UDC 616.858-008.6:616.8-009.3]-073.97
DOI: 10.14739/2310-1237.2022.1.246660

Diagnostic value of motor evoked potential parameters in patients with Parkinson's disease stage II

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Key words: Parkinson disease, motor symptoms, motor evoked potentials, transcranial magnetic stimulation.

Pathologia 2022; 19 (1), 40-46

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The aim of our study was to identify the most informative parameters of motor evoked potential (MEP) based on clinical and neurophysiological comparisons in patients with Parkinson's disease (PD) stage II.

Materials and methods. The study included 90 patients aged 45 to 75 years with stage II PD according to Hoehn–Yahr. Examination of patients was performed according to the following scheme: clinical and neurological examination with MDS UPDRS scale and neurophysiological examination to determine the latency, amplitude and duration of MEP after 4 tests with a gradual increase of magnetic field induction. Our study involved patients with predominantly right and left-sided motor symptoms, so for correct statistical analysis, the dominant side was considered as the debut side or the side with more pronounced motor symptoms, the subdominant side was considered as the opposite one.

Results. In cases of patients with stage II PD the MEP latency significantly decreased, and the amplitude and duration of MEP significantly increased in samples with increasing magnetic field induction in the right and left hemispheres of the brain. It was found significant positive moderate correlation between UPDRS part III total score and MEP latency in the ipsilateral premotor cortex to the dominant side of motor symptoms with samples of magnetic induction (1.1 TI – r = 0.34, P < 0.05; 1.32 TI – r = 0.32, P < 0.05; 1.76 TI – r = 0.31, P < 0.05). Also positive mild correlation was found between MEP latency in the ipsilateral premotor cortex to the subdominant side of motor symptoms and UPDRS part III total score (1.54 TI – r = 0.22, P < 0.05; 1.76 TI – r = 0.29, P < 0.05). Mild positive correlation (r = 0.29, P < 0.05) was found between MEP duration of ipsilateral premotor cortex to the subdominant side of motor symptoms and UPDRS part III total score in sample with 1.54 TI magnetic induction. No significant correlations were found to the amplitude parameter and the severity of clinical symptoms in investigated patients with PD stage II.

Conclusions. The most informative neurophysiological indicators in patients with PD stage II are the MEP latencies. The MEP latencies of the premotor cortex, which is ipsilateral to the side with more pronounced motor symptoms, have a particularly close relationship with UPDRS part III total score in the samples with 1.10–1.76 TI magnetic inductions (r = 0.31–0.34, P < 0.05). The MEP duration of premotor cortex, which is ipsilateral to the side with less pronounced motor symptoms, is most closely associated with the severity of motor manifestations on the subdominant side in patients with PD stage II (r = 0.27, P < 0.05).

Ключові слова: хвороба Паркінсона, моторні симптоми, викликаний моторний потенціал, транскраніальна магнітна стимуляція.

Патологія. 2022. Т. 19, № 1(54). С. 40-46

Діагностична цінність параметрів моторного викликаного потенціалу в пацієнтів із хворобою Паркінсона II стадії

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Мета роботи – визначити найбільш інформативні параметри моторного викликаного потенціалу (МВП) у пацієнтів із хворобою Паркінсона (ХП) II стадії на підставі клініко-нейрофізіологічних зіставлень.

Матеріали та методи. У дослідження залучили 90 хворих віком від 45 до 75 років із ХП II стадії за Хен–Яром. Хворим здійснили клініко-неврологічне обстеження з оцінюванням за шкалою MDS UPDRS, а також нейрофізіологічне дослідження з визначенням латентності, амплітуди, площі та тривалості МВП після проведення 4 проб з поступовим підвищенням індукції магнітного поля. У дослідженні брали участь переважно пацієнти з право- та лівобічними моторними симптомами, тому для коректного статистичного аналізу домінантний бік вважали дебютним або боком із більш вираженими руховими симптомами, субдомінантний бік вважали протилежним домінантному.

Результати. Виявили, що в обстежених із ХП II стадії латентність МВП вірогідно зменшувалася, а амплітуда та тривалість МВП достовірно збільшувались у пробах із підвищенням індукції магнітного поля у правій і лівій гемісферах головного мозку. Визначили вірогідну помірну кореляцію між загальним балом UPDRS частини III та латентністю МВП в іпсилатеральній премоторній корі до домінантного боку моторних симптомів у пробах із магнітною індукцією (1,1 Тл – r = 0,34, p < 0,05; 1,32 Тл – r = 0,32, p < 0,05; 1,76 Тл – r = 0,31, p < 0,05). Також встановили позитивну слабку кореляцію між латентністю МВП в іпсилатеральній премоторній корі до субдомінантного боку моторних симптомів із загальним балом UPDRS частини III (1,54 Тл – r = 0,22, p < 0,05; 1,76 Тл – r = 0,29, p < 0,05). Виявили слабку позитивну кореляцію (r = 0,29, p < 0,05) між тривалістю МВП іпсилатеральної премоторної кори до субдомінантного боку моторних симптомів і загальною оцінкою UPDRS частини III у зразку з магнітною індукцією 1,54 Тл. Вірогідні кореляції амплітуди та вираженості клінічних симптомів у пацієнтів із ХП II стадії не визначили.

