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THE CORRELATION BETWEEN NEUROPSYCHOLOGICAL AND NEUROPHYSIOLOGICAL PARAMETERS IN EARLY STAGES OF PARKINSON'S DISEASE

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Summary. *Cognitive status of patients with Parkinson's disease is characterized by disorders of attention, short-term memory, constructive abilities, as well as by visuospatial disorders. The aim of our study was to establish the level of correlation between applied neurophysiological and neuropsychological tests in early diagnosis of initial cognitive disturbances in patients with Parkinson's disease.*
A group of 30 patients, both males and females, were examined. According to the clinical scale by Hoehn and Yahr, the patients were in the first and second stage of Parkinson's disease. Patients did not show any clinical signs of dementia and depression. Tests for frontal functions, visuomotor skills, visual organization, memory and P300 event-related potential were administered.
By the analysis of partial correlations we established a statistically highly significant correlation between Mini Mental State Examination scores and P300 parameters latencies for Parkinsonian patients. The results showed that latencies of N2 and P3 waves depended on the level of global cognitive functioning. The statistically highly significant correlation between the achievements in Trail Making Test and latency values for P300 parameters suggested the existence of attention and concentration disorders in the early stages of the disease. Due to dopamine deficit, visual information was difficult to evaluate, even in initial stages of the disease. The existence of executive functional disorders evaluated through Wisconsin Card Sorting Test scores were in a statistically significant correlation with P3 wave mean latency value. This result suggested a relationship between the processes of stimulus evaluation, that is, conscious recognition of change in the stimuli sequence, and correct performance of the task.

Key words: *Parkinson's disease, cognitive disturbances, neuropsychological testing, event-related potential, P300*

Introduction

Cognitive impairment is now a well-recognized feature of idiopathic Parkinson's disease. While Parkinson's disease primarily impairs motor function, numerous studies have shown that it also affects cognition. Patients exhibit decrements in multiple spheres of cognition. The cognitive status of these persons is characterized by disorders of attention, short-term memory, constructive abilities, as well as by visuospatial disorders and bradyphrenia.

Recent studies have shown that dementia is accompanied by Parkinson's disease in 14-40% of ill subjects. Dementia is of the "subcortical-frontal" type, the genesis of which is triggered by lesions to subcortical structures, leading to cognitive programme "deactivation" in the cerebral cortex. Dementia presents with dysexecutive syndrome marked by slowness of mental processes, memory disorders, change in personality, as well as by impaired usage of accomplishments.

Parkinson's disease, associated with nigrostriatal and mesocorticolimbic dopamine depletion, is accompanied by cognitive impairments even in early stages. Numerous studies of patients with Parkinson's disease suggest that the characteristics of motor symptoms are accompanied by impairments in cognition that are most profound in tasks of executive function. Every form of a psychic and intellectual effort significantly worsens motor disorders, which is the evidence for the integrative role of basal ganglia. However, selective cognition deficits can be found even in Parkinsonian patients with no mental deterioration. Cognitive disorders and disorders in new manual skills and concentration deficits are evident. Patients with 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 inevitably an eminence of Parkinson's disease but its expression depends on the nature of the task (visuomotor, cognitive) and on the usage of dopaminergic medication.

The Aim of the Study

The aim of this paper is to establish the level of correlation between applied neurophysiological and neuropsychological tests in early diagnosis of initial cognitive disturbances in patients with PD.

Patients and Methods

A group of 30 patients, 18 males and 12 females, were examined. According to the clinical scale by Hoehn and Yahr, the patients were in the first and second stage of Parkinson's disease. They met diagnostic criteria of idiopathic Parkinson's disease. Using other clinical methods, we preliminary excluded other etiological possibilities for Parkinsonian syndrome genesis. The patients did not have any clinical signs of dementia and depression. The subjects under study did not get substitution therapy. There were 15 healthy subjects of either sex and various age that served as controls.

