Readiness potential as a neurophysiological marker of functional movement disorders

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Functional movement disorders (FMD) are widespread and have a significant negative impact on the quality of life of patients. The pathogenesis is not completely clear, but currently there is ongoing research on searching for biological markers using methods such as functional magnetic resonance imaging and electroencephalography (EEG).

Objective: *detection of the features of the amplitude-frequency characteristics of the readiness potential (RP) formed during FMD.*

Material and methods. *We examined 22 patients with a clinically diagnosed FMD and 22 healthy volunteers (all participants were right-handed). Both patients and the control group underwent an EEG in Erickson's Flanker paradigm with registration of the RP. RP was recorded in the projection area of the precentral gyrus (electrodes C3/C4/C5/C6 in the standard 10–20 overlay scheme).*

Results. *Comparative analysis of RP parameters showed the presence of significant frequency-amplitude differences between the main group and the control group in the right hemisphere in the absence of significant differences in the left hemisphere. At the same time, significant differences were demonstrated between the FMR group and the control group both in terms of the latent period (time to the onset of RP): 33.66±23.69 ms versus 276.28±176.1 ms ($p<0.05$), and its amplitude: -0.85±0.294 μV versus -0.35±0.26 μV ($p<0.05$).*

Conclusion. *The results of the present study suggest that neurophysiological parameters such as RP can be considered as a potential diagnostic marker to improve the diagnosis of FMR.*

Keywords: *functional movement disorders; readiness potential; electroencephalography; biomarker.*
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Functional movement disorders (FMDs) represent a heterogenous group of psychomotor disorders, all of which share the common feature of motor disturbances that cannot be explained either by a somatic or by a neurologic condition, allowing us to qualify these disturbances as pseudo-neurological [1–4]. From a clinical standpoint, FMDs may be divided into positive (functional gait disturbances, dystonias, tremor, psychogenic non-epileptic seizures, myocloni etc.) and negative (functional paralyses and pareses) [5, 6].

Available data suggest that FMDs are quite common in the population, with an incidence rate of 50 cases per 100,000 people; in neurological practice, a definitive FMD diagnosis is established in approximately 5% of patients, and some of its symptoms that are likely functional in nature are observed in 30% of patients [7]. FMDs appear to be more common in females (74% of the total number of patients) and tend to manifest, on average, at the age of 40 years (range: 8–77 years). The majority of patients (93%) experience an acute onset of symptoms and may develop a long-term, persistent disease in the future [8]. The clinical presentation of FMDs often involves two or more motor disturbances affecting different parts of the body [9].

FMDs have a negative impact on the daily functioning of patients and are characterized by a poor response to treatment, resulting in long-term disability comparable to that in organic movement diseases [10–12].

The important peculiarities of FMDs are the feelings of movements being made involuntarily, and the absence of a neuroanatomical substrate [13–15]. To date, both the etiology and the pathogenesis of FMDs are not completely understood, which makes it difficult to establish reliable diagnostic criteria for these disorders [16–19].

Due to their clinical heterogeneity, the lack of established diagnostic criteria, and difficulties in making the diagnosis, FMD often tends to be the diagnosis of exclusion [20].

In the past decades, attempts were made to identify the "positive diagnostic criteria" of FMDs based on their specific clinical symptoms [21–23]. The selected diagnostic criteria were shown to be highly specific but had low sensitivity, making it difficult to use these as a screening tool [24]. Thus, researchers are beginning to draw more and more attention to the search for reliable FMD markers based on various instrumental investigations [25].

The most actively exploited method in FMDs is functional magnetic resonance imaging (fMRI) that enables real-time observation of changes in the functional activity of the brain. A series of studies using fMRI showed an increase in the

functional activity of the postcentral gyrus, the precuneus, the posterior cingulate cortex, and the cerebellar vermis, as well as impaired integration of neuronal contours responsible for emotional and motor control [26]. Nevertheless, fMRI remains a relatively rare, expensive method, the routine use of which is unavailable.

Moreover, recently there has been a growing interest in methods based on electroencephalography (EEG) and transcranial magnetic stimulation (TMS). Thus, in the studies using evoked potentials and EEG, patients with FMDs demonstrated impaired perception of the voluntary nature of their movements, with a reduced amplitude and a later onset of premotor potentials as well as an increase in the latency of movement production [27, 28].