Висновки. Найбільш інформативний нейрофізіологічний показник у пацієнтів із ХП II стадії – латентність МВП. Латентність МВП премоторної кори іпсилатерального боку з більш вираженими моторними симптомами має особливо тісний зв'язок з оцінкою UPDRS частини III у пробах із магнітною індукцією 1,10–1,76 Тл (r = 0,31–0,34, p < 0,05). Тривалість МВП премоторної кори іпсилатерального боку з менш вираженими руховими симптомами найтісніше пов'язана з вираженістю моторних проявів на субдомінантному боці в пацієнтів із II стадією ХП (r = 0,27, p < 0,05).

Parkinson's disease (PD) is a common neurodegenerative disease characterized by motor and non-motor symptoms. The number of patients with PD covers 1 % of the population over the age of 60 and tends to increase with age [6]. The problem of the spread of PD is of great medical and social importance, as their clinical manifestations lead to impaired quality of life of patients already in the early stages of the disease.

It is known that patients with PD have a wide range of disorders of neurophysiological parameters in the primary motor cortex, which are correlated in direct proportion to the severity of clinical motor symptoms of PD [2,8]. Neurophysiological parameters of the central nervous system (CNS) can be assessed using transcranial magnetic stimulation (TMS) [4,10]. The method of diagnostic TMS makes it possible to assess the excitability of the nervous system using the parameters of motor evoked potential (MEP), which include latency, amplitude and duration [8].

The presence of oligobradykinesia, muscle rigidity and rest tremor significantly impairs the quality of life of patients with PD. It is a proven fact that dopaminergic therapy improves the motor activity of patients with PD and has a positive effect on neurophysiological parameters [2,8].

The availability of research on the objective assessment of the course of the disease and the effectiveness of treatment of PD determines the relevance of studying changes in neurophysiological parameters of the CNS in these patients. However, the sources that we have analyzed provide insufficient amount of often contradictory data about the diagnostic value of neurophysiological parameters of CNS excitability in patients with PD [8,9]. That is why the search for diagnostically reliable neurophysiological parameters is promising for the possibility of objective assessment of the treatment results with neurophysiological methods.

Aim

Was to identify the most informative parameters of motor evoked potential based on clinical and neurophysiological comparisons in patients with Parkinson's disease stage II.

Materials and methods

The study was conducted on the basis of the educational and scientific medical center "University Clinic" of Zaporizhzhia State Medical University. 90 patients (51 women and 39 men) aged 45 to 75 years with stage II PD according to Hoehn–Yahr were examined. The mean age was 66.22 ± 8.07 years. The average duration of the disease was 3.69 ± 2.19 years. At the onset of the disease, the predominance of motor symptoms was observed in 71 patients on the right and 19 patients on the left.

The diagnosis of Parkinson's disease was established according to the criteria of the British Society for Parkinson's Brain Bank and the Clinical Protocol (Guideline 00798), recommended by the Ministry of Health of Ukraine on 08.08.2018 and formulated according to class G20 (Extrapyramidal and other motor disorders) of the International Classification of Diseases, 10th revision. The stage of PD was determined by the classification of Hoehn–Yahr (1967). Exclusion criteria were: patients with stages I, III–V PD, other extrapyramidal disorders, inflammatory, autoimmune, cancer and mental illness; with decompensated stage of somatic pathology.

All patients who agreed to participate in the study signed an informed voluntary agreement. The study was conducted in accordance with the ethical standards of the Commission on Bioethics of Zaporizhzhia State Medical University, as well as the Helsinki Declaration of 1975 and its revised version of 2000. Levodopa/carbidopa and pramipexol were prescribed for all patients. The dose of pharmacotherapy was stabilized during 1 month before patients' including in investigation.

Examination of patients was performed according to the following scheme: clinical and neurological using the Unified Parkinson's Disease Rating Scale of the International Movement Disorders Society (Movement Disorder Society Unified Parkinson's Disease Rating Scale – MDS UPDRS) and neurophysiological study. Diagnostic TMS was performed on an extended therapeutic magnetic stimulator Neuro MS/D from Neurosoft (RF) with the ability to regulate magnetic pulses from 0 to 2.2 Tl. To assess the parameters of MEP, with the registration of the muscular response in m. abductor pollicis brevis bilaterally, used the software and hardware complex of the neuromyograph Neuron-Spectrum/4MEP with transcranial magnetic stimulator Neuro MS/D. The latency, amplitude and duration of MEP were studied after 4 tests with a gradual increase of the induction of the magnetic field (1.1 Tl – 50 %, 1.32 Tl – 60 %, 1.54 Tl – 70 % and 1.76 Tl – 80 %) from the maximum possible device Neuro MS/D (2.2 Tl – 100 %). The latent period of MEP is defined as the time (in ms) from the beginning of stimulation of the premotor zones to the moment of MEP in the corresponding muscle. The amplitude of the MEP (mV) is defined as the deviation from the isoline of the positive peak to the negative peak potential. The duration of MEP (ms) is determined by the beginning of the deviation of the motor potential before its return to the isoline.

