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EXPERIMENTAL PAPERS

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# Neuromarkers of the Effects of Transcranial Direct Current Stimulation (tDCS) in Children with Mental Development Disorders

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**Abstract**—The study aimed to reveal neurophysiological markers of the effects of transcranial direct current stimulation (tDCS) in children with speech disorders, learning disability, emotional and communicative problems, etc. Comparative EEG studies were carried out in eyes-closed and eyes-open resting conditions in children aged 3–8 years: in the control group without developmental lags (28 children) and in the group with mental development disorders (after conventional treatment—27 children, after tDCS treatment—28 children). A significant increase in alpha peak frequency in the occipital cortex and a decrease in the spectral power of the slow ( $\theta$ ) activity in the occipitoparietal cortex in the left and right hemispheres after tDCS were shown. This indicates a systemic influence of local tDCS on the brain function both in the stimulated and contralateral hemispheres. These EEG parameters are more similar to those in the control group than in children with mental development disorders without tDCS. The data obtained are interpreted as neurophysiological markers of tDCS effects (formation of the age-related dynamics of EEG rhythms in children with mental development disorders). A higher efficiency of the first tDCS session in 494 children was found in the case of tDCS applied near the cortical projection of the Wernicke's area in the left hemisphere (systemic effect on speech, motor functions, behavior, emotional sphere, etc).

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**Keywords:** mental development disorders, perinatal pathology, EEG, ICA, tDCS

## INTRODUCTION

The interest in the transcranial direct current stimulations (tDCS) in the world over the past decade has increased, but more than 90% most

studies have been done in healthy adults, neurological and psychiatric patients [1, 2] A significant contribution to the study of tDCS in children was made by domestic authors [3, 4] including IHB RAS [5, 6].

So, earlier we found, that in cases of severe mental retardation of perinatal origin, a significant increase in the power density spectra of the  $\theta$  band are revealed in the left-sided frontotemporal and right-sided temporal cortices, including the presence spectral peaks at frequencies of 5–6 Hz in the left hemisphere [7]. Data obtained allows us to consider these regions to be putative sources of slow activity and markers for a lesion or immaturity in the fronto-thalamic system, as well as for the temporal areas responsible for the auditory analysis and synthesis of speech signals and the integration of audiovisual information. The use of the hypothetic generators of slow frequencies as the targets of action in performing tDCS significantly increases the correctional effect of this action on speech functions and can serve as an indirect confirmation in favor of association of the described phenomena with one of the brain mechanisms underlying the formation of speech disorders of perinatal origin.

Longitudinal analysis of main EEG bands spectral power was performed in eyes-closed and eyes-open condition in children with mental developmental disorders at different stages of treatment with tDCS [8]. A significant increase in the power of  $\alpha$ -rhythm in the occipitoparietal cortex and a significant decrease in the power of  $\theta$ -rhythm in the left frontotemporal areas were observed in the course of the correction process. The data obtained may be considered as the neurophysiological markers of the tDCS effects (formation of age-related EEG parameters in children with mental developmental disorders).

The EEG investigation showed differences in the gIC (global independent components, which is related to widespread synchronous activity across the entire cortex, with a maximum amplitude in the frontal cortex) spectral power in the theta and beta EEG frequency bands for two groups of ASD (autism spectrum disorders) children with differing of cognitive and communicative dysfunction severity (with severe and with non-severe—ASD-S and ASD-nonS respectively) compared to the EEG activity in the control group [9].

More number of gIC spectral power differences were observed between the ASD-S and ASD-nonS cognitive and social dysfunctions and con-

trol groups of children than between the ASD-nonS group and control group that was hypothesized to be an index of cognitive dysfunction severity in the population with ASD. The whole group of children with autism was characterized by higher power in both theta and beta frequency bands in global gIC, which is related to widespread synchronous activity across the entire cortex, with a maximum amplitude in the frontal cortex. We can assume ASD markers (sources of abnormal EEG activity, gathering activity from all cortex areas) can be detected, showing maximum amplitude in the frontal cortex related to executive function and social cognition systems. The enhanced right occipital gIC spectral power in the beta frequency also differentiated the groups with ASD from the Control group. Those regions may also be the potential sources of the abnormal activity related to ASD.