Literature analysis has enabled us to conclude that the most adequate way to investigate the formation of a voluntary movement is the analysis of bioelectrical activity of the brain based on total EEG data [29] as well as the analysis of shifts of biopotentials arising in the human brain before any movement is produced and at the time of the movement [30].

The readiness potential (RP) generated before a voluntary movement is produced is considered to be an electrographic equivalent of the process of launching an entire program for realization of a voluntary movement.

It may be assumed that the amplitude and frequency characteristics of the readiness potential reflect the disturbances associated with functional disorders within the central nervous system structures. The present study is aimed at testing the hypothesis of the readiness potential being impaired in patients with FMDs.

The aim of this study was to identify specific amplitude and frequency characteristics of the readiness potential generated in patients with FMDs, and to compare these characteristics with those in the control group.

The goals of this study included the following:

1. To assess the sociodemographic (in comparison with the control group) and the clinical profiles of patients with FMDs.
2. To identify the amplitude and frequency characteristics of the readiness potential in patients with FMDs using the Erickson's flanker test.
3. To detect statistically significant deviations of the amplitude and frequency characteristics of the readiness potential in patients with FMDs as compared to the control group.

Patients and methods. The study was a result of collaboration between the Clinic of Neurological Disease named after A. Ya. Kozhevnikov and the Department of Normal Physiology of N.V. Sklifosovsky Institute of Clinical Medicine of Sechenov University.

To objectivize the obtained results, two patient groups were recruited: the main group which consisted of patients with a clinically established diagnosis of FMD and the control one which consisted of healthy volunteers. Given the strong impact of one's right- or left-handedness on the neurophysiological parameters associated with hand movement, the study focused on the right-handed participants.

Inclusion criteria for the main group:

1) age from 18 to 70 years;
2) voluntary informed consent for participation in the study;
3) right-handedness;
4) FMD diagnosis established in line with the diagnostic criteria specified in the International Classification of Diseases, 10th revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).

Exclusion criteria for the main group:

1) presence of an objectively verified neurological condition that could explain the symptoms of FMD or interfere with the results of the neurophysiological examination (epilepsy, pyramidal or extrapyramidal disease);
2) severe psychiatric or somatic comorbidity that precludes comprehensive clinical and psychopathological examination during a consilium;
3) regular use of medications that may lead to a significant distortion of the neurophysiological examination results (anticonvulsants, benzodiazepines, barbiturates).

Inclusion criteria for the control group:

1) age from 18 to 70 years;
2) voluntary informed consent;
3) right-handedness;
4) the presence of a health passport concluding that the patient is “practically healthy”.

Exclusion criteria for the control group:

1) information communicated by a patient about his/her chronic condition not recorded in the health passport;
2) withdrawal of the voluntary informed consent.

The search of patients with FMDs was conducted at the Clinic of Neurological Diseases among both inpatients and outpatients. An in-depth clinical interview and instrumental and laboratory testing was required for the FMD diagnosis to be established, including compulsory history taking and the evaluation of the patient's psychiatric and neurological status. Laboratory investigations encompassed both routine tests and the detection of specific markers of neurological conditions that may mimic FMDs (Wilson's disease etc.), if necessary. All patients underwent brain MRI examination and EEG with provocative tests. The final clinical diagnosis was established by a consilium chaired by Prof. B. A. Volel with the engagement of both neurologists and psychiatrists. After the diagnosis had been reliably established, the patients were referred to the Department of Normal Physiology for neurophysiological examination, including the determination of the readiness potential. Healthy volunteers were recruited via the ad posted at the Clinic and via the Internet. Before enrolment, healthy volunteers had to complete a brief interview with a neurologist and a psychiatrist to rule out any overt somatic, neurological, or psychiatric conditions not specified in the health passport.

In this study, the readiness potential was registered in the projection of the precentral gyrus (placement of electrodes C3/C4/C5/C6 using the standard 10–20 system). The readiness potential was calculated as the difference wave between the activity in the contra- and ipsilateral hemisphere during the preparation of the participant for producing a movement by his/her right or left hand, respectively.

The right hemisphere shows enhanced activity as compared to the left hemisphere when one moves his/her left hand, enabling the numerical presentation of the readiness potential by subtracting the activity of the right and the left hemispheres.