Given that our study involved 71 patients with predominantly right-sided motor symptoms and 19 patients with predominantly left-sided symptoms, for correct statistical analysis, the dominant side was considered the debut side or the side with more pronounced motor symptoms, the subdominant side was considered the opposite. A score of part III of the UPDRS scale, which reflects the severity of motor symptoms, was also used to determine the lateralization of clinical symptoms. The sum of the UPDRS Part III scores, reflecting the severity of symptoms on the dominant and subdominant side, was considered separately to assess clinical symptoms. The calculation of MEP parameters for the ipsilateral premotor cortex to the dominant and subdominant sides of motor symptoms was also calculated separately.

The results of the study were processed using the statistical package of the licensing program Statistica® for Windows 13.0 (No. JPZ8041382130ARCN10-J), as well as Microsoft Excel 2010. The nature of the variable's distribution in the variation series was determined using

the Shapiro–Wilk test. Also in the case of normal distribution of variables, the descriptive statistics is presented in the form of arithmetic mean and standard deviation (M ± SD), in case of abnormal distribution – in the form of median and interquartile range Me (Q1; Q3). The probability of discrepancies in indicators was assessed by the criteria of Mann–Whitney U test, Wilcoxon test, Kruskal–Wallis test and Friedman–Kendall test. Also correlation coefficient was calculated using Spearman coefficient. For the criteria differences were considered significant at P < 0.05.

Results

Complaints of tremor were reported by 87.00 % of patients, muscle stiffness 73.33 % and slowness of movement by 62.11 % of patients. The presence of disturbances and changes in handwriting was noted by 81.11 % of patients, difficulty in getting up from a sitting position – 38.89 %, difficulty in walking and maintaining balance – 45.56 %, freezing while walking – 35.56 %. Restriction of habitual activity and hobbies due to the influence of motor symptoms of PD was noted by 65.56 % of patients, including slowness of chewing and swallowing – 44.44 %, difficulty in cooking – 52.22 %, dressing – 58.89 %, hygienic procedures – 55.56 % of patients.

In addition to motor symptoms, patients also complained of immobile symptoms: fatigue from habitual activity – 80.00 %, anxiety – 78.89 %, low mood – 73.34 %, apathy – 61.11 %, memory loss – 64.45 %, concentration – 55.56 %, frequent night awakenings – 76.67 %, daytime sleepiness – 60.00 %, frequent (imperative) urges to urinate – 58.89 %, frequent urination at night – 52.23 % and constipation – 61.12 % of patients. Less often, patients complained of dizziness – 44.44 %, increased salivation – 33.34 % and periodic benign hallucinations in 12.22 %.

Neurological examination of patients with stage II PD revealed muscle rigidity of the plastic type in the muscles of the upper extremities in all patients and in the lower extremities in 98.89 % of patients; asymmetry of muscle rigidity in the form of predominance in the right extremities in 78.89 % and in the left extremities in 21.11 % of patients; bradykinesia was detected in the right upper extremity muscle in all patients and in the left upper extremity muscle in 98.89 % of patients. Rest tremor was determined in 98.89 % of patients, including its predominance in the right extremities in 75.56 % and in the left extremities in 24.44 % of patients. Violation of the physique (stiffness and stooping) was observed in 97.78 % of patients, violation of the test with getting up from a chair without the help of hands – in 95.56 %, gait disorders – in 81.11 %, stiffness when walking – in 60.00 %, speech disorders (in the form of decreased modulation, diction and volume) – in 62.22 %, decreased facial expression – in 90.00 % of patients.

The overall score on the MDS UPDRS scale in patients with stage II PD was 76.00 (70.00; 83.00) points; score on part I (non-motor manifestations that affect everyday life) – 15.00 (13.00; 19.00) points, on part II (motor aspects that affect daily life) – 13.00 (9.00; 15.00) points and on part III (objective assessment of motor functions) – 49.00 (46.00; 52.00) points, part III dominant side – 13.00 (11.00; 14.00), part III subdominant side – 11.00 (10.00; 12.00).

According to the studied neurophysiological parameters of the premotor cortex excitability, in the examined patients when comparing 4 samples with increasing induction of magnetic stimulus there was a significant (according to Friedman test) decrease in the latent period of MEP in the ipsilateral (P < 0.001) premotor cortex to the predominant side of motor symptoms, but in the contralateral premotor cortex there was only a tendency to reduce the latency of MEP (P = 0.08) (*Table 1*).

