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Neurophysiological Markers of Abnormal Development in Children with Mental Disorders

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Abstract—Longitudinal analysis of the spectral power of the main EEG bands was performed in the wakeful state with the eyes open and the eyes closed in children with mental disorders at various stages of correction by transcranial direct current stimulation (tDCS). A significant increase in the power of α-rhythm in the parietal-occipital areas and a significant decrease in the slow wave activity in the left frontotemporal areas were observed in the course of the correction process. The data obtained can be considered as the neurophysiological markers of the tDCS effects (formation of age-related EEG parameters in children with mental disorders). The data also prove the relations between the described phenomena and the cortical mechanisms of speech disorders and other psychic processes caused by perinatal CNS disorders.

Keywords: electroencephalogram (EEG), transcranial direct current stimulation (tDCS), mental disorders, perinatal CNS disorders, longitudinal studies

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Steady growth of the number of children with mental disorders makes important the search for the early markers of the risk of developmental delay, as well as analysis of the age-related dynamics of retardation of mental processes at different stages of ontogeny, including those influenced by various effects (pharmacotherapy, electrical stimulation, etc.), it is a topical issue. Earlier, we identified the hypothetical sources of slow wave activity in the frontotemporal cortical divisions and showed an increase in the power of slow wave components according to the degree of delay in mental development [1]. The course effects of tDCS in relation to behavior and the state of higher mental functions (HMF) were described by us earlier [2]. A substantially improved effectiveness was shown when left hemispheric tDCS were used.

The character of interrelations between the administered courses of transcranial direct current stimulation (tDCS) and the parameters of bioelectrical activity restructuring in different divisions of the right and left hemispheres, as well as individual features of age-related dynamics in children with various initial EEG types, remain to be understood. Longitudinal studies in neurophysiology in children with learning and communicative difficulties are scarce [3, 4].

The aim of this study was to investigate the features of reorganizations of bioelectrical activity in the main EEG bands (1–20 Hz) at different stages of the correction process using tDCS in children with perinatal mental disorders (longitudinal study).

METHODS

Longitudinal EEG studies were conducted in children aged 4–12 years, including 38 subjects with perinatal mental disorders during the course of correction using tDCS (group 1) and 17 children without mental disorders but with a history of perinatal encephalopathy (group 2, controls). The average age in group 1 in primary studies was 6.13 years ($SD = 1.76$); in repeated studies, 7.03 years ($SD = 1.84$); in group 2, 6.35 ($SD = 2.15$) and 7.29 years ($SD = 2.31$), respectively. The interval between longitudinal surveys (repeated EEG in the same children) in both groups was about 11 months.

The EEG studies were carried out in the wakeful state with the eyes open and closed for 2–4 min. The silver chloride electrodes were arranged according to the International 10–20 System; the recording was made in the monopolar referent in relation to the right and left silver chloride ear electrodes. The EEGs were recorded using the Mitsar 21 channel EEG system (Mitsar, Ltd. St. Petersburg). All electrode impedances were kept below 5 kΩ; the signal digitized at a rate of 250 Hz. The monopolar montage with a common average reference electrode were used. The high-pass (HPF) and low-pass filer (LPF) parameters constituted 1.5 and 35 Hz, respectively. Correction of the eye movement artifacts was performed using the method of filtration of independent components corresponding to these movements [5].

Comparative analysis of the power spectra of the main EEG bands was performed using Student's t-test: θ, (4–8 Hz); α, (8–13 Hz); β, (13–20 Hz). The spectrum calculation parameters were as follows: the standard epoch of analysis, 2 s; overlapping of epochs, 50%; and Hanning window.

tDCS were carried out with emphasis on the left hemispheric regions—near the projections of Broca's, Wernicke's, fine motor skill (manual), and some other areas (the schemes and parameters of exposure are described in detail in [2, 6]).

RESULTS

Analysis of the EEG power spectra in children with mental disorders is used the following at various stages of correction by tDCS. In group 1, with the eyes open, significant differences in longitudinal studies were found only in the central lead on the left (C_3 region) and represented by the power increase at 8–10 Hz as the tDCS courses progressed (at $p < 0.03$).