Tests for frontal functions, visuomotor skills, visual organization and memory were administered. P300 event-related potential of long latency was used to test cognitive functions of the patients suffering from Parkinson's disease. We used the following neuropsychological tests: Mini Mental State Examination, Ray Auditory Verbal Learning Test, Trail Making Test (form A and B), Hooper Visual Organisation Test, Wisconsin Card Sorting Test. Mini Mental State Examination is a test which evaluates the low grade of cognition in patients with dementia. It is a screening test primarily made for the evaluation of dementia stage. Due to its simplicity, it is widely used. Ray Auditory Verbal Learning Test evaluates verbal learning and memory. The test is short and convenient for direct and postponed verbal memory evaluation. While testing these functions, direct memory (attention span) is measured, learning strategy is defined, the curve of learning is formed, proactive and retroactive interference is found, tendency to confabulation is detected, and recognition and retention are evaluated. Attention is defined as the ability to focus on a specific stimulus without distraction by another stimulus. This test is a prerequisite for cognitive functioning. Concentration refers to prolonged attention, i.e., the ability of focused attention within a long period of time. Trail Making Test consists of two parts, A and B, each of which defines a specific assignment. Part A mostly evaluates attention, visual perception, visuospatial orientation and visuomotor abilities. In addition to the abilities in Part A, Part B evaluates complex conceptual following as an executive ability. Hooper Visual Organisation Test is a test of visual organisation, independent of sex, education and age of persons under testing. The tasks require a visuoperceptive analysis and conceptual reorganization including mental rotation of fragmented objects. The test is convenient for differentiation of the visuospatial from visuomotor component at certain constructive tasks. It has no localization value but is sensitive to detection of brain pathology, as well as to quality detection of fragmentary observation. Wisconsin Card Sorting Test is the most known test for perseveration and mental rigidity detection (ability of set change and maintenance). Originally, it was used for abstraction evaluation in healthy people. Card sorting is a good method of testing the path in which problems are solved. This test measures perseveration, conceptual ability, non-perseverant aspects of mistake and learning improvement.

P300 event-related potential can be evaluated in everyday clinical practice, using healthy subjects and patients with some cognitive dysfunctions. Subjects under evaluation should be adequately cooperative during the procedure, because the registration requires relatively simple experimental conditions. The subjective factors that can influence the characteristics of P300 parameters include the subject's age, level of alertness and active attention. Important factors for clinical application of P300 method in clinical conditions are stability and ability to reproduce results. Neurophysiological assessment of cognitive disorders is performed by means of registering the waves of P300 event-related potential by application of the "oddball" paradigm (sound stimulus of a certain intensity and frequency) using a Medelec "Sapphire" apparatus. P300 event-related potential is an electrical response that is registered when the subject follows a sequence of regular, expected auditory signals and detects the appearance of "target" signals that differ from "standard" signals by their pitch (frequency). The "oddball" paradigm is a task that requires both attention and concentration on the part of the subject. As stimuli, we used 1000Hz and 2000Hz tones, 80db in strength and 60ms in duration. The subjects were required to count 2000hz tones, defined as target stimuli. The subjects frequently ignored 1000Hz tones since they were "non-target" stimuli. The procedure was defined as successful if the error was not higher than 10%. This was established at the end of the procedure by comparison of the real number of emitted "target" stimuli with the number reported by the subject. The time of the analysis was 1000ms, frequency ranged from 0.1 to 50 Hz, and mean value was 125 stimuli. P300 event-related potential is created as response to the "target" stimulus. The standard tone creates a series of negative and positive waves marked as N1, P2 and N2 whose latencies are shorter compared to P3 wave whose latency was around 300ms.

Statistical processing of the results obtained during this research was performed using a Microsoft Excel program. The following statistical parameters were analyzed: arithmetical mean (X), standard deviation (SD), result variations (minimal and maximal values), and variation quotient (CV). The evaluation of the statistical significance of the result difference was performed using "t-test" and calculating the linear correlation quotient (r). The significance of the difference between the patient group and the controls was marked as $p < 0.05$ for statistically significant and $p < 0.01$ for statistically highly significant differences. The linear correlation quotient was calculated for all results, and the borderline value $p < 0.05$ was accepted.

Results

The age group of patients according to the stage of Parkinson's disease is shown in Table 1. According to

examination results, the average value was 61.4 years for males, and 64.8 years for females. The period from the onset of the disease to neuropsychological examination was 1 to 2 years. The patients were at Stadiums I and II, and classified according to the classic clinical scale of Hoehn and Yahr. At Stadium I, when signs of the disease are expressed only on one side of the body, there were 18 patients (60%), 12 men (40%) and 6 women (20%). At Stadium II, when signs are present on both sides but without postural disorders, there were 12 patients (40%), 6 men (20%) and 6 women (20%).