In a pairwise comparison of MEP latency in samples with increasing magnetic stimulus, it was determined that in the contralateral premotor cortex to the predominant side of motor symptoms in pair of samples with stimulus induction 1.10–1.76 TI there was a significant decrease (P = 0.03) in the latent period of MEP, when comparing pairs of data samples with a stimulus intensity of 1.10–1.32 TI and 1.10–1.54 TI was insignificant (P > 0.05) (*Table 1*). Comparing the latent period of MEP of the ipsilateral premotor cortex to the predominant side of motor symptoms in pairs of samples with magnetic stimulus induction, significant decrease was found in all pair of samples (P < 0.01) (*Table 1*). The MEP latency parameters were also compared between the contra- and ipsilateral premotor cortex to the predominant side of motor symptoms: significant differences were not found in any samples of induction of magnetic stimulus (1.1 TI – P = 0.61; 1.32 TI – P = 0.72; 1.54 TI – P = 0.86; 1.76 TI – P = 0.91).

In the examined patients with samples with increasing induction of the magnetic stimulus, a significant increase in amplitude was observed according to the Friedman test in the contra- (P < 0.001) and ipsilateral (P < 0.001) premotor cortex to the predominant side of motor symptoms (*Table 2*). Comparing the amplitude of the MEP between the contra- and ipsilateral premotor cortex, interhemispheric asymmetry of the MEP amplitude was not found in any samples of magnetic stimulus induction (1.1 TI – P = 0.12; 1.32 TI – P = 0.35; 1.54 TI – P = 0.20; 1.76 TI – P = 0.38).

The duration of MEP in both premotor areas of the brain increased (P < 0.001) with the increase of induction of the magnetic field (*Table 3*). Comparing the amplitude of the MEP between the contra- and ipsilateral sides of the premotor cortex in all samples with increasing induction of the magnetic impulse, no significant difference between the parameters was found (1.1 TI – P = 0.86; 1.32 TI – P = 0.77; 1.54 TI – P = 0.99; 1.76 TI – P = 0.26).

To compare motor clinical symptoms with investigated neuruphysiological parameters, we calculate the Spearman's correlation coefficient between UPDRS score (UPDRS, part III total score, part III dominant side, part III subdominant side) and of MEP parameters (*Table 4*).

Significant positive moderate correlation was found between UPDRS part III total score and MEP latency in the ipsilateral premotor cortex to the dominant side of motor symptoms with samples of magnetic induction (1.1 TI – r = 0.34, P < 0.05; 1.32 TI – r = 0.32, P < 0.05; 1.76

Table 1. Latency of MEP in the contra- and ipsilateral premotor cortex to the predominant side of motor symptoms in patients with stage II PD, Me (Q1; Q3)

Parameters	Magnetic field induction				P	P^{1-2}	P^{1-3}	P^{1-4}
	1.1 TI[1]	1.32 TI[2]	1.54 TI[3]	1.76 TI[4]				
Latent period of MEP on the contralateral premotor cortex, ms	22.50 (21.60; 24.00)	22.60 (21.90; 23,70)	22.60 (21.40; 23,80)	22.45 (21.40; 23.70)	0.08	0.92	0.21	0.03
Latent period of MEP on the ipsilateral premotor cortex, ms	22.85 (21.70; 23.70)	22.60 (21.60; 23.70)	22.65 (21.50; 23.50)	22.35 (21.40; 23.30)	<0.001	0.01	0.002	<0.001

P: according to Friedman test; P^{1-2}, P^{1-3}, P^{1-4}: by Wilcoxon test.

Table 2. Amplitude of MEP in the contra- and ipsilateral premotor cortex to the predominant side of motor symptoms in patients with stage II PD, Me (Q1; Q3)

Parameters	Magnetic field induction				P	P^{1-2}	P^{1-3}	P^{1-4}
	1.1 TI[1]	1.32 TI[2]	1.54 TI[3]	1.76 TI[4]				
Amplitude of MEP on the contralateral premotor cortex, mV	0.80 (0.25; 2.12)	1.74 (0.51; 3.62)	2.71 (1.07; 4.08)	2.69 (1.43; 4.13)	<0.001	<0.001	<0.001	<0.001
Amplitude of MEP on the ipsilateral premotor cortex, mV	0.58 (0.10; 1.61)	1.45 (0.47; 3.13)	2.04 (0.82; 3.52)	2.38 (0.80; 3.93)	<0.001	<0.001	<0.001	<0.001

P: according to Friedman test; P^{1-2}, P^{1-3}, P^{1-4}: by Wilcoxon test.