The goal of the comparative study was to reveal the neurophysiological markers in children with mental development disorders under the influence tDCS (in the stimulated hemisphere and in the contralateral one) and without it. We suppose that there is a connection between the tDCS effects and the area of the first application tDCS.

## RESEARCH METHODS

### *1. Groups of children*

#### *1.1. Control group (No. 1)*

Control group (No. 1) of children without developmental lags The control group (No. 1) included 28 children (12 girls, mean age: 6.1 years old,  $SD = 1.5$ ) without developmental lags. The development of social and communicative functions according to the age norm was the main criterion for inclusion in the control group. The control group included children that were pupils of mass kindergartens and schools. The criteria for exclusion included the existence of organic brain damage and neurologic diseases. The groups of children were age-matched and did not differ in age by the Mann–Whitney criterion.

#### *1.2. Developmental lags groups (No. 2 and 3)*

These groups (diagnoses F 83, F 80.1, F 80.2, F 81.0, F 81.1, F 81.3 F 84.0 according to the International Classification of Diseases-10, 2010)

included: a group No. 2: 27 children (4 girls, mean age: 5.6 years old,  $SD = 1.1$ ) are received traditional treatment (including pharmacotherapy, logotherapy, etc.); a group No. 3: 28 children (7 girls, mean age: 6.1 years old,  $SD = 1.4$ ) are received tDCS treatment. Children with severe organic brain dysfunctions and concurrently diagnosed diseases, such as epilepsy and cerebral palsy, were excluded from the examined group.

## 2. EEG recording

EEG was recorded using Mitsar-EEG 201-21 system (Mitsar, Ltd). WinEEG software was used for acquisition and analysis of data. 19 silver-chloride electrodes were applied according to the International 10–20 system at sites Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2. The ground electrode was placed on the forehead. The input signals referenced to the linked ears were filtered between 0.5 and 50 Hz and digitized at a rate of 250 Hz. All electrode impedances were kept below 5 kOhm. EEG was recorded in eyes-closed (EC) and eyes-open (EO) resting conditions, at least 2 min for every period. The eye-blink artifacts were corrected by zeroing the activation curves of the individual PCA components corresponding to eye blinks [10]. In addition, epochs with excessive amplitude of filtered EEG and/or excessive faster and/or slower frequency activity were automatically excluded from further analysis. The artifacts rejection thresholds were set as follow: (1) 120  $\mu$ V for non-filtered EEG; (2) 50  $\mu$ V—for slow waves extracting by digital filtering in 0–1 Hz band; (3) 40  $\mu$ V—for fast waves filtered in the band 20–35 Hz. These threshold values were chosen empirically using multiple data processing and subsequent visual inspection. The first test effectively eliminates artifacts related to eye blinks and other rapid movements, but skipping almost all the EEG signals. The second test identifies the artifacts associated with the slow head or body movements. The third test detects high-amplitude EMG—artifacts related to the tension of muscles when clenching the teeth, swallowing, etc. Before further processing the entire array of EEG recordings are re-calculated to the “common average reference montage” (Av). The quantitative data were obtained using WinEEG software

(Ponomarev V.A., Kropotov Yu.D. The register for the computer programs of RF No. 2001610516, 08.05.2001) [11].

### 2.1. Independent component analysis (ICA)

The InfoMax algorithm was used, in order to obtain estimates of the unmixing matrix  $W$ . We used a C++ implementation of the InfoMax algorithm, which is the part of WinEEG software and it is practically identical to the Runica procedure from the package EEGLAB except the stopping weight change which was reduced from  $10^6$  (default value) to  $10^7$ , and the maximum number of iterations which was increased from 512 to 3000 [12]. As a result of these changes, the algorithm became to work stably in the processing of EEG of different durations varying over a wide range from 40 s to several hours. The estimation of  $W$  matrix was carried out for the EO and EC condition separately.