Table 1. Patients age structure in accordance with stage of Parkinson's disease

Sex	Stage of disease	N	%	Average age of patients	
Males	I	12	40	59.6	61.4
	II	6	20	63.2	
Females	I	6	20	62.4	64.8
	II	6	20	67.2	

N - number of patients with Parkinson's disease

For neuropsychological evaluation of patients and healthy controls, we used the following tests: Mini Mental State Examination, Trail Making Test, Ray Auditory Verbal Learning Test, Wisconsin Card Sorting Test and Hooper Visual Organisation Test. Table 2 shows statistic parameters of the tests used, as well as the elements for evaluation of differences between the groups.

Mini Mental State Examination was used for differentiation of demented from non-demented patients with Parkinson's disease, that is, for evaluation of the person's global cognitive functioning. Statistically, our results showed a significant difference between the patients and healthy controls with respect to the average values of Mini Mental State Examination scores, although all the scores were above the border values indicating dementia (Table 2).

The evaluation of direct and postponed verbal memory was done using Ray Auditory Verbal Learning Test. Attention was focused on a total number of directly memorized words, evocation, and recognition. Statistically, there was a significant difference between Parkinsonian patients and controls with respect to the total number of directly memorized words. The obtained results suggest a dysfunction of direct memory in non-demented patients, which was already detected in previous studies. A statistically highly significant difference is evidenced in postponed verbal memory between patients and control subjects. By accomplishment evaluation in the part of the test corresponding to recognition, a statistically significant difference between controls and patients was not detected, which is in line with some earlier study results (Table 2).

We used Trail Making Test for evaluation of attention, concentration, visual observation, visuospatial orientation and visuomotor abilities (Part A), as well as complex conceptual following as part of executive abilities (Part B). A highly significant difference in accomplishments on the test was registered between Parkinsonian patients and healthy controls, thus indicating the presence of the assessed functional disorders in non-demented patients (Table 2). This result also corresponds to the available literature data.

The ability of visuoperceptual analysis and conceptual reorganization in the tested subjects of both groups was evaluated using Hooper Visual Organisation Test. There was a statistically highly significant difference in score average values between controls and patients. These results confirm that Hooper Visual Organisation Test, in addition to being a sensitive test for dementia onset and for duration of Parkinson's disease, can be indicative of early dysfunctions of visual organization in non-demented patients (Table 2).

We used Wisconsin Card Sorting Test as the method for evaluation of the problem-solving path. This test evaluates perseveration, conceptual ability, and learning improvement. When used for evaluation of executive functions, Wisconsin Card Sorting Test shows that Parkinsonian patients have more difficulty in forming concepts and a greater number of total and non-pre-

Table 2. Statistic parameters of used neuropsychological tests

NPT	MMSE	TMT-A	TMT-B	RAVLT			WCST CATEG.	HVOT
				N	E	R		
Patients								
X_1	26.5	110.4	261.6	31.5	4.5	6.20	1.10	20.25
SD_1	2.5	21.6	48.2	8.80	1.5	1.2	0.05	2.5
CV_1	0.05	0.2	0.22	0.24	0.22	0.21	0.08	0.55
Control group								
X_2	29.5	70.50	145.60	39.50	8.60	8.90	3.20	26.50
SD_2	0.5	10.5	21.2	2.4	0.80	0.50	1.5	1.6
CV_2	0.05	0.15	0.16	0.06	0.15	0.08	0.3	0.05
Te	2.2	6.4	7.5	2.5	6.8	1.9	6.2	77.6

NPT – neuropsychological test
MMSE – Mini Mental State Examination
TMT – Trail Making Test (form A and B)
RAVLT – Ray Auditory Verbal Learning Test
N – number of memorized words
E – evocation
R – recognition
WCST CATEG. – Wisconsin Card Sorting Test categories
HVOT – Hooper Visual Organisation Test
X – average value
SD – standard deviation
CV – coefficient of variation
Te – empiric value of T-test

servative mistakes compared to controls. A statistically highly significant difference was established between Parkinsonian patients and controls for a number of accomplished categories. By analyzing the patients' behavior during this test, dissociation between thinking and action was detected and no adequate action was generated after a precisely formulated verbal answer. These results are in accordance with the literature data in that they suggest the presence of executive function disorders even in non-demented patients in incipient stadiums of Parkinson's disease (Table 2).

From the table of t-test for probability level 0.05, the theoretical error for level of freedom is defined as DF = 43 and for border values t = 2.01. For the risk level 0.01, the theoretical t-test value is t = 2.69.