In the control group under the same conditions (wakefulness, the eyes open), the age-related changes were represented by an increase in spectral power of the θ range in the anterofrontal and temporoparietal divisions with the predominance in the right hemisphere; however, they displayed merely a tendency (were not statistically significant).

At the same time, in group 1 (children with mental disorders), with the eyes closed, a significant increase in the spectral power of α activity was revealed in the parietal–occipital focus with tDCS course progression (Figs. 1a, 1b). At the same time in group 2 (control), no significant differences were revealed in longitudinal studies (Fig. 1c) as this α rhythm focus had initially been formed according to age.

As to slow waves, a significant decrease in θ-activity power was revealed at later tDCS courses in the left frontotemporal region in group 1 (leads Fp_1, F_7, F_3; $p < 0.05$) (Figs. 1a, 1b). In group 2, significant differences were multidirectional with age: in Fp_1, an increase in the slow wave power was noted; in Fz, their decrease (at $p < 0.04$ and $p < 0.03$, respectively).

As far as the age-related aspect is concerned, it should be noted that the tendency towards the α-activity increase with the eyes closed in the occipital divisions (leads O_1 and O_2) as the tDCS courses progressed was more noticeable in those who were under nine years (see Fig. 2 for individual increment values).

In the F_7 projection, inverse correlation between slow activity and repeated tDCS courses was also observed: as the correction process lengthened, the θ-band spectral power decreased (Fig. 3), $r = -0.67$ at $p < 0.002$. A similar correlation was also revealed in relation to the total number of sessions of these tDCS courses ($r = -0.46$ at $p < 0.05$).

When the results of repeated tDCS courses given to children with a variable degree of retardation were compared, the described correlation was more noticeable in the cases of gross disorders (mental disorders, autism spectrum disorders) compared to children with general speech impairment, motor alalia, etc., whose disorders of cortical rhythmicity before a tDCS course were initially less severe [1, 2].

DISCUSSION

The novelty of the patented tDCS regimens employed by us was determined by the choice of the left hemisphere as the main target and departure from the dominant arm principle and other criteria [7–9]. This change allowed us to substantially reduce the time of the appearance of positive effects of tDCS with respect to speech and other high mental functions and to increase the percentage of efficiency of a single use of tDCS in the projections of the left hemispheric speech centers [2, 6]. However, the neurological mechanisms of the advantages of choosing the left hemisphere were not understood in detail.

The available data of many years' observations of children (from the early age to 18 years) demonstrate predominantly the left hemispheric dysfunction upon exposure to health hazards in the pre- and perinatal periods, which is more characteristic of premature infants and infants with delayed intrauterine development and hypotrophy [10]. At the same time, the right hemispheric symptoms were more often associated with peri- and intranatal hazards and were typical of mature and overdue infants born with a large body mass. The right hemispheric preference of changes in the EEG spectral power in the frontocentral divisions was noted in the studies of children with mental disorders [11].

There are hypotheses about a pathological origin of left-handedness due to unfavorable environmental influences shifting handedness towards left-handedness, which makes the suggestion about a relationship between the changes in motor dominance and the anomalous development of interhemispheric interrelations probable [12–16]. Earlier, the authors compared the EEG normative base of apparently healthy children and children with the consequences of perinatal encephalopathy (single studies without tDCS performance) [2, 17]. In the presence of significant intergroup differences in the power spectra for the "group" and "group–localization" factors, inversion of interhemispheric asymmetry was noted in the left hemispheric divisions: in particular, in the θ and α bands, in leads F_3 and C_3; in the β_1 band (12–15 Hz), in F_3, C_3, and P_3; in the β_2 band (15–18 Hz), in C_3, T_3, T_5, and P_3.