### 2.2. Spectral and statistical analysis

For each individual, each condition and for each independent component the power spectra were computed as follows: Artifact-free continuous EEG was divided into 4.096 s epochs using a Hanning time window (epochs were overlapped by 50%) and submitted to Fast Fourier Transform (FFT). Comparative analysis of the power spectra was performed in the EEG ranges:  $\theta$  (4–8 Hz) and  $\alpha$  (8–11 Hz). Power spectra with a number of averaged epochs less than 10 were eliminated from further analysis, therefore the numbers of subjects were slightly different for eyes-closed and eyes-open conditions. To normalize distributions, the logarithms of the mean power spectra were calculated. To quantify the effect sizes of the differences in the EEG spectral characteristics, the Cohen's  $d$  statistic was computed. The statistical significance of the Cohen's  $d$  effect size was defined for  $d > 0.6$ . MANOVA was used to evaluate significant differences within the three groups of children: 1—Control, 2—non-tDCS and 3—tDCS group. One-way ANOVA was used to estimate the statistical significance differences of EEG power (in eyes open) and  $\alpha$ -peak frequency (in eyes-closed and O2 by “10–20” EEG system) of the ICA components separately. The individual frequency of the  $\alpha$ -peak was determined visually

**Table 1.** The distribution of the examined children at the first session of tDCS

| Compared areas of the tDCS targets (cortex projections)        | Number of children ( <i>n</i> ) |
|--|---------------------------------|
| Wernicke's area in the left hemisphere                         | 214                             |
| Broca's area in the left hemisphere                            | 66                              |
| TPO (temporoparietal-occipital area) in the left hemisphere    | 93                              |
| auditory cortex (BA 22) in the left hemisphere                 | 77                              |
| motor cortex (BA 8) in the left hemisphere                     | 121                             |
| premotor cortex (BA 6)—between Fz and Cz by “10–20” EEG system | 106                             |

by average values of the spectrum power, the average values was calculated with a step of 1 Hz by WinEEG in the 6–12 Hz range. The ICA components topographies together with the sLORETA imaging approach were used for data visualization. The free software was provided by the Key Institute for Brain-Mind Research in Zurich, Switzerland (<http://www.uzh.ch/keyinst/loreta.htm>). For theoretical issues of this method see [13].

### 3. tDCS procedure

tDCS was performed in children with mental development disorders aged 2 to 10 years. tDCS was performed using a medical device ELFOR-prof (License No. FSR 2010/08893). The electrodes made of conductive rubber (an area of about 3 cm<sup>2</sup>), which were arranged under the EEG cap on a child's head skin through cotton moistened with tap water, were used. The exposure time was 20 min; the intensity of exposure 0.03–0.12 mA; current density 0.01 to 0.004 mA/cm<sup>2</sup>, respectively. The number of sessions per course was determined by the child age  $\pm$  1 scheme and varied in preschool children between 2 and 7 days (based on the wellbeing). The cathode was arranged on the mastoid process or in the projection of the occipital bone near the occipital foramen of the ipsilateral (relative to the anodal position) hemisphere. The anodal position was selected based on the principle of neuropsychological correspondence between disordered mental functions (impressive, expressive speech, coarse and fine motor skills, associative activity, etc.) and the target region (Brodmann's areas, BA) connected with this function [14].