P300 event-related potential was administered in diagnosis of the patients' cognitive disturbances. Table 3 shows the mean latency values for P300 parameters for both the Parkinsonian group and controls, expressed in milliseconds (ms). The significance of the latency differences for P300 parameters for the Parkinsonian patients and controls was determined by comparing the calculated Te with the theoretical value of t-test. From the table for borderline values of t-test for risk probability 0.05 and degree of freedom DF = 43, the theoretical value of t-test is 2.01.

In previous studies, the average latency value of N1 wave was usually registered within the range from 89.4 to 109.1 ms. In our study, the value obtained was 102.0 ms for the Parkinsonian patients and 97.7 ms for controls. The mean latency value of P2 wave found in literature ranges from 159.1 to 193.9 ms whereas ours is 180.0 ms for the patients and 173.0 ms for controls. In earlier studies, the mean latency value of N2 wave ranges from 208.0 to 260.1 ms, while in our study it is 260.0ms for the patients and 243.0 for controls. The mean latency value of P3 wave registered in literature was within the range 320.8 - 385.0 ms and in our research it is 360.0 for the patients and 340.0 for controls (Table 3).

Between the Parkinsonian patients and controls, no statistically significant differences in the mean latency values for N1 and P2 waves were noticed, all registered latencies being within the range of normal values. We noticed a statistically significant difference in the mean latency values between N2 and P3 waves for the Parkinsonian patients and the controls, although all registered values were within the normal range (Table 3).

On the basis of the obtained results, we performed a complete cross-examination of correlation degree of latencies of P300 parameters and scores from applied neuropsychological tests. Correlation quotients are given in Table 4. In order to facilitate viewing, only a half of

Table 3. Latencies of P300 parameters in patients with Parkinson's disease and control group (in milliseconds)

Latency	Patients					Control group					
(ms)	X	SD	CV	MIN	MAX	X	SD	CV	MIN	MAX	Te
N1	102	8.51	0.08	86	120	98	6.01	0.06	86	108	1.72
P2	180	11.80	0.07	158	198	173	6.81	0.04	164	184	1.94
N2	260	24.00	0.09	210	292	243	22.40	0.09	206	275	2.14
P3	360	28.70	0.08	310	407	340	21.50	0.06	302	378	2.36

X – average value of P300 parameter
SD – standard deviation
CV – coefficient of variation
MIN – minimal registered value
MAX – maximal registered value
Te – empiric value of t-test

Table 4. The correlation degree of latencies of P300 parameters and scores from applied neuropsychological tests in patients with Parkinson's disease

	P2	N2	P3	MMSE	TMT-A	TMT-B	RAVLT			WCST	HVOT
							N	E	R		
HVOT											
WCST											0.78
R										0.48	0.43
E									0.30	0.65	0.48
N								0.76	0.48	0.53	0.33
TMT-B							–0.32	–0.41	–0.42	–0.52	–0.56
TMT-A						0.92	–0.40	–0.47	–0.57	–0.53	–0.53
MMSE					–0.60	–0.60	0.54	0.53	0.56	0.79	0.76
P3				–0.50	0.45	0.48	–0.31	–0.26	–0.09	–0.38	–0.57
N2			0.45	–0.76	0.60	0.60	–0.42	–0.48	–0.49	–0.73	–0.68
P2		0.60	0.45	–0.84	0.55	0.49	–0.52	–0.55	–0.54	–0.70	–0.71
N1	0.54	0.69	0.62	–0.66	0.56	0.62	–0.43	–0.52	–0.33	–0.72	–0.59

N1, P2, N2, P3 – parameters of P300 event-related potential
MMSE – Mini Mental State Examination
TMT-A, TMT-B – Trail Making Test (form A and B)
RAVLT – Ray Auditory Verbal Learning Test
WCST – Wisconsin Card Sorting Test
HVOT – Hooper Visual Organisation Test
N – number of memorized words
E – evocation
R – recognition

the table is shown, because the values for correlation quotients are the same for reversed association of the given parameters. To determine correlation association of the parameters given in Table 4 we used the table of borderline values for the linear correlation quotient, and for degree of freedom DF = 28 and security degree 0.95 we obtained the theoretical value of $R_{0.05} = 0.361$, while for security degree 0.99 the theoretical value was $R_{0.01} = 0.463$.

Discussion

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 an increased impact of tonically active inhibitory output of basal ganglia upon the thalamo-cortical 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 the activity in the globus pallidus, leading to disinhibition of the desired thalamocortical and brainstem programmes. The existence of large corticostriatal projections that subserve main cognitive functions indicates that the basal ganglia could play an important role in cognition (1).