In this study, the Erickson flanker task was used as the paradigm.

The test in the flanker task was represented by a set of five arrows, where the participant was expected to react to the direction of the central arrow by pressing the corresponding key. In some tests, the direction of the central arrow was identical to the that of other arrows (congruent), while in the rest of the tests its direction was opposite (incongruent).

To average the results, epochs for correct responses were chosen for the congruent test types. For each participant, the average number of tests for the purpose of averaging was 90.

The neurophysiologist who conducted the test was not aware of the group allocation of the participant.

The testing protocol was developed in line with the bioethical considerations for human studies and was approved by the Bioethics Board of Sechenov University.

Data were analyzed using the Statistica 10.0 software and presented as means and standard deviations (M±SD). Normal distribution was evaluated using the Kolmogorov–Smirnov test; the Student's t-test and the non-parametric Wilcoxon Mann Whitney test were used to assess the significance of differences for quantitative variables with normal and abnormal distribution, respectively. The significance of differences for qualitative variables was evaluated using the χ^2 test.

Result. The final study population included a total of 22 patients with FMDs and 22 healthy volunteers. The key sociodemographic parameters in the main and the control groups are provided in Table 1.

Analysis of the sociodemographic and clinical parameters presented in Table 1, allows to conclude that the selected patients were comparable with respect to their gender, age, and education but showed significant differences in their marital and occupational status; thus, among patients with FMDs, there were more patients who had never been married as well as more patients who divorced or became widows / widowers. It is also of note that there was a significant proportion of unemployed patients who did not apply for disability in this group.

Another important finding is a relatively early onset (average age 27 years) and quite a long-term history of the disease (average duration 10 years). This finding may explain the comparable level of education in the FMD group with apparently unfavorable marital and occupational status.

In this study, the clinical structure of FMDs was found to be heterogenous, and included patients presenting with positive, mixed, and negative symptoms. Most commonly, the patients presented with positive symptoms (n=12; 55%), with psychogenic non-epileptic seizures, psychogenic tics, blepharospasm, and writer's cramp being the dominant clinical manifestations. The number of patients experiencing mixed FMD symptoms was equal to that with negative symptoms – five (22.5%) patients in each of these subsets. Negative symptoms included pareses and paralyses. A more detailed description of the clinical structure of FMDs is provided in Table 2.

A comparative analysis of the RP parameters demonstrated significant differences in frequency and amplitude characteristics between the main and the control groups for the right hemisphere but revealed no significant differences for the left hemisphere. Notably, significant differences were observed both for the latent period (time before the onset of RP) and for its amplitude (see Table 3). The latent period of the readiness potential and its amplitude in the left hemisphere did not show any significant differences.

The small sample size precludes any inference regarding the statistical significance of this conclusion, yet the differences identified were generally observed in all clinical phenotypes of FMDs: positive, mixed, and negative.

Discussion. The results of this study support the idea that FMDs have a considerable negative impact on the key sociodemographic parameters of patients. Particularly of note, such patients tend to have a poorer marital and occupational status. It is also notable that the findings obtained are highly consis-

Table 1. *Sociodemographic and clinical parameters of patients in the study groups*

Parameter	Main group (n=22)	Control group (n=22)	p
Number of males, n (%)	7 (32)	8 (36)	0.487
Age, years, M±SD	38.96±14.78	35.17±18.9	0.293
Education, n (%):			0.631
secondary	4 (18)	6 (27)	
secondary vocational	6 (27)	2 (9)	
higher	12 (55)	14 (64)	
Marital status, n (%):			0.011
married	6 (27)	12 (55)	
never married	8 (36)	8 (36)	
divorced/widow(-er)	8 (36)	2 (9)	
Occupational status, n (%):			<0.01
employed	5 (23)	12 (55)	
disabled	2 (9)	0	
retired	2 (9)	4 (18)	
unemployed without applying for disability	13 (59)	6 (27)	
Duration of symptoms, years, M±SD	10.5±5.7	Not applicable	–
Age of onset, years, M±SD	27.24±6.7	Not applicable	–