Table 3. Duration of MEP in the contra- and ipsilateral premotor cortex to the predominant side of motor symptoms in patients with stage II PD, Me (Q1; Q3)

Parameters	Magnetic field induction				P	P^{1-2}	P^{1-3}	P^{1-4}
	1.1 TI[1]	1.32 TI[2]	1.54 TI[3]	1.76 TI[4]				
Duration of MEP on the contralateral premotor cortex, ms	13.05 (10.60; 16.50)	16.10 (12.90; 19.20)	17.80 (14.80; 20.80)	20.35 (15.50; 23.30)	<0.001	<0.001	<0.001	<0.001
Duration of MEP on the ipsilateral premotor cortex, ms	12.95 (10.10; 16.50)	15.40 (12.80; 20.80)	17.75 (13.50; 22.50)	19.50 (14.80; 21.90)	<0.001	<0.001	<0.001	<0.001

P: according to Friedman test; P^{1-2}, P^{1-3}, P^{1-4}: by Wilcoxon test.

TI – r = 0.31, P < 0.05). Also positive mild correlation was found between MEP latency in the ipsilateral premotor cortex to the subdominant side of motor symptoms and UPDRS part III total score (1.54 TI – r = 0.22, P < 0.05; 1.76 TI – r = 0.29, P < 0.05). We found mild positive correlation (r = 0.29, P < 0.05) between MEP duration of ipsilateral premotor cortex to the subdominant side of motor symptoms and UPDRS part III total score in sample with 1.54 TI magnetic induction. The MEP latency on the ipsilateral premotor cortex to dominant side positively correlates with Part III Dominant side score in the sample with 1.1 TI magnetic induction (r = 0.21, P < 0.05). The MEP duration on the ipsilateral premotor cortex to the dominant side had positive mild correlation with Part III Subominant side score (1.54 TI – r = 0.25, P < 0.05). Also \positive mild powered correlation was found between MEP duration on the ipsilateral premotor cortex to the subdominant side with Part III Subominant side score in samples with 1.32 TI (r = 0.26, P < 0.05) and 1.54 TI (r = 0.27, P < 0.05) magnetic induction. There were no statistically significant relationships between MEP amplitude and the severity of motor symptoms. It was found that UPDRS total score only correlated with Duration of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms (r = 0.29, P < 0.05).

Based on a comparative analysis using the Kruskal–Wallis test, it was found that groups of patients with different severity of motor symptoms (according to the total score of Part III UPDRS) also had significant differences in the value of MEP latency both in the premotor cortex ipsilateral to Dominant side of motor symptoms (in tests

Table 4. Spearman's correlation coefficient between UPDRS Score and parameters of MEP

Parameters	Magnetic field induction	UPDRS total score	UPDRS Part III total score	UPDRS Part III dominant side score	UPDRS Part III subdominant side score
Latency of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 TI	0.12	0.34*	0.21*	0.19
	1.32 TI	0.11	0.32*	0.19	0.13
	1.54 TI	0.01	0.17	0.08	0.02
	1.76 TI	0.14	0.31*	0.20	0.16
Latency of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 TI	-0.04	0.10	0.00	0.00
	1.32 TI	0.04	0.13	-0.04	-0.02
	1.54 TI	0.08	0.22*	0.06	0.02
	1.76 TI	0.10	0.29*	0.11	0.12
Amplitude of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 TI	-0.13	-0.15	-0.14	-0.09
	1.32 TI	0.00	-0.11	-0.17	-0.14
	1.54 TI	-0.04	-0.09	-0.16	-0.08
	1.76 TI	-0.02	-0.02	-0.13	-0.13
Amplitude of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 TI	0.10	-0.02	-0.05	-0.07
	1.32 TI	0.09	0.08	0.10	0.09
	1.54 TI	0.06	0.02	0.01	0.10
	1.76 TI	0.08	-0.04	-0.05	-0.02
Duration of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 TI	-0.05	-0.09	-0.08	-0.02
	1.32 TI	0.11	0.12	0.14	0.20
	1.54 TI	0.03	0.13	0.14	0.25*
	1.76 TI	-0.05	0.01	0.01	0.08
Duration of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 TI	0.04	-0.03	-0.04	0.01
	1.32 TI	0.12	0.15	0.19	0.26*
	1.54 TI	0.29*	0.27*	0.18	0.27*
	1.76 TI	0.00	0.06	0.03	0.15

*: P < 0.05

Table 5. Motor evoked potential parameters according to the motor symptoms severity using UPDRS Scale Part III Score