The interest in EEG age-related dynamics in the α-band in neurophysiology is traditional [18–21]. It is known that the risk group children (with long-term

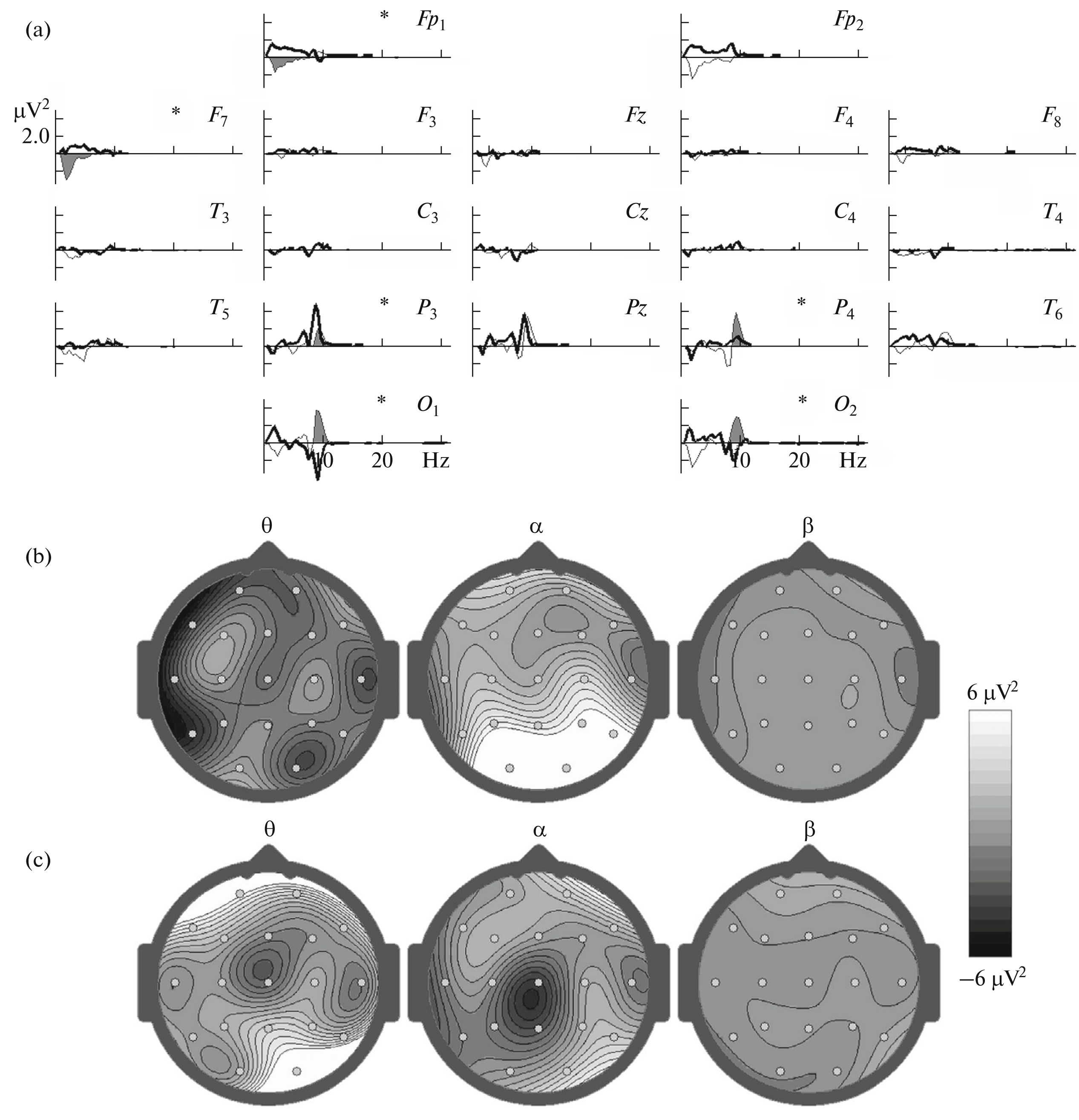

Fig. 1. Comparative analysis of the EEG spectral power in the wakeful state with the eyes closed (longitudinal study—the later data minus the earlier ones). (a) Local power spectra of the 10–20 system leads; abscissa: frequency (Hz); ordinate: power values (μV^2); thin line, group 1 data (children with mental disorders on the tDCS course); thick line, the control group (2) data, the regions of significant differences between the groups are filled (designated with an asterisk); (b) topography of the above-mentioned spectral differences in the main EEG bands in group 1 children; (c) in group 2 children (controls).

consequences of perinatal CNS pathology) have initially a number of limitations for acquisition of age-related loads in the process of ontogeny, despite natural growth reserves as well as tremendous compensatory possibilities of the brain [2, 12, 22–24]. This is manifested, among other things, by immaturity of the age-related biorhythm structure, i.e., non-formation of the α-rhythm parietal-occipital focus, as well as by an increase in the proportion of the θ-band slow waves compared to the age-related reference values [18, 19, 25].