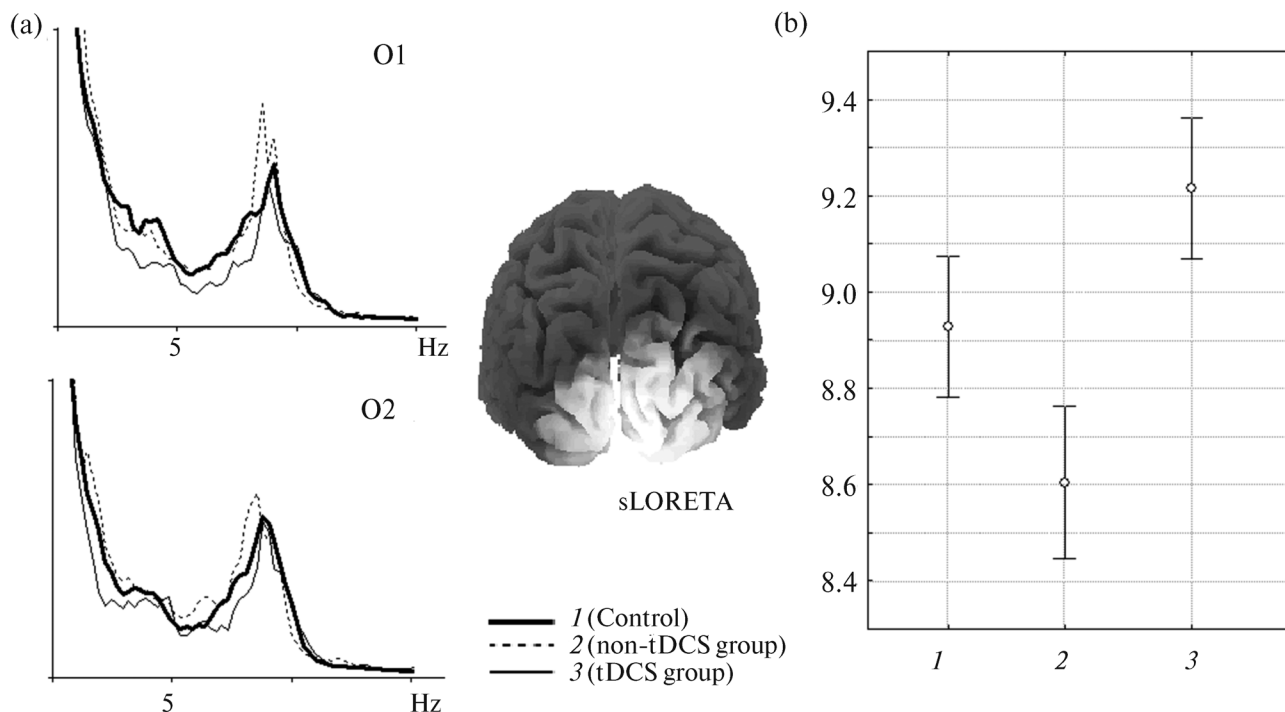
The tDCS carried out in according to the our patents RU 2 248 227 C1 and RU 2 402 973 C1.

The innovation of modifications of the well-known tDCS schemes [3, 4, 15–17] is to select the left hemispheres as the main goals. This change has significantly reduced the time required for tDCS to elicit positive effects in children with mental disorders.

The effects of tDCS were investigated depending on the choice of the area of the first session. We used following criteria's for patient selection: time exposition 20 min, the tDCS' targets (cortex projections) were selected mostly within in the left hemisphere, without pharmacotherapy and without previous tDCS. The effects of the first tDCS sessions were analyzed in 677 children near the six cortex projections (Table 1).

### 4. Estimation of behavioral effects of the tDCS procedure

After a first session of tDCS were rated: positive shifts in the communicative and emotional spheres, expressive speech etc. The proportion of children from the general sample who had some changes after the procedures was estimated. Since the state evaluation period of the child was short (less than a week), standardized scales were not applied. At this stage the study is phenomenological character. We used the information of specialists and parents about children's behavior: contact with the specialist in the examination situation, social development (social interactions), attention, working efficiency, behavior, cognitive interest, performance of the instructions, perception, reasoning, speech production, speech comprehension, calculating abilities, and self-care skills, etc. As a result, the caused changes were grouped as follows: I—emotional state; II—expressive speech; III—motor function; IV—cognitive interest; V—activity; VI—behavior; VII—