Parameters	Magnetic field induction	UPDRS Scale Part III total score			
		<45 points, n = 20	46–50 points, n = 39	>50 points, n = 31	P
Latency of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 TI	22.10 (21.15; 23.40)	22.75 (21.40; 23.90)	23.20 (22.70; 24.60)	0.005
	1.32 TI	21.70 (20.75; 22.90)	22.60 (21.30; 23.50)	23.10 (22.40; 24.90)	0.008
	1.54 TI	21.85 (21.20; 23.50)	22.50 (21.40; 23.70)	22.80 (21.90; 23.60)	0.331
	1.76 TI	21.45 (20.80; 22.45)	22.45 (21.70; 23.40)	22.80 (22.10; 23.80)	0.012
Latency of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 TI	22.50 (21.55; 23.70)	22.30 (21.00; 24.10)	22.50 (21.90; 24.20)	0.490
	1.32 TI	22.55 (21.70; 23.35)	22.25 (21.60; 23.60)	22.90 (22.00; 24.00)	0.388
	1.54 TI	22.00 (20.90; 23.15)	22.50 (20.90; 24.20)	22.90 (22.20; 24.00)	0.135
	1.76 TI	21.85 (21.10; 22.50)	22.35 (20.80; 23.60)	23.10 (21.70; 23.80)	0.027
Amplitude of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 TI	0.94 (0.28; 2.21)	0.581 (0.097; 1.610)	0.480 (0.085; 1.270)	0.026
	1.32 TI	2.11 (0.77; 3.81)	1.270 (0.299; 2.680)	1.510 (0.417; 3.480)	0.456
	1.54 TI	2.74 (1.77; 3.58)	1.550 (0.623; 3.520)	1.880 (0.483; 4.250)	0.198
	1.76 TI	3.70 (1.33; 4.70)	1.990 (1.000; 2.790)	3.110 (0.600; 4.390)	0.283
Amplitude of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 TI	1.70 (0.33; 2.22)	0.614 (0.097; 1.520)	0.841 (0.454; 1.490)	0.144
	1.32 TI	1.64 (0.42; 3.66)	1.435 (0.453; 3.220)	1.920 (0.858; 4.070)	0.216
	1.54 TI	2.69 (1.79; 5.06)	2.170 (0.600; 3.210)	3.320 (1.980; 4.300)	0.521
	1.76 TI	3.56 (2.38; 4.67)	2.200 (0.778; 3.270)	3.160 (2.030; 4.520)	0.055
Duration of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 TI	13.55 (11.35; 16.40)	12.80 (9.490; 16.90)	12.60 (9.740; 16.70)	0.008
	1.32 TI	15.00 (11.85; 18.90)	15.35 (13.30; 20.00)	17.50 (14.40; 21.40)	0.792
	1.54 TI	16.50 (12.30; 20.65)	18.90 (13.50; 22.80)	18.90 (14.10; 22.70)	0.249
	1.76 TI	18.90 (15.00; 21.70)	20.00 (14.70; 23.90)	19.60 (15.20; 22.60)	0.415
Duration of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 TI	12.65 (9.41; 16.80)	13.35 (11.10; 16.50)	12.60 (9.620; 16.10)	0.802
	1.32 TI	14.90 (12.40; 18.10)	16.60 (13.70; 19.00)	17.60 (13.10; 20.10)	0.880
	1.54 TI	15.30 (11.27; 17.35)	19.05 (15.80; 22.10)	20.40 (15.60; 24.20)	0.006
	1.76 TI	20.55 (12.45; 22.20)	20.75 (16.00; 24.10)	20.10 (17.60; 24.00)	0.574

P: according to Kruskal–Wallis test.

Table 6. Motor evoked potential parameters according to the motor symptoms severity on the Dominant side using UPDRS Part III Score

Parameters	Magnetic field induction	UPDRS Part III Dominant Side score		
		≤12 points (n = 56)	>13 points (n = 34)	P
Latency of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 TI	22.70 (21.50; 23.70)	23.00 (22.00; 24.00)	0.028
	1.32 TI	22.20 (21.20; 23.40)	22.60 (21.60; 23.90)	0.045
	1.54 TI	22.50 (21.50; 23.60)	22.70 (21.50; 23.50)	0.244
	1.76 TI	22.30 (21.20; 23.10)	22.40 (21.60; 23.50)	0.010
Latency of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 TI	22.50 (21.70; 24.00)	22.50 (21.50; 24.10)	0.176
	1.32 TI	22.90 (22.00; 24.30)	22.60 (21.60; 23.70)	0.320
	1.54 TI	22.60 (21.70; 24.00)	22.60 (20.90; 23.70)	0.130
	1.76 TI	22.40 (21.40; 23.70)	22.70 (21.40; 23.80)	0.023
Amplitude of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 TI	0.56 (0.09; 1.60)	0.58 (0.09; 1.91)	0.106
	1.32 TI	1.91 (0.68; 3.14)	0.99 (0.40; 3.02)	0.223
	1.54 TI	2.36 (0.82; 3.73)	1.79 (0.62; 3.52)	0.318
	1.76 TI	2.58 (1.00; 5.11)	2.33 (0.67; 3.73)	0.362
Amplitude of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 TI	0.79 (0.19; 2.27)	0.81 (0.27; 1.66)	0.677
	1.32 TI	1.53 (0.45; 3.62)	1.77 (0.69; 3.83)	0.597
	1.54 TI	2.70 (0.63; 4.08)	2.72 (1.17; 4.25)	0.800
	1.76 TI	3.00 (1.41; 4.44)	2.59 (1.48; 3.88)	0.746
Duration of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 TI	12.90 (10.30; 16.50)	13.00 (9.74; 16.70)	0.294
	1.32 TI	15.00 (12.00; 20.20)	16.20 (13.70; 20.90)	0.161
	1.54 TI	16.60 (12.50; 21.00)	18.90 (14.10; 22.70)	0.371
	1.76 TI	17.60 (14.50; 21.90)	19.60 (15.10; 22.50)	0.686
Duration of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 TI	13.20 (11.10; 17.20)	12.60 (10.40; 16.10)	0.829
	1.32 TI	15.10 (12.20; 18.80)	16.30 (13.40; 19.80)	0.285
	1.54 TI	15.70 (12.60; 20.80)	18.90 (15.70; 21.10)	0.203
	1.76 TI	21.00 (11.60; 23.00)	20.10 (16.30; 23.60)	0.671