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 behavioral problems, as well as motor disturbances. However, even when untreated, non-demented patients can show cognitive deficits. The neuropsychological investigations by Girotti *et al*. (2) have indicated that non-demented patients with Parkinson's disease are impaired in several cognitive tasks. 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 some patients' motor manifestations (3). Early detection of pre-clinical signs predictive of late dementia would have a considerable clinical and therapeutic value.

In this paper, the neuropsychological evaluation of patients with Parkinson's disease and healthy controls was performed using a series of chosen tests. The evaluation of cognitive functions means establishing the level and quality of their damage. Cognitive dysfunctions are manifested as measurable activity, skills, knowledge and intellectual capacity disorders so that their influence on the subject's behavior can be monitored. The evaluation of cognitive dysfunctions allows for an analysis of these dysfunctions' neuroanatomical substrate. Impaired dopaminergic projections in the nigrostriatal pathway form the pathophysiological basis of Parkinson's disease (4).

Previous research studies evidenced certain cognitive deficits insufficient for diagnosis of dementia in 93% ill persons in the 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 evolve to developed clinical picture of dementia and can be diagnosed in those Parkinsonian patients who perform their professional activities successfully. Bodis-Wolner (5) investigated the profile and extent of cognitive deficits in Parkinsonian patients who function successfully in leadership positions. While patients showed relative preservation of higher executive functions, they exhibited a significant reduction in episodic memory and visual-spatial function. This observation implicates cognitive and memory deficits as consistent features of Parkinson's disease. Compared to normal values, the results that Parkinsonian patients show at neuropsychological tests for memory and recognition of previously learned data after period of delay are worse, although still at the level of direct free memory. Patients with Parkinson's disease have a damaged mechanism for recalling information; they keep in memory only that number of learned information that is stored in the system of short-term memory (6).

Performance on the Wisconsin Card Sorting Test crucially depends on concept formation in addition to set shifting. Cools *et al.* (7) showed a specific cognitive set-shifting deficit in patients at the earliest stages of Parkinson's disease, in a non-learning context. The impairment in task-set switching was only apparent when competing information were present. The data show that the shifting deficit is only present when stimuli activate currently inappropriate tasks. Dujardin *et al.* (8) described the effect of Parkinson's disease on the ability to maintain a mental set. The pattern of errors has shown that the difficulty arises from instability of cognitive set rather than increased distractibility or loss of reasoning ability.

Press *et al.* (9) suggest that procedural learning deficits may explain impairments in working memory performance in Parkinson's disease. Procedural learning is thought to be subservient 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 is 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 subcorticofrontal systems has also been considered 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.* (10) suggested that 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 leads to larger disruption of the dopaminergic and nondopaminergic loops. Cholinergic deprivation has also been considered a cause of cognitive impairment in Parkinson's disease.

Various cognitive symptoms that have been found in Parkinson's disease are secondary to executive dysfunction. The memory deficit has 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.* (6) 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. We agree with Dujardin *et al.* (8) who found that in Parkinsonian patients there is an impairment of planning and initiating a systematic search in semantic memory.

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. Studies of eye movements suggest that cognitive deficits in Parkinsonian patients are linked to the visual system (11). Synchrony of signals is essential for the cooperation of distributed neuronal network engaged in sensory-motor coordination. It is suggested that to understand visuocognitive changes we should consider the pathology affecting neuronal connections, necessary for binding parallel-distributed networks. However, it is conceivable that visuo-cognitive impairment in Parkinson's disease reflects on dysfunction of neural assemblies, involving basal ganglia, dorsal visual stream and frontal-prefrontal circuits (12).

Deficits in visual-spatial ability can be associated with Parkinson's disease, and there are several possible reasons for these deficits. Dysfunction in frontal-striatal and frontal-parietal systems, that are associated with dopamine deficiency, might disrupt cognitive processes (13). We assessed the visuospatial orientation ability in individuals with Parkinson's disease, using the Hooper Visual Organisation Test. Non-demented persons with Parkinson's disease were significantly less accurate at this test than matched controls. These results indicate that Parkinson's disease is associated with visuospatial orientation deficits.

P300 event-related potential was used to show cognitive functions of the patients suffering from Parkinson's disease. Cognitive status of these persons is characterized by disorders of attention, short-term memory, constructive abilities, as well as by visuospatial disorders and bradyphrenia. In Parkinsonian patients, P300 has a special significance for early detection of cognitive dysfunctions, before the clinical manifestation of dementia (14).