The authors also described a significant growth of the proportion of immature EEG type according to the degree of severity of developmental deviations [2]. For example, while the immature type proportion in normal preschool children constituted no more than

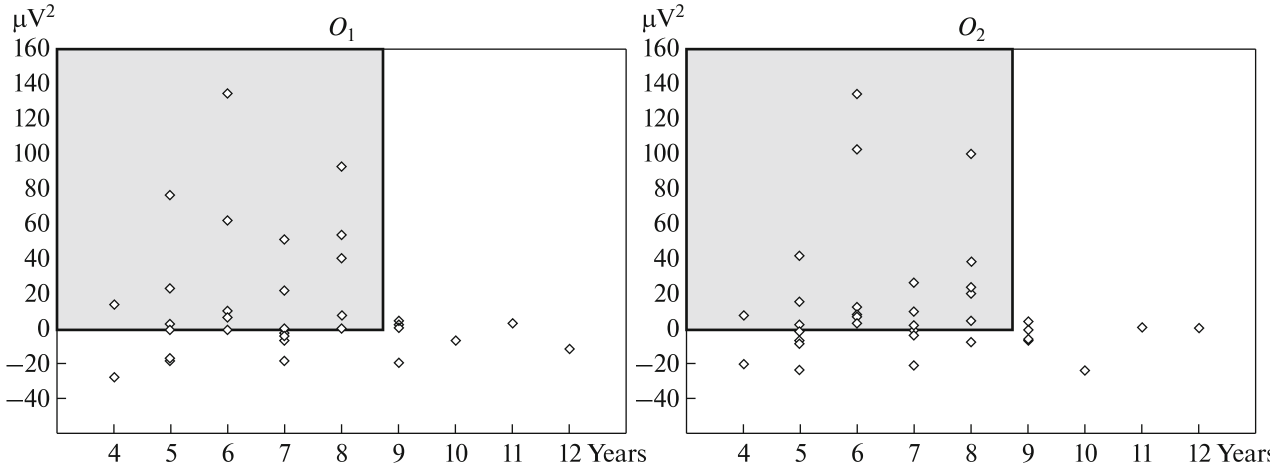

Fig. 2. Age-related dynamics of the α-activity increase in the occipital cortical divisions during tDCS course administration (wakefulness, the eyes closed). Abscissa: the age of children on the tDCS course (years); ordinate: an increase in the spectral power of α-activity at 8.5–10 Hz (μV^2); the area of the age-dependent positive power increase is designated with a gray color.