P: according to Mann–Whitney U test.

with magnetic field induction: 1.1 TI – P = 0.005; 1.32 TI – P = 0.008; 1.76 TI – P = 0.012), and in the premotor cortex ipsilateral to Subdominant side (sample 1.76 TI – P = 0.027). The MEP amplitude in the premotor cortex of the ipsilateral to Dominant side significantly decreased as the severity of motor manifestations increased (sample 1.1 TI – P = 0.026). The duration of the MEP in the premotor cortex ipsilateral to Dominant side significantly decreased with the worsening in severity of motor symptoms (sample 1.1 TI – P = 0.008), while in the premotor cortex ipsilateral to Subdominant side, on the contrary, it significantly increased as the severity of motor symptoms worsened (test 1.54 TI – P = 0.006).

Based on a comparative analysis using the Mann–Whitney test, it was found that patients with a total score of Part III UPDRS for the Dominant side of more than 13 points, had higher MEP latency values of the prefrontal cortex on the ipsilateral to Dominant side (sample 1.1 TI – P = 0.028; 1.32 TI – P = 0.045; 1.76 TI – P = 0.010), and to a lesser extent to the ipsilateral Subdominant side (sample 1.76 TI – P = 0.023) in comparison with patients who had UPDRS Part III Dominant side score 13 points and less (*Table 6*).

Based on a comparative analysis using the Mann–Whitney test, it was found that patients with a total score of Part III UPDRS for the subdominant side of more than 10 points, had higher values of the MEP duration of the prefrontal cortex of the ipsilateral subdominant side (sample 1.54 TI – P = 0.027) in comparison with patients who had a total score of Part III UPDRS for the Subdominant side 10 points and less (*Table 7*).

Discussion

Studies by K. Kolmancic et al. confirmed the change in excitability and plasticity of the sensorimotor cortex of the brain in the early stages of PD [8]. The interhemispheric imbalance and asymmetry of MEP parameters in patients with stage II PD were not found in our investigation. In M. Kojovic and K. Kolmancic researches contraversal results were found: interhemispheric asymmetry of MEP parameters depends, among other reasons, on the sex of the patient [7,8].

Dileone M. et al. analyzed the effect of TMS on CNS excitability depending on pharmacotherapeutic treatment of PD (use of levodopa and dopamine receptor agonists) and used MEP amplitude as a marker of motor cortex response in their studies [5]. Dileone M. et al. indicated that TMS induces dopamine-dependent changes in cortical excitability (increase in the amplitude of MEP) in 13 examined patients with PD [5]. However, the results of our study indicate that the amplitude of the MEP of the premotor cortex didn't correlate with clinical motor symptoms assessed by UPDRS Scale, which does not allow to be used as a diagnostically reliable parameter to assess the effectiveness of TMS therapy in patients with stage II PD. The study by A. Anzak et al. demonstrated the dependence of MEP amplitude on stimulus intensity, which is also consistent with our results on the highest MEP amplitude at the highest induction of magnetic stimulus (1.76 Tl) [1]. Also in the study of S. Casarotto it is noted that levodopa induces an asymmetric increase in motor excitability on the affected side of the brain, but in our investigation it wasn't proved [3].

Dileone M. et al. and Kolmancic K. et al. note in their studies that MEP parameters are useful objective markers of early disease progression that can be used to identify the effectiveness of disease-modified therapy [5,8]. In our study, we relied on the diagnostical significance of the studied data, using the correlation between MEP parameters with expressiveness of motor symptoms assed by UPDRS Scale, and which allowed us to clarify the data and reveal that the severity of motor symptoms, regardless of their lateralization, is more associated with the MEP latency parameter (latency of the ipsilateral premotor cortex to the dominant side of motor symptoms with a total UPDRS score and, to a lesser extent, due to the score of the part III dominant side) which is consistent to the M. Dileone et al. and K. Kolmancic et al. researches [5,8]. This fact is the reason to use the MEP latency as a marker for neurophysiological assessment of the severity of motor manifestations and monitoring the effectiveness of therapy. No significant correlations were found to the amplitude parameter and the severity of clinical symptoms. The mild correlations which were found for the MEP duration with the severity of motor symptoms draw attention, however, a positive-proportional correlation of prefrontal cortical structures ipsilateral to the subdominant side of motor symptoms with a total UPDRS score, the UPDRS motor part III on the subdominant side which also was reflected in M. Dileone et al. and K. Kolmancic et al. investigations [5,8]. It is possible to consider MEP duration as indicators markers for monitoring the progression of PD.

