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Specificity of spontaneous EEG associated with different levels of cognitive and communicative dysfunctions in children

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ABSTRACT

This study aimed to reveal electrophysiological markers of communicative and cognitive dysfunctions of different severity in children with autism spectrum disorder (ASD). Eyes-opened electroencephalograms (EEGs) of 42 children with ASD, divided into two groups according to the severity of their communicative and cognitive dysfunctions (24 with severe and 18 children with less severe ASD), and 70 age-matched controls aged 4–9 years were examined by means of spectral and group independent component (gIC) analyses. A predominance of theta and beta EEG activity in both groups of children with ASD compared to the activity in the control group was found in the global gIC together with a predominance of beta EEG activity in the right occipital region. The quantity of local gICs with enhanced slow and high-frequency EEG activity (within the frontal, temporal, and parietal cortex areas) in children 4–9 years of age might be considered a marker of cognitive and communicative dysfunction severity.

1. Introduction

Cognitive and communication skills are disrupted in children with neurodevelopmental disorders, such as autism spectrum disorders. Autism spectrum disorder (ASD) is defined by impaired social interactions and the existence of limited, repetitive behavior (stereotypes, rituals). Most cases of ASD also exhibit retardation and a distortion of mental and speech development, resulting in a life-long disability. The timely detection of behavioral and physiological abnormalities offers an opportunity for therapeutic intervention in early development. One of the traditional approaches used to detect abnormalities in a child is electroencephalography. Early detection of electroencephalogram (EEG) abnormalities may be an early marker of cognitive impairment and ASD. In an investigation by Small (Small, 1976), 42% of individuals diagnosed with autism that had a “normal” EEG in childhood were able to obtain an education and adapt in life, whereas 75% of individuals with abnormal EEG patterns in childhood were not able to live an independent life. In other words, normal EEG development may be a positive predictor for the rehabilitation of children with neurodevelopmental disorders, and differences in EEG patterns are expected in children with autism with varying social and cognitive dysfunction severity. Searching for neurophysiological markers of autism and social and cognitive abnormalities related to autism is a relevant aim in neuroscience research (Oberman et al., 2014).

There are several views on the neural bases of ASD that have arisen from electrophysiological and neuroimaging studies. ASD is characterized by the anomalous function of social brain regions (McPartland et al., 2011) and impaired executive functioning (Hill, 2004). Abnormalities in perception and information processes have been discussed in the literature (Markram and Markram, 2010). There is evidence for abnormal functional connectivity in ASD samples, including both hypo- and hyperconnectivity (Supekar et al., 2013; Duan et al., 2017), leading to the idea that closely related areas are overconnected but there is decreased connectivity between regions further apart (O'Reilly et al., 2017). An imbalance between excitation and inhibition and increased excitability as a common mechanism of ASD has been discussed in the literature (Uzunova et al., 2016). Resting-state EEG spectral power analysis may provide information regarding the functioning of cortical areas involved in brain networks disrupted in ASD. The relative theta power is higher in the frontal, central, and posterior

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regions, and the absolute delta and beta power are lower in children with ASD than in normally developing children (Coben et al., 2008). In other investigations, there was a marked increase in the absolute theta power in the parietal and occipital regions, in the relative delta power in the frontal areas and in both the relative and absolute alpha in the temporal and occipital cortex (Cornew et al., 2012). Several studies have described increased beta and gamma spectral power in children and adults with ASD compared to the observed power in the control groups in both the eyes-closed and eyes-opened conditions (Cornew et al., 2012; Orekhova et al., 2007; Mathewson et al., 2012). The most consistent result of EEG spectral power analysis is a higher absolute gamma power in subjects with ASD than in non-ASD subjects (Gurau et al., 2017). These rather inconsistent data have not allowed for the identification of robust resting-state EEG markers of ASD, mainly because of the high variance of the disorder and the different experimental conditions. EEG analysis in children with different levels of psychological function disturbances can provide some insight into the understanding of the physiological markers of ASD. Most children with ASD, 75%, have mental retardation and a low intelligence quotient (IQ) (Rutgers et al., 2004). The EEG characteristics of children with severe impairment, including those who are non-responsive, have not been thoroughly studied. The present study examined children with pronounced cognitive and social behavioral dysfunctions. These children hardly make contact with others or are entirely non-responsive including following instructions in physiological investigations. As EEG registration in non-responsive children is rather difficult and sometimes impossible to perform on subjects with their eyes closed, we registered the EEG in the eyes-opened condition. Until now, only a few studies have been performed in children with ASD of different severity, including non-responsive patients. There are different approaches to resting-state EEG data analysis. An EEG is usually considered to be a superposition of the activity of different EEG generators. In this case, common spectral power analysis does not provide a good spatial resolution due to the volume conduction effect from neighboring brain areas. In recent years, the evolution of approaches to EEG data analysis has achieved better spatial resolution through different methods of cortical source localization, i.e., Independent Component Analysis (ICA) (Bell and Sejnowski, 1995; Makeig et al., 1996, 1997; Jung et al., 1998; Zhukov et al., 2000; Michel et al., 2004). The ICA method is based on the decomposition of the EEG signal into sufficiently independent sources of EEG activity. The assumptions that underlie the application of ICA for EEG data analysis data are as follows: 1) the sources are statistically independent, 2) the mixing process is linear and instantaneous, 3) each source signal can be modeled as an independent and identically distributed (i.i.d.) process, 4) the sources have non-Gaussian probability density functions, and 5) the number of independent sources is the same as the number of sensors (Comon and Jutten, 2010). In theory, scalp-recorded EEGs do not precisely meet these assumptions, but in practice, the application of ICA for EEG analysis gives reasonable results (for review see (Onton and Makeig, 2006; Onton et al., 2006). In the current study, we used the group ICA approach (gICA) in which we assumed that the mixing process (i.e., matrix A) is the same for all subjects. The validation of this assumption was performed in our previous study (Ponomarev et al., 2014), which showed that the differences between the matrices A that were separately obtained for individual subjects were relatively small. Moreover, this assumption can be accepted as a first approximation. The gICA approach may provide greater sensitivity for the evaluation of ASD severity biomarkers. We expected the decomposition of the group independent components (gICs) to be more informative and reveal better localized and pronounced effects than the spectral power analysis.