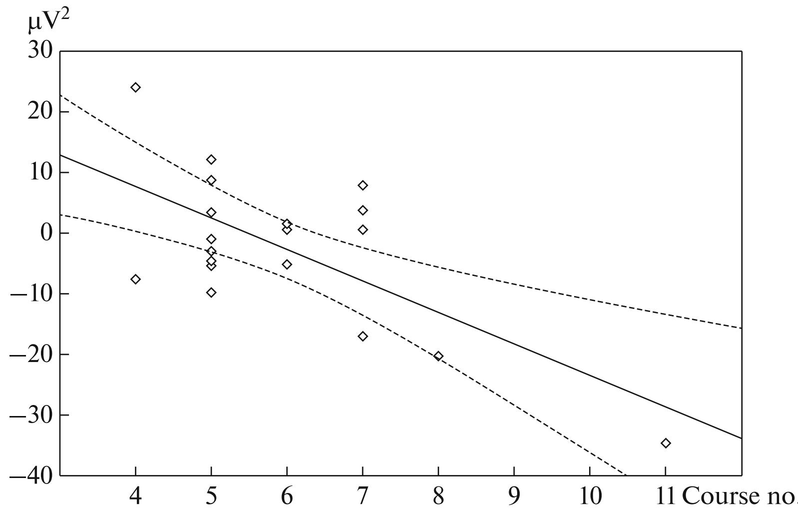

Fig. 3. Analysis of correlations of changes in the EEG spectral power in children with mental disorders in the state of wakefulness with the eyes closed upon repetition of tDCS courses. Abscissa: the ordinal number of a tDCS course; ordinate: changes in the power of 3–5-Hz slow frequencies in the left frontotemporal region (lead F_7) in μV^2.

15%, in children with mental disorders it attained 55.3%. Moreover, when the EEG of retarded children with no positive dynamics on conventional therapeutic regimens (pharmacotherapy) were compared, their proportion of immature EEG was found to be 61.0% versus 43.6% in the group of children with positive dynamics on drug correction (significant differences at $p < 0.001$), all the more so because earlier longitudinal studies have demonstrated that the immature EEG type in children at risk is retained at later stages of ontogeny.

As shown by this study, substantial positive changes (with the eyes closed when the α rhythm is usually more markedly pronounced) occur in the α band in the course of correction by tDCS. What matters is the rhythm increase precisely in the age-related (parietal–occipital) focus rather than a diffuse rhythm power increase. According to the periods of active HMF formation due to the forthcoming schooling, more pronounced positive dynamics is observed before nine years, when the resource of development of the child brain and the level of its neuroplasticity are still rather high.

It is worth noting that during tDCS the spectral power of slow frequencies in the left frontotemporal region was also found to be decreased. Earlier, we revealed "deceleration generators" of the EEG rhythms in the frontotemporal divisions of the cortex

[1], and the predominance of the first tDCS in these regions could have been a peculiar source of slow rhythm acceleration. Coupled with the effect of tDCS, the dynamics of α-activity in the cortical regions adjacent to and remote from current localization may, on the one hand, indicate an activation of relatively safe functional relations or closure; on the other hand, the formation of new relations also demonstrates a systemic effect of local exposure of the brain. The experimental data of the first investigations of the effects of tDCS gave evidence of similar dynamics of the electrosubcorticogram [26].

Rehabilitation measures in neurology (electromagnetic stimulations etc.) are known to be less efficacious in relation to a damaged structure (e.g., in strokes) but more beneficial in relation to intact links of the system, which take over a compensatory function [27]. It so happens in the studies that damage to the speech anlage in the pre/perinatal period does not seem to indicate a complete loss of the functional reserve for development. Using tDCS, it is possible to arouse, to stimulate the potentialities of the neuroplasticity reserve, although minimal, likely to be possessed by every child afflicted even with serious mental disorders. Learning in such cases may be successful due to the involvement of safer (or intact) brain systems into work [12, 28]; hence the differences in the effects of tDCS when mild impairments (speech impediment) occur on a parallel with severe forms of developmental disorders (e.g., severe mental retardation).

According to one of the schemes of interhemispheric interaction, the relations between the right and left hemispheres may be based on the part–whole principle: the right hemisphere regulates part of the mental processes, and the left hemisphere regulates their integrity, including the activity of the right hemisphere [13]. It is possible that precisely this hypothesis, according to which the pathway to central processes, regulatory brain systems is shorter and more efficient by means of tDCS via the left hemisphere structures, is better suited for data interpretation.

To what extent this model corresponds to the features of interhemispheric asymmetry in the studies, what it should represent in health, or whether it reflects the features of abnormal asymmetry in children with the consequences of perinatal CNS affliction are the tasks we must address urgently in subsequent studies.

