, indicates that the basal ganglia could play important role in cognition (8).

Domains of cognition that are related to frontal network function appear to be most affected, including executive function, set switching and working memory. Working memory refers to the ability to maintain information and manipulate it in the service of guiding behavior. Working memory is thought to be subserved by components of a frontostriatal circuit that includes the dorsolateral prefrontal cortex and the caudate nucleus. Deficit of dopamine in the caudate nucleus or deficiencies of other neurotransmitters projecting to the dorsolateral prefrontal cortex are possible mechanisms for working memory deficits (9).

Press et al. suggest that procedural learning deficits may explain impairments in working memory performance in Parkinson's disease (10). Procedural learning is thought to be subserved by a frontostriatal network parallel to the working memory circuit, with cortical nodes in the primary motor, premotor and supplementary motor cortices, and the striatal node in the putamen. Working memory circuits and procedural learning circuits have separate striatal nodes. The caudate nucleus being preferentially involved in working memory. These findings may have important implications for studies of cognitive function in Parkinson's disease. As the putamen acts as the striatal node in the procedural learning circuit, parkinsonian patients have more difficulty with the procedural component of cognitive tasks.

Disruption of nondopaminergic subcortico-frontal systems has also been considered as a cause of cognitive disturbances in Parkinson's disease. The cholinergic system has been implicated in frontal lobe dysfunction. Many other neurotransmitter systems, such as serotoninergic and noradrenergic pathways, are damaged, and their projections to the prefrontal cortex could be involved.

Vingerhoets et al. investigated in familial Parkinson's disease, a genetically determined metabolic defect could be responsible for lesions involving the dopaminergic structures of the striatoprefrontal circuits, leading to a moderate cognitive impairment. In sporadic Parkinson's disease, an acquired metabolic defect involving more widespread structures of the striatoprefrontal circuits, leading to larger disruption of the dopaminergic and nondopaminergic loops (11). Cholinergic deprivation has also been considered as a cause of cognitive impairment in Parkinson's disease.

In the early stages of Parkinson's disease the most frequent cognitive abnormalities are reported in executive functioning, memory and spatial behavior. These cognitive dysfunctions indicate frontal lobe involvement, an observation that correlates with the nigrostriatal dopamine deficiency in Parkinson's disease (12).

Trail Making Test is, at our work, used for evaluation of attention, concentration, visual observation, visuospatial orientation and visuomotor abilities (part A) as well as complexes conceptual following, belonging to executive abilities (part B). We noticed statistically highly significant difference of accomplishments on these test between a group of patients with Parkinson-
son's disease and healthy subjects in control group, indicating presence of these functions disorders in non-demented patients, and this is according to the literature data.

Studies in patients with Parkinson's disease suggest that the characteristic motor symptoms of the disorder are frequently accompanied by impairments in cognition, that are most profound in tasks of executive function. To determine the underlying neural correlate of these cognitive deficits, Bodis-Wollner used functional magnetic resonance imaging (13). This examination revealed significant signal intensity reductions during a working-memory paradigm in specific striatal and frontal lobe sites, in patients with cognitive impairment. These results demonstrate that cognitive deficits in Parkinson's disease are accompanied by neural changes that are related to, but distinct from, those changes that underlie motoric deficits in these patients.

In our study, tests depending on executive function were affected. Our results were thus in agreement with those of previous studies, showing an enhancement of set-shifting difficulties and working memory deficits in parkinsonian patients.

The various cognitive symptoms found in Parkinson's disease are secondary to executive dysfunction. The memory deficits resulted from executive dysfunction. Patients with Parkinson's disease have difficulties in self-elaboration of internal strategies for organizing material when its organization is not explicit, and for retrieving it from long term memory. Higginson et al. suggest that working memory is a key factor in recall memory and may mediate the relationship between other executive measures and recall in Parkinson's disease (14).

In our study, evaluation of direct and postponed verbal memory is done by using Rey Auditory Verbal Learning Test. Attention is focused on total number of directly memorized words, evocation and recognition. Our results show dysfunction of direct memory at nondemented patients, which is already detected at past works. Statistically highly significant difference is evidenced in postponed verbal memory between patients and control subjects, indicating to dysfunction and those forms of memory at parkinsonian patients. By accomplishment evaluation in the part of test corresponding to recognition, statistically significant difference between control group and group of patients isn't detected, same as some earlier studies about this theme.

We agree with Djuardin et al. who found an impairment of planning and initiating a systematic search in semantic memory, in parkinsonian patients (15). They suggested the predictive value of impaired verbal fluency as an impairment of planning and initiating a systematic search in semantic memory, rather than a primary impairment of language.