**Fig. 1.** An intergroup comparison of the raw EEG spectral power in the range from 0.5 to 15 Hz in the occipital cortex in eyes closed condition. The ICA components for the occipital localizations O1 and O2 (a). Thick line—the control group (1), dotted line—the non-tDCS group (2), thin line—the tDCS group (3). X-axis—frequency in Hz, Y-axis—standard units. The differences in the alpha peak frequency in O2 by “10–20” EEG system (b), whiskers represent 95% of the standard error interval. X-axis—the groups, Y-axis—frequency in Hz.

sleep; VIII—communicative function; IX—imitation activity; X—reasoning; XI—impressive speech; XII—reading, watching cartoons; XIII—self-care skills. We used quantitative analysis of positive changes not severity (“yes/no” principle). One-way ANOVA was used to estimate the statistical significance differences of the positive psychological changes after the first session of the first course tDCS (6 areas).

## RESULTS

### 1. EEG data

The analysis of spectral power of the EEG in a state with eyes-closed condition showed a significant increase (by ANOVA) in the  $\alpha$ -peak frequency to 9.2 Hz in the occipital areas (O2 by “10–20” EEG system) in group No. 3 (tDCS) compared with group No. 2 (non tDCS) and the control group  $F(2,77) = 4.02, p < 0.02$ . The  $\alpha$ -peak frequency was 8.6 Hz for the group No. 2, it was 8.9 Hz for the control group. These effects

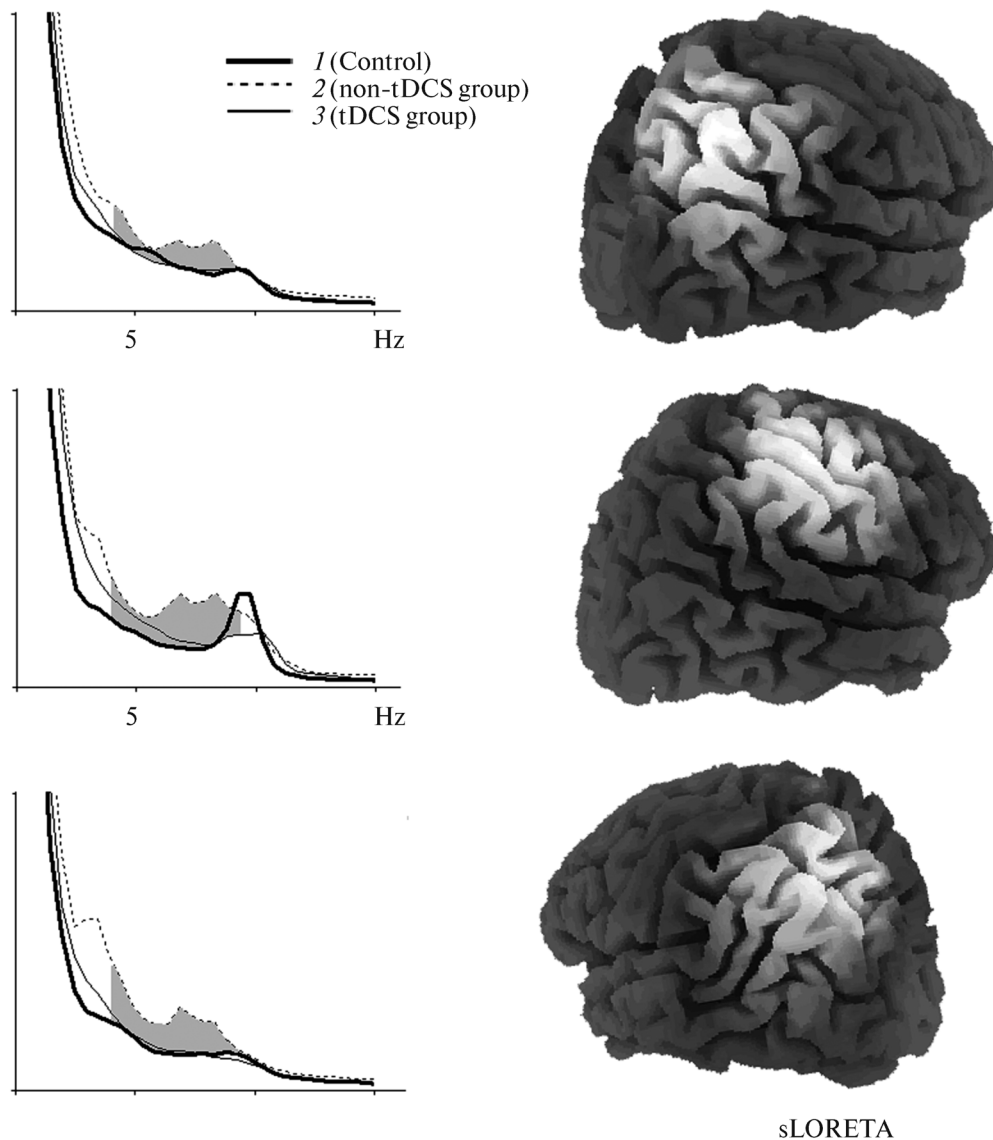
are illustrated in Fig. 1.