Event-related potentials are widely accepted as a useful procedure to assess cognitive functions. The P300 event-related potential is influenced by various factors, such as attention and mental fatigue. It also depends on stimulus conditions. Abnormal event-related potentials in idiopathic Parkinson's disease have been extensively studied, and P3 latency is prolonged even in non-demented Parkinsonian patients. Presumably, frontal lobe dysfunctions, including deficits in concept formation, maintenance and shifting, may contribute to the abnormality of event-related potentials in non-demented Parkinsonian patients. Hozumi *et al.* (15) suggest that prolongation of N1 latency might be related to frontal lobe dysfunction, and abnormality of P3 wave to dysfunction in both the frontal lobe and hippocampus in Parkinson's disease.

When registering P300 parameters, we obtained two records. The first record represents a response to standard stimuli to which the subject does not pay any attention because the potential of long latency is exogenously evoked. Its configuration depends on the integrity of sensory structures and stimulus modality. As a response to standard sound there is one negative N1 wave and one positive P2 wave. The negative N1 wave with the peak between 90-200ms after the initiation of stimulus is followed by the positive P2 wave. This complex is generated in primary auditory cortex, in the planum supratemporalis area and represents an exogenous ("stimulus-dependent") cortical auditory potential. N1 is the earliest evoked potential that can be modulated by psychological processes associated with selective attention. The responses similar to N1-P2 complex can also be obtained during the registration that does not require a conscious and voluntary activity of the subject (16). This complex is followed by N2-P3 complex composed of one negative and one positive wave. In the record that is registered as a response to "targeted" stimuli, the dominant component is P3 wave. It is a positive wave whose latency in healthy persons is 300-500ms and represents a neurophysiological parameter that is in correlation with the speed of cognitive processes (17).

Following the theory that predicts multiple areas for generation of P300 event-related potential, we assume its subcortical neural correlates exist. Subcortical P300 activity can be an electrophysiological reflection of mechanisms of program selection of a certain response from a set of possible programs. It is supposed that P3 waves are generated by the medial structure of the temporal lobus, that is, by hippocampal formation and the

temporo-parietal associative zone. The generation of P3 waves involves multiple, simultaneously active structures in the frontal, parietal and temporal lobus.

The psycho-physiological basis of P300 components that are registered as a response to "target" stimuli is very complex and not clearly defined. P300 event-related potential is generated when attention is directed to the processing of a new stimulus that is different from the mental model of the expected stimuli. P3 wave is a manifestation of the process of maintaining working memory. It is created during the change of structure of the mental model, thus constituting the memory representation of the stimulus. The amplitude of P3 wave, as well as other P300 components, is higher in informatively more significant, i.e., "richer" stimuli which require more attention than when applied to less important stimuli. P3 wave latency corresponds to the speed of stimuli classification based on discrimination between two events, when there is an adaptation of the mental model of structure of the stimulus to the actual event. Variations in P3 amplitude are manifestations of redirection of attention capacity and they correspond to the speed of redirection of these capacities (18).

N2-P3 complex is the most characteristic component of P300 because it corresponds to the processes associated with the evaluation of informative importance of stimuli and selection of a possible response. It can also be a reflection of redirection of active attention to change in the environment. It is considered that P3 latency, that is, N2-P3 complex represents an index of the cognitive functioning of the subject.

N1 and P2 wave latencies are correlates of CNS sensory processes. They reflect the time of depolarization wave conduction within primary auditory cortex. N2 wave latency is a reflection of early cognitive processes. It is a correlate of conscious recognition of the change in stimuli sequence. P3 wave latency corresponds to the time of stimulus evaluation. It reflects the speed of the classification of the stimulus based on discrimination of one event in relation to the other.

The results of Koberskaia *et al.* (19) and Ijima *et al.* (20) show that P300 event-related potential recording may be useful for diagnosis of subclinical cognitive disturbances in Parkinson's disease without dementia. Compared to controls, Parkinsonian patients exhibited a significantly prolonged P3 latency. The P300 changes in these patients can be interpreted as a decrease in directed activity level and partial defect of mental recognition processes and stimuli differentiation related mostly to the nonverbal cognitive processes.

In our study, we did not notice any statistically significant differences between Parkinsonian patients and controls with respect to the mean latency values of N1 and P2 waves. Nevertheless, we noticed a statistically significant difference in the mean latency values between N2 and P3 waves for the patients and controls, although all registered values were within the normal range. This points to a certain difference in time needed for stimulus evaluation between the patients and controls. Conscious recognition of the change in a stimuli sequence takes more time in patients with Parkinson's disease, although they do not have clearly manifested signs of dementia. Classification of stimuli, based on discrimination between two events, is slower in these subjects than in healthy ones. Naturally, these assumptions require further evaluation through involvement of a greater number of subjects in initial stages of Parkinson's disease.