CONCLUSIONS

Longitudinal EEG studies in children with mental disorders revealed at various stages of correction by tDCS a significant increase in the spectral power of α activity in the age-related (parietal–occipital) focus as well as a significant activity decrease in the left hemispheric frontotemporal divisions where earlier we described the hypothetical sources of deceleration of cortical rhythmicity. The systemic psychophysiological effect of local exposures may reflect activation with respect to intact functional relations of the brain structures, and the results of exposure are then of immediate nature (appear during the tDCS course). It may also be related to stimulation of the formation of age-related cortical rhythm parameters when the results are of delayed nature. tDCS near projections of the brain speech centers in the left hemisphere play a leading role in the process, and it is assigned to an exceptional importance of speech in the formation of other mental processes, acquisition of social environment, and learning through verbal interaction.

REFERENCES

1. Kozhushko, N.Y., Evdokimov, S.A., Matveev, Y.K., Tereshchenko, E.P., and Kropotov, Y.D., Study of local EEG specificities in children with mental development disorders using independent component analysis, *Hum. Physiol.*, 2014, vol. 40, no. 5, p. 497.
2. *Mikropolyarizatsiya u detei s narusheniem psikhicheskogo razvitiya ili kak podnyat' planku ogranichennykh vozmozhnostei* (Micropolarization in Children with Mental Disorders or How to Raise the Level of Limited Potential?), Kozhushko, N.Yu., Ed., St. Petersburg: Karo, 2011.
3. Gorbachevskaya, N.L. and Kozhushko, L.F., Dynamics of EEG formation in boys and girls of school age (according to 9-year observation), *Zh. Nevropatol. Psikhiatr. im. S.S. Korsakova*, 1990, vol. 90, no. 8, p. 75.
4. Gorbachevskaya, N.L., Karakhanyan, K.G., and Davydova, E.Yu., A talented child. Longitudinal study of memory and EEG, *Klin. Spets. Psikhol.*, 2016, vol. 5, no. 2, p. 63. doi 10.17759/psyclin.2016050205
5. Vigario, R., Extraction of ocular artifacts from EEG using independent component analysis, *Electroencephalogr. Clin. Neurophysiol.*, 1997, vol. 103, no. 3, p. 395.
6. Kozhushko, N.Y., Kropotov, Y.D., Matveev, Y.K., Semivolos, V.I., Tereshchenko, E.P., and Cholyavin, A.I., Brain structural and functional characteristics in children with mental disorders and the possibilities of transcranial direct current stimulation, *Hum. Physiol.*, 2014, vol. 40, no. 4, p. 383.
7. Pinchuk, D.Yu., *Transkranial'nye mikropolyarizatsii golovnogo mozga: klinika, fiziologiya* (Transcranial Micropolarizations of the Brain: Clinics and Physiology), St. Petersburg: Chelovek, 2007.
8. Amatachaya, A., Jensen, M.P., Patjanasoontorn, N., et al., The short-term effects of transcranial direct current stimulation on electroencephalography in children with autism: a randomized crossover controlled trial, *Behav. Neurol.*, 2015, vol. 9, no. 28, p. 631.
9. Schneider, H.D. and Hopp, J.P., The use of the bilingual aphasia test for assessment and transcranial direct current stimulation to modulate language acquisition in minimally verbal children with autism, *Clin. Ling. Phonetics*, 2011, vol. 25, nos. 6–7, p. 640.
10. Brin, I.L. and Dunaikin, M.L., Functional asymmetry and congenital hemihypoplasia in children, *Vserosiiskaya konferentsiya "Aktual'nye voprosy funktsional'noi mezhpolusharnoi asimmetrii"* (All-Russ. Conf. "Current

Problems in Functional Interhemispheric Asymmetry"), Moscow, 2001, p. 45.