One-way ANOVA revealed a significant shift in the spectral power in eyes-open condition for the group No. 2 (non-tDCS) compared to the group No. 1 (Control) in the parietal leads bilaterally: P3  $F[1,52] = 5.01, p < 0.03$ , Cohen  $d = 0.6$ , P4  $F[1,52] = 3.94, p < 0.05$ , Cohen  $d = 0.5$  and the right central region (C4)  $F[1,52] = 8.07, p < 0.006$ , Cohen  $d = 0.77$  for the theta range (4–8 Hz). These effects are illustrated in Fig. 2. Differences in the spectral power for the group No. 1 (Control) and the group No. 3 (tDCS) were not detected for both states for eyes-closed condition and eyes-open condition.

### 2. tDCS data

As the obtained data showed, negative reactions to the first tDCS session were noted in 18% of children (whims, dyssomnia etc.). They disappeared, as a rule, the day after tDCS, without special treatment.

We found significant positive changes after the



**Fig. 2.** Grand average power spectra of the ICA components in the eyes-open condition. The coordinate axes and the groups are the same as in Fig. 1a. The sLORETA localizations are shown to the right. Areas of significant difference are highlighted in grey ( $p < 0.05$ ).

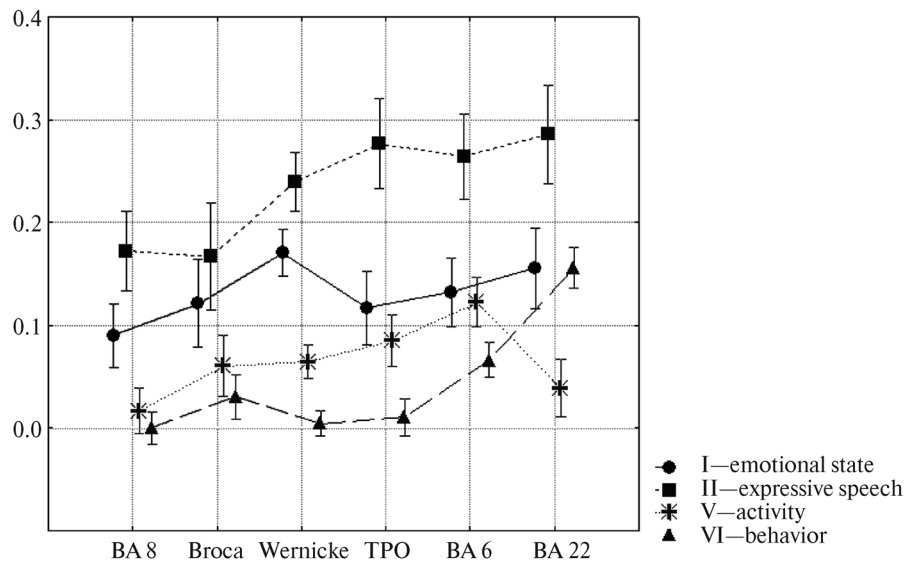
first tDCS session in different areas of the brain in four parameters: I—emotional state; II—expressive speech; V—activity; VI—behavior (Fig. 3).