Table 2. *Clinical structure of FMR in the considered sample, n (%)*

Clinical presentation of functional movement disorder	Number of patients, n (%)
Positive:	12 (54.5)
Psychogenic non-epileptic seizures	3 (14)
Dystonic disorders (blepharospasm, writer's cramp etc.)	7 (32)
Tics and hyperkineses	2 (9)
Negative:	5 (23)
Lower paraparesis with functional gait disturbances	4 (18)
Hemiparesis	1 (5)
Mixed:	5 (23)
Tetraparesis with functional tremor	3 (14)
Lower paraparesis combined with psychogenic non-epileptic seizures	2 (9)

Table 3. *Comparison of RP in the main and control groups, M±SD*

Group	RP Parameters			
	Latent period, right hemisphere, ms	Amplitude, right hemisphere, μV	Latent period, left hemisphere, ms	Amplitude, left hemisphere, μV
Main (n=22)	33.66±23.69*	-0.85±0.294*	52.00±29.816	-0.76±0.179
Control (n=22)	276.28±176.1	-0.35±0.26	42.85±49.59	-0.90±0.42

Note. * – significant intergroup differences (p<0.05).

tent with the previous data that point to a significant negative impact of FMDs on sociodemographic parameters [7, 9, 16]. The long duration of FMDs confirming the chronic course of these disorders is also in line with the currently available data [7, 26].

Voluntary movements are produced as the result of interaction between different brain structures, each of which makes its unique contribution to the formation of the movement. Impairment at any step of motor regulation may cause movement dysfunction. However, unequivocal data that would help identify the level of impairment or its localization within the nervous system in functional movement disorders are still missing [31].

We did not manage to identify any publications on the peculiar features of the readiness potential in patients with FMDs in the available literature; changes in the readiness potential as compared to normal were observed in patients suffering from a range of neuropsychiatric conditions, such as schizophrenia [32], autism [33], and obsessive-compulsive disorder [34].

Modern understanding of the readiness potential implies that it is a complex phenomenon, the appearance of which may be associated not only with the initiation of movement and preparation for it but with a broad spectrum of other psychic functions, too. In particular, expectation of possible results, processing of proprioceptive and visual information, including via mirror neurons, as well as various unconscious psychic processes1 are known to play a crucial role in the formation of the readiness potential [36].

Given the phenomenology and psychopathology of FMDs (unconscious movements or absence of movements), the readiness potential appears to be a perspective, logically relevant marker of this condition in patients. Our results obtained using the flanker task paradigm are largely consistent with the data from previous EEG studies that used other paradigms [27,28].

There are two aspects in which identification of changes of the readiness potential in the right hemisphere of patients with FMDs may be of great practical value. Firstly, the results of this study serve as a preliminary confirmation of the existence of reliable biological markers of the condition. Further research in this field will help evaluate the sensitivity and the specificity of the RP changes demonstrated in this study and understand the role of neurophysiological methods in diagnosing FMDs, whether as a screening tool or a way of objectivizing and clarifying the diagnosis (by identifying specificity and sensitivity parameters for the selected values of amplitude and latency).

In the second place, the identified changes of the readiness potential enable us to correlate the clinical manifestations of FMDs with the changes in the activity of the right hemisphere, thus making it possible to develop neurophysiologically justified protocols of nonpharmacological biologic treatment in the future. Thus, the motor cortex appears to be a perspective target for intervention using both transcranial magnetic and transcranial electric stimulation.

Study limitations. This study only involved right-handed patients, so its results may not be extrapolated to all patients with FMDs. An independent study would be required to identify the neurophysiological peculiarities in left-handed patients with FMDs. Moreover, in this study the readiness potential was analyzed without differentiating between various clinical types of FMDs, precluding the assessment of the neurophysiological differences between patients experiencing positive symptoms and those with negative symptoms. Finally, from a fundamental standpoint, the results under discussion were obtained only in the Erickson's flanker paradigm and, therefore, need to be reproduced using other paradigms.

Conclusion. Despite the high prevalence and clinical importance of FMDs, their etiology, clinical manifestations, and the neurophysiological mechanisms that lie at the core of these conditions are not completely understood [37]. In this study, patients with FMDs showed alterations in the frequency and amplitude parameters of the readiness potential in the right hemisphere. These findings support abnormal functioning of the sensorimotor cortex in this group of patients. The obtained results appear to be highly promising in terms of further research and may be helpful in optimizing both diagnostic and treatment approaches in FMDs in the future.

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