11. Gorbachevskaya, N.L., Yakupova, L.P., Kozhushko, L.F., and Bashina, V.M., Topographic EEG-mapping in children's psychiatry, *Fiziol. Chel.*, 1992, vol. 18, no. 6, p. 40.
12. Semenovich, A.V., *Neiropsikhologicheskaya korrektsiya v detskom vozraste* (Neuropsychological Correction in Childhood), Moscow: Genezis, 2017.
13. Leutin, V.P. and Nikolaeva, E.I., *Funktsional'naya asimmetriya mozga: mify i deistvitel'nost'* (Functional Asymmetry of Brain: Myths and Reality), St. Petersburg: Rech', 2005.
14. Floris, D.L., Chura, L.R., Holt, R.J., et al., Psychological correlates of handedness and corpus callosum asymmetry in autism: the left hemisphere dysfunction theory revisited, *J. Autism Dev. Disord.*, 2013, vol. 43, no. 8, p. 1758.
15. Lindell, A.K. and Hudry, K., Atypicalities in cortical structure, handedness, and functional lateralization for language in autism spectrum disorders, *Neuropsychol. Rev.*, 2013, vol. 23, no. 3, p. 257.
16. Dobrokhotova, T.A., *Neiropsikhiatriya* (Neuropsychistry), Moscow: Binom, 2013, 2nd ed.
17. Kozhushko, N.Y., Ponomarev, V.A., Matveev, Y.K., and Evdokimov, S.A., Developmental features of the formation of the brain's bioelectrical activity in children with remote consequences of a perinatal lesion of the CNS: II. EEG typology in health and mental disorders, *Hum. Physiol.*, 2011, vol. 37, no. 3, p. 271.
18. Machinskaya, R.I. and Kurgansky, A.V., Frontal bilateral synchronous theta waves and the resting EEG coherence in children aged 7–8 and 9–10 with learning difficulties, *Hum. Physiol.*, 2013, vol. 39, no. 1, p. 58.
19. Yakovenko, E.A., Chutko, L.S., Ponomarev, V.A., Surushkina, S.Y., Nikishena, I.S., and Kropotov, Y.D., Features of the power spectra of the main EEG rhythms in children with different types of attention deficit hyperactivity disorder, *Hum. Physiol.*, 2013, vol. 39, no. 1, p. 22.
20. Strzelecka, J., Electroencephalographic studies in children with autism spectrum disorders, *Res. Autism Spectrum Disord.*, 2014, vol. 8, no. 3, p. 317.
21. Semenova, O.A. and Machinskaya, R.I., The influence of the functional state of brain regulatory systems on the efficiency of voluntary regulation of cognitive activity in children: II. neuropsychological and EEG analysis of brain regulatory functions in 10–12-year-old children with learning difficulties, *Hum. Physiol.*, 2015, vol. 41, no. 5, p. 478.
22. Otellin, V.A., Khozhai, L.I., and Ordyan, N.E., *Prenatal'nye stressornye vozdeistviya i razvivayushchiisya golovnoi mozg. Adaptivnye mekhanizmy, neposredstvennye i otsrochennye effekty* (Prenatal Stresses and Developing Brain. Adaptive Mechanisms, Direct and Postponed Effects), St. Petersburg: Desyatka, 2007.
23. Shalimov, V.F., School adaptation of children with border mental disorders, *Zh. Nevropatol. Psikhiatr. im. S.S. Korsakova*, 2007, vol. 107, no. 7, p. 24.
24. Zavadenko, N.N. and Nemkova, S.A., *Narusheniya razvitiya i kognitivnye funktsii u detei s zabolevaniyami nervnoi sistemy* (Disorders of Development and Cognitive Functions in Children with Nervous System Disorders), Moscow: Ross. Nats. Issled. Med. Univ. im. N.I. Pirogova, 2016.
25. Gorbachevskaya, N.L., Zavadenko, N.N., Yakupova, L.P., et al., Electroencephalographic study of children's hyperactivity, *Fiziol. Chel.*, 1996, vol. 22, no.\ 5, p. 49.
26. Vartanyan, G.A., Gal'dinov, G.V., and Akimova, I.M., *Organizatsiya i modulyatsiya protsessov pamyati* (Organization and Modulation of Memory Processes), Leningrad: Meditsina, 1981.
27. Voitenkov, V.B., Málly J., Skripchenko, N.V., and Klimkin, A.V., Transcranial magnetic stimulation as a diagnostic and therapeutic technique, *Nevrol. Zh.*, 2015, vol. 20, no. 5, p. 4.
28. Gorbachevskaya, N.L., Yakupova, L.P., Kozhushko, L.F, et al., Neurobiological reasons of school disadaptation, *Fiziol. Chel.*, 1991, vol. 15, no. 5, p. 72.

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