MANOVA found significant positive psychological changes after the first session of the first tDCS (Wilks lambda = 0.89,  $F(20,2233) = 3.77$ ,  $p < 0.001$ ). As can be seen from Fig. 3, tDCS in the projection of different areas of the brain (motor, sensory, associative) has a systemic effect on mental processes (primarily speech) and child behavior in general. These changes are less pronounced in cases of expo-

sure to the motor speech center (Broca's area), BA 8. At the same time, tDCS near the cortical projections of the sensory and associative centers of the left hemisphere (Wernicke's area, the auditory cortex—BA 22, TPO), as well as the BA 6 (premotor cortex, between Fz and Cz by "10–20" EEG system), have a significantly higher effect.

## DISCUSSION

The data obtained showed a positive effect



**Fig. 3.** Effective hypothesis decomposition of positive psychological changes after the first session of the first tDCS. X axis—the tDCS' targets, Y axis—fraction of total subjects. Vertical bars denote  $\pm 95\%$  of the standard error intervals.

tDCS in children with mental development disorders according to the EEG for open and closed eyes states. In particular, in the occipitoparietal cortex  $\alpha$ - and  $\theta$ -bands in these children were approximated to the data of the control group: an increase in the frequency of  $\alpha$ -waves and a decrease in slow activity ( $\theta$ ) after tDCS. Previously, in longitudinal studies, we also showed an increase in the  $\alpha$ -frequency in the occipital cortex in eyes closed condition after tDCS courses [8]. A similar dynamics of EEG after tDCS was also found by other authors [16].

However, the age-related EEG dynamic in the non-tDCS group was insufficient. This group had the lowest values of the  $\alpha$ -peak frequency, and the highest values of the spectral power of slow ( $\theta$ ) activity. Previously, at the Bechtereva Institute of the Human Brain, it was demonstrated that significant psychological changes without tDCS were noted six months later in comparison with the tDCS group. Our study of the  $\alpha$ -peak frequency changes supported the W. Klimesch's point of view on the significance of this parameter for the investigation of the brain mechanisms of mental activity [18].

The left-hemispheric tDCS caused significant changes in power spectra of the main EEG rhythms in wakefulness not only in the left hemisphere, but also in the central parietal cortex and

occipital cortex of the right hemisphere. Thus, the local application of tDCS has a systemic effect through hemispheric connections.

The data obtained can be used as neurophysiological markers of the clinical efficacy of predominantly left-hemispheric tDCS on the age-related dynamics of the EEG rhythms. We have previously obtained evidence of the effectiveness of repeated tDCS in cases of severe developmental disorders, when the  $\alpha$ -rhythm frequency increased after the third course of tDCS [19]. It was also shown that the ability of the child's brain to mental development is significantly higher when tDCS is carried out up to 9 years, while being actively formed the motor, speech and associative functions, etc.

Significant changes in the state of mental functions and speech after several sessions of the left-hemispheric tDCS we described previously. Even with severe forms of ASD, a significant improvement of the child's state was shown (communication skills, speech understanding, and learning ability, etc). It was showed, that the left-hemispheric tDCS treatment of children with ASD led to reduce the symptoms of ASD according to the international ADOS questionnaire and the Woodcock—Jonson independent behavior scale; for example, ADOS values were decreasing after tDCS from  $42.5 \pm 7.7$  (severe degree of autism)

up to  $32.6 \pm 6.6$  (moderately severe/mild).

Many years ago it was shown that the left hemisphere in children has more possibilities to compensate for speech disorders than in adult patients [20]. Using our predominantly left-brain tDCS circuits has also significantly reduced the overall duration of tDCS exposure in a child's brain. Specifically, in comparison with the known schemes, the total duration of the tDCS course in preschoolers decreased from 10–15 to 3–7 sessions, the current strength—from 0.4–2 mA to 40–120  $\mu$ A, and the session time decreased from 30–60 to 20 min.