McNamara et al. attempted to document counterfactual processing abilities in patients with Parkinson's disease (16). Counterfactuals are mental representations of alternatives to past events. On the other hand, counterfactuals are mental simulations of "what might have been". Recent research of these authors, has shown them to be important for other cognitive processes, such as causal reasoning, decision making and problem solving. All of these processes have been linked to the frontal lobes. Counterfactuals play a significant role in conceptual learning and performance improvement. These authors found that parkinsonian patients were impaired on tests of counterfactual thinking. This impairment was related to prefrontal dysfunction, rather than to general cognitive impairment.

Visuo-cognitive impairment is prevalent in Parkinson's disease. Retinal dopaminergic deficiency has been shown in parkinsonian patients. Dopaminergic neuronal groups in the retina, basal ganglia and frontal cortical memory system are affected in Parkinson's disease. Visuo-spatial deficits are not passive reflections of retinal deficiency. Saccadic eye movements are affected in Parkinson's disease. Functional magnetic resonance imaging studies show an essential role of the occipital cortex in saccadic eye movements. Visual and eye movement studies suggest that cognitive deficits in parkinsonian patients are linked to the visual system. Synchrony of signals is essential for the cooperation of distributed neuronal network engaged in sensory-motor coordination. It is suggested that to understand visuo-cognitive changes, we should consider pathology affecting neuronal connections, necessary for binding parallel distributed networks.

Deficits in visuo-spatial ability can be associated with Parkinson's disease, and there are several possible reasons for these deficits. Dysfunction in fronto-striatal and fronto-parietal systems, associated with dopamine deficiency, might disrupt cognitive processes (17). The goal of our study was to assess visuo-spatial orientation ability in individuals with Parkinson's disease, using the Hooper Visual Organisation Test. Nondemented persons with Parkinson's disease were significantly less accurate on this test than matched control persons. Our results indicate that Parkinson's disease, even in early stages, is associated with visuo-spatial orientation deficits.

The basal ganglia have numerous connections not only with the motor cortex but also with the prefrontal and limbic cortical areas. Therefore, basal ganglia lesions can disturb motor function but also cognitive function and emotion processing. Early in the course of Parkinson's disease, non-verbal emotional information processing is disturbed. This suggests that in Parkinson's disease, nigrostriatal dopaminergic depletion leads not only to motor and cognitive disturbances, but also to emotional information processing deficits (18).

Several studies have investigated the relation between motor symptoms and the risk of cognitive impairment in Parkinson's disease. Mahieux et al. found an association between tremor at onset and impairment on specific cognitive measures (19). Tremor at onset may be a marker for damage to non-dopaminergic neuronal systems that contribute to an increased risk for cognitive impairment. The finding that the patients with tremor at
onset showed more pronounced impairment on variables of memory and attention, than the akinetic/rigid group of patients, suggests possible non-dopaminergic involvement.

Benbunan et al. investigated the cognitive state of patients with early onset autosomal recessive parkinsonism and a large deletion in the parkin gene (20). They compared it to that of patients with sporadic young onset Parkinson's disease. Patients with parkin mutation performed poorly on neuropsychological test compared to those without parkin gene. This difference could reflect the nature of the degenerative process, or the longer disease duration.

A growing body of evidence suggests that the various cognitive symptoms found in early stages of Parkinson's disease are secondary to executive dysfunction. Although the present results need to be confirmed with a larger number of patients, the observation of cognitive impairment further implicates cognitive and memory deficits as consistent features of Parkinson's disease.

**Conclusion**

The Hooper Visual Organisation Test, besides being a sensitive test in dementia and according to the time of Parkinson's disease existence, indicates an early dysfunction of the visual organisation in such patients. Accomplishments in the Trail Making Test indicate the existence of attention, concentration, visual observation, visuospatial orientation and visuomotor abilities disorders (part A) as well as conceptual following (part B) in nondemented patients with Parkinson's disease. By using the Rey Auditory Verbal Learning Test disorder of direct memory and postponed verbal memory in nondemented parkinsonian patients is registered. The Wisconsin Card Sorting Test indicates the existence of executive dysfunctions at sick subjects in an early phase of the disease, without the clinical signs of dementia. Used neuropsychological tests have diagnostic value in cognitive dysfunction detection, in an early phase of Parkinson's disease. By neuropsychological testing we can get data on the cerebral dysfunction that can be used for diagnostic, therapeutic, rehabilitational and research purposes.

**References**

ISPITIVANJE KOGNITIVNIH FUNKCIJA OSOBA OBOLELIH OD PARKINSONOVE BOLESTI

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Ključne reči: Kognitivni poremećaji, Parkinsonova bolest, neuropsihološko testiranje