It should be noted that the results of the nonparametric comparative analysis were in complete agreement with the results of the correlation analysis. So, according to our results, the latent period and duration of MEP are reliable and valuable indicators of premotor cortex excitability, which allows us to use these MEP parameters to evaluate the effectiveness of treatment of PD using the method of TMS in our further research.

Table 7. Motor evoked potential parameters according to the motor symptoms severity on the Subominant side using UPDRS Part III Score

Parameters	Magnetic field induction	UPDRS Part III Subominant Side score		
		≤10 points, n = 38	>10 points, n = 52	P
Latency of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 Tl	22.70 (21.50; 23.50)	23.10 (22.00; 24.40)	0.097
	1.32 Tl	22.30 (21.20; 23.60)	22.60 (21.65; 24.05)	0.323
	1.54 Tl	22.65 (21.50; 23.60)	22.60 (21.55; 23.65)	0.980
	1.76 Tl	22.20 (21.10; 22.90)	22.70 (21.90; 23.65)	0.089
Latency of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 Tl	22.40 (21.80; 23.90)	22.50 (21.40; 24.15)	0.806
	1.32 Tl	22.65 (21.90; 23.70)	22.60 (21.60; 23.95)	0.861
	1.54 Tl	22.45 (21.50; 23.50)	22.70 (21.25; 24.15)	0.598
	1.76 Tl	22.10 (21.40; 23.50)	22.80 (21.45; 23.95)	0.256
Amplitude of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 Tl	0.85 (0.11; 1.95)	0.45 (0.08; 1.50)	0.500
	1.32 Tl	1.85 (0.64; 3.73)	1.27 (0.40; 2.68)	0.222
	1.54 Tl	2.35 (1.01; 3.74)	1.63 (0.48; 3.17)	0.172
	1.76 Tl	2.88 (1.35; 4.29)	2.01 (0.61; 3.69)	0.098
Amplitude of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 Tl	0.93 (0.32; 2.05)	0.74 (0.19; 2.43)	0.480
	1.32 Tl	1.64 (0.64; 3.05)	1.76 (0.50; 4.19)	0.576
	1.54 Tl	2.43 (1.53; 3.74)	2.93 (1.00; 4.29)	0.627
	1.76 Tl	2.85 (1.48; 4.12)	2.50 (1.31; 4.19)	0.674
Duration of MEP on the ipsilateral premotor cortex to the dominant side of motor symptoms	1.10 Tl	13.20 (10.30; 16.50)	12.80 (9.92; 16.60)	0.806
	1.32 Tl	15.30 (12.00; 20.00)	16.05 (14.10; 20.85)	0.387
	1.54 Tl	16.60 (12.00; 19.70)	19.30 (14.15; 22.65)	0.070
	1.76 Tl	19.25 (14.90; 22.00)	19.50 (14.60; 21.80)	0.756
Duration of MEP on the ipsilateral premotor cortex to the subdominant side of motor symptoms	1.10 Tl	12.95 (9.06; 17.50)	13.05 (11.20; 15.40)	0.990
	1.32 Tl	14.90 (12.60; 17.80)	17.65 (13.65; 19.70)	0.068
	1.54 Tl	15.70 (12.60; 20.50)	19.30 (15.70; 21.60)	0.027
	1.76 Tl	20.10 (11.60; 23.20)	20.55 (17.45; 23.50)	0.323

P: according to Mann–Whitney test.

Conclusions

1. The most informative neurophysiological indicators in patients with PD stage II are the MEP latencies. The MEP latencies of the premotor cortex, which is ipsilateral to the side with more pronounced motor symptoms, have a particularly close relationship with UPDRS part III total score in the samples with 1.10–1.76 Tl magnetic inductions ($r = 0.31–0.34$, $P < 0.05$).

2. The MEP duration of premotor cortex, which is ipsilateral to the side with less pronounced motor symptoms, is most closely associated with the severity of motor manifestations on the subdominant side in patients with PD stage II ($r = 0.27$, $P < 0.05$).

Prospects for further research are to study changes in the parameters of the excitability of the premotor cortex in patients with stage II Parkinson's disease during treatment with TMS.

Funding

The study was performed within the research of Zaporizhzhia State Medical University: "Optimization of diagnosis and treatment tactics in patients with Parkinson's disease", state registration No. 0119U100453.

Конфлікт інтересів: відсутній.
Conflicts of interest: authors have no conflict of interest to declare.

Надійшла до редакції / Received: 10.12.2021
Після доопрацювання / Revised: 14.03.2022
Прийнято до друку / Accepted: 22.03.2022

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