In our study, we noticed a significant correlation between poor results at neuropsychological tests for global cognitive abilities, such as Mini Mental State Examination, and the lengthening of N2 and P3 latencies. A significant correlation was noticed between the latencies of N2-P3 complex and tests that more specifically examine short-term memory, active attention and abstract thought, with time limit for completion. In our research, by the analysis of partial correlations we established a statistically highly significant correlation between Mini Mental State Examination score and P300 parameter latencies for Parkinsonian patients. These results show that P300 parameter latencies, especially those of N2 and P3 waves, depend on the level of global cognitive functioning which is indicated by Mini Mental State Examination score.

We also established a statistically highly significant correlation between the achievements in neuropsychological attention tests and complex conceptual following (Trail Making Test A and B), concentration, visual perception, visuospatial orientation and latency values for P300 parameters. These results suggest the existence of attention and concentration disorders in the early stages of Parkinson's disease.

In previous studies, it was established that N1 and P2 wave latencies were not in a significant correlation with the previously mentioned neuropsychological parameters, which were also indicators of Central Nervous System functional integrity. P3 wave latency was in correlation with specific cognitive deficits of Parkinsonian patients. The most pronounced correlation was established with short-term memory and visual perception disorders. Abnormally lengthened or abnormal P3 wave was associated with difficulties in performance of selective cognitive tasks including memory, visual perception and abstract judgment.

The achievements in the test of verbal learning (Ray Auditory Verbal Learning Test) in our study were not in a significant correlation with the mean latency value of P3 waves registered in patients with Parkinson's disease.

In our study, the existence of executive functions disorders was evaluated through Wisconsin Card Sorting Test. Statistically, there was a significant correlation between its score and P3 wave mean latency value. Statistically, there were highly significant correlations with latencies of other P300 parameters. These results suggest a possible relationship between the processes of stimulus evaluation, that is, the conscious recognition of the change in a stimuli sequence, and the correct performance of the task.

Statistically, a highly significant correlation was established between mean latency values of P300 parameters and Hooper Visual Organisation Test scores. The task of visual organization tests required visuoperceptual analysis and conceptual reorganization. Due to dopamine deficit in Parkinsonian patient's Central Nervous System, there was a difficulty in the evaluation of visual information, even in initial stages of the disease.

The correlation between P300 event-related potential and activities of daily living was studied in Parkinson's disease (21). All patients were also evaluated using the Mini Mental State Examination. These patients showed prolonged P3 latencies. P3 latency showed to be in a significant relationship to the Mini Mental State Examination. It was concluded that P300 method should be useful in predicting difficulties in everyday activities of patients with Parkinson's disease.

To clarify the neuropsychological disturbances in Parkinson's disease, Hozumi *et al.* (15) used the Wisconsin Card Sorting Test, which was simpler and less ambiguous than other methods. They also examined P300 components evoked by auditory stimuli. In the Wisconsin Card Sorting Test, Parkinsonian patients had fewer categories achieved and a higher percentage of total errors, perseveration errors and difficulty in maintaining a set, compared to controls. In the latencies and the amplitudes of P300 components, there were no significant differences between the two groups. In the group of Parkinsonian patients, significant correlations were demonstrated between the P3 latency and the scores of the Wisconsin Card Sorting Test. These results showed that the Wisconsin Card Sorting Test was useful for detection of neuropsychological disturbances in Parkinson's disease and that P300 components evoked by simple task could not disclose it.

Low *et al.* (22) used the auditory event-related potential to detect dysfunction of mental switching (perseveration) in non-demented patients with Parkinson's disease. Patients were instructed to count the target tones. The Wisconsin Card Sorting Test was used to evaluate the frontal lobe function. Patients with Parkinson's disease showed a significant decrease in the achieved categories and an increase in perseveration errors at Wisconsin Card Sorting Test. When compared to the control group, Parkinsonian patients had longer P3 latencies. These results indicate that the cognitive impairment of Parkinsonian patients can be characterized as failure of mental switching related to frontal lobe dysfunction based on basal ganglia disturbance.