Perhaps, the hypothesis of interhemispheric interaction on the “part-whole” principle is supported: the right hemisphere regulates part of mental processes, and the left hemisphere regulates all processes, including the activity of the right hemisphere. The efficacy of left hemispheric tDCS has been demonstrated in adults and adolescents, as well as in other studies [21–23].

According to many authors, the tDCS mechanisms are associated with modulation of the processes of cortical excitability and plasticity. However, as we can see from the literature, the effects of tDCS exposure depend on a number of factors: age, patient's diagnosis, severity of the disease, location of electrodes (left/right hemisphere), areas of the cortex, area of electrodes, direct current value, exposure time, position of the anode and cathode, number of electrodes, number of sessions per course, interval between sessions and courses [1]. This significantly complicates the comparative analysis and interpretation of the data obtained.

However, to localize a lesion responsible for speech impairment and to localize speech functions are completely different things. There are differences between the mechanisms of the impairment of a function (due to head injuries, brain tumors, etc.) and the brain dysfunctions/function immaturity under the influence of hypoxia/ischemia factors of pre- or perinatal origin. There is evidence that speech disorders in children may be associated with functional dysfunction, but not with a damage to the brain structure. The systemic behavioral effects after only a single tDCS course is an indirect support of this point of view, despite the descriptive (phe-

nomenological) nature of our investigation.

The comparative analysis of the tDCS effect in the projection of different brain areas, predominantly left-hemispheric (motor, sensory, associative), showed the relationships with a wide representation of expressive and impressive speech, as well as the extensive functional connections of speech with the emotional sphere and behavior of a child (speech regulation of activity). The special role of the Wernicke's area was noted previously in neurosurgical patients [24, 25].

Part of the data obtained can be interpreted in terms of the behaviorism model, specifically, we stimulated the child's brain and examined a number of consequences of the tDCS effects during few days or weeks. However, the experimental investigation after micropolarization (DC, direct current) in the animal's brain showed changes in the functional activity level of the brain, which are based on the correspondence between the changes in the ultrastructure of glia, neurons and synapses [26]. Part of the theoretical position was supported by up-to-date methods of neuroimaging [2].

So, in this way, it can be assumed, that tDCS in children with mental disorders can be to give a stimulus to a whole range for positive psychomotor changes. We assume that quick positive effects after a single session of tDCS (predominantly left-hemispheric) may be associated with the starting and activation of relatively intact functional connections between brain areas, and an increase in the functional state of these structures during the formation of a polarization dominant. The processes of “maturation” of insufficiently formed mental functions, habilitation/compensation of damaged connections in the child's brain require regularly repeated courses of treatment, special training programs. In cases of severe mental disorders, learning disabilities (F 70, F 72, F 84.0, F 84.1), we need more time to get positive results (few weeks, months).

## CONCLUSION

Our data make it possible to further investigate the activity of the child's brain in conditions of mental development disorders under the influence of hypoxia/ischemia factors of pre- or perinatal origin. tDCS can be both an effective method to



treat the developmental lags and to study the neurophysiological mechanisms of mental activity (speech, behavior, attention, etc). We showed significant changes in EEG oscillations both in the stimulated and contralateral hemispheres, which indicates a systemic influence of the local tDCS application in expressive speeches and impressive speeches, perceptive speeches, behavior, emotional sphere, etc., of the abnormal children. A higher quantitative efficiency of the first tDCS session for mental and speech functions was found in the cases of tDCS near the cortical projection of the sensory and associative centers of the left hemisphere (Wernicke's area, TPO, BA 22), as well as the BA 6 (premotor cortex, between Fz and Cz by "10–20" EEG system).

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#### AUTHORS' CONTRIBUTION

N. Kozhushko recruited subjects, participated in experimental design, data acquisition, interpretation and drafting the manuscript. S. Evdokimov performed statistical analysis, interpreted the data and drafted the manuscript. Yu. Kropotov supervised the study, was involved in study design and critical review of the manuscript.

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#### CONFLICT OF INTEREST

The authors have no conflict of interest to

declare in relation with the publication of this material.

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