The purpose of Ijima *et al.*'s study (20) was to evaluate the relationship between P300 event-related potential and frontal cognitive functions in Parkinson's disease without clinically apparent dementia. The results that all Parkinsonian patients achieved at the Mini Mental State Examination were within normal limits. P300 was elicited with an auditory oddball paradigm. The cognitive functioning of the frontal lobe was evaluated using the Wisconsin Card Sorting Test. P3 latency significantly correlated with the number of subcategories achieved at the Wisconsin Card Sorting Test. These results suggest that cognitive dysfunction which is linked partly to the frontal lobe might begin in Parkinson's disease even without clinically apparent dementia.

Conclusion

The applied neuropsychological tests have a diagnostic value in cognitive dysfunction detection in the early phase of Parkinson's disease. Hooper Visual Organisation Test, besides being sensitive to dementia presence and duration of Parkinson's disease, indicates an early dysfunction of visual organisation in these patients. Accomplishments in Trail Making Test suggest the existence of attention, concentration, visual observation, visuospatial orientation and visuomotor abilities disorders (part A), as well as conceptual following (part B) in non-demented patients with Parkinson's disease. By using the Ray Auditory Verbal Learning Test, a disorder in direct memorizing and postponed verbal memory in non-demented Parkinsonian patients was registered. The Wisconsin Card Sorting Test indicates the existence of executive function disorders in sick subjects in early phase of the disease without clinical signs of dementia. We may conclude that neuropsychological tests are important for identification of early cognitive disturbances in Parkinson's disease.

The statistically significant difference in the mean latency values for N2-P3 complex P300 event-related potential registered between patients with Parkinson's disease and healthy controls confirms that conscious recognition of change in a stimuli sequence takes more time in Parkinsonian patients, although they do not have clearly manifested dementia signs. Based on the results of current research study we can conclude that neurophysiological P300 method has a diagnostic value in objectification of cognitive disturbances in early phases of Parkinson's disease without clinical signs of dementia.

Latencies of P300 parameters, and especially N2 and P3 waves depend on the level of global cognitive functioning, which is indicated by the Mini Mental State Examination score. The statistically significant correlation between Wisconsin Card Sorting Test scores and P3 waves mean latency values points to the relationship between the stimuli evaluation processes, that is, conscious recognition of change in the stimuli sequence, and correct performance of the given task.

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KORELACIJA IZMEĐU NEUROPSIHOLOŠKIH I NEUROFIZIOLOŠKIH PARAMETARA U RANIM STADIJUMIMA PARKINSONOVE BOLEST

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Kratak sadržaj: *Kognitivni status pacijenta obolelih od Parkinsonove bolesti se karakteriše poremećajima pažnje, kratkotrajnog pamćenja, konstruktivnih sposobnosti kao i vizuospacijalnim poremećajima. Cilj ovog rada je da ustanovi nivo korelacije između primenjenih neurofizioloških i neuropsiholoških testova u ranoj dijagnostici početnih kognitivnih poremećaja kod pacijenata sa Parkinsonovom bolešću.*

Ispitivana je grupa od 30 pacijenata, muškaraca i žena. Prema kliničkoj skali Hoehn-ove i Yahr-a, oni su bili u prvom i drugom stadijumu Parkinsonove bolesti. Pacijenti nisu imali kliničke znake demencije i depresije. Testovi frontalnih funkcija, vizuomotorne sposobnosti, vizualne organizacije, pamćenja i P300 kognitivni evocirani potencijal su primenjeni.

Analizom parcijalnih korelacija ustanovili smo statistički visoko značajnu korelaciju između skorova Mini Mental State testa i latencija P300 parametara kod parkinsonih pacijenata. Rezultati pokazuju da vrednosti latenca N2 i P3 talasa zavise od nivoa globalnog kognitivnog funkcionisanja. Statistički visoko značajna korelacija između postignuća na Trail Making testu i vrednosti latenca P300 parametara ukazuju na postojanje poremećaja pažnje i koncentracije u ranim stadijumima bolesti. Usled deficita dopamina otežana je evaluacija vizualnih informacija, čak i u početnim stadijumima bolesti. Poremećaji egzekutivnih funkcija procenjeni skorovima Wisconsin Card Sorting testa su u statistički značajnoj korelaciji sa srednjom vrednošću latence P3 talasa. Ovi rezultati ukazuju na uzajamnu povezanost procesa evaluacije stimulusa, kao što je svesno prepoznavanje promene u sekvenci stimulusa i korektnog izvođenja datog zadatka.

Ključne reči: *Parkinsonova bolest, kognitivni poremećaji, neuropsihološko testiranje, kognitivni evocirani potencijal, P300*