The goal of the study was to reveal the electrophysiological markers of communicative and cognitive dysfunctions of different severity in children with ASD. We hypothesized that the distribution of abnormal EEG activity sources is an ASD marker that correlates with the severity of the communicative and cognitive dysfunctions in children with ASD.

2. Material and methods

2.1. Groups of children

In total, EEGs of 112 children (80 boys, age ranging from 4 to 9, mean age - 6.4, SD = 1.6) were taken for examination. The EEG study was approved by the Ethics Committee of the Institute of the Human Brain of the Russian Academy of Sciences (IHB RAS). All procedures were performed in accordance with the Helsinki declaration (1974).

2.1.1. Autism spectrum disorder (ASD) group

The ASD group (diagnoses F 84.0 (childhood autism) or F 84.1 (atypical autism) according to the International Classification of Diseases-10 (2010)) included 42 children (36 boys and 6 girls, age range: 4–9 years old, mean age: 5.9 ± 1.7 [SD]). Children with severe organic brain dysfunctions and concurrently diagnosed diseases, such as epilepsy and cerebral palsy, were excluded from the examined group.

2.1.2. Control group of children without autistic features and without developmental lags

The control group included 70 children (44 boys, age range: 4–9 years old, mean age: 6.4 ± 1.4 [SD]) without developmental lags or autistic behavior. 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.

2.2. Psychological examination and group separation

The clinical psychologists and speech pathologists at IHB RAS qualitatively examined the mental, social and speech development of the children with ASD. Each child was examined by two specialists who gave detailed reports. Further, two independent clinical psychologists subjectively evaluated the results of the psychological examination using a points scale to quantify the mental function development level of each child in each of the following areas: (1) contact with the specialist in the examination situation, (2) social development (social interactions), (3) attention, (4) working efficiency, (5) behavior, (6) cognitive interest, (7) performance of the instructions, (8) perception, (9) reasoning, (10) speech production, (11) speech comprehension, (12) calculating abilities, (13) and self-care skills. All parameters were estimated using an elaborated 4-point scale, where 1 point indicated the lowest level of development of the corresponding mental function, and 4 indicated the highest level of development of the corresponding mental function within the group of examined children. The psychological developmental levels evaluated by two independent clinical psychologists were correlated to each other with a standardized alpha Cronbach from 0.70–0.93 for each of the evaluated cognitive and communicative functions. Next, Ward's hierarchical cluster analysis and the K-means cluster analysis (Lecavalier, 2006) were applied to reveal the subgroups of children based on their quantitative score results. The thirteen values (one value for every estimated function) have been presenting averaged experts' scores (from 1 to 4 points scale) for each child and were used for cluster analysis. Ward's hierarchical clustering with the Euclidean distance (geometrical distance in multidimensional space, estimated as $d(x,y) = \{i\,(xi - yi)^2\}^{1/2}$) revealed that the group of children with ASD who had delays in mental, speech and communicative development was heterogeneous and could be divided into two subgroups with different severities of cognitive and social behavior dysfunctions (Fig. 1).

We used value of distance between clusters equal to a half of the general Euclidean distance for determination of possible quantity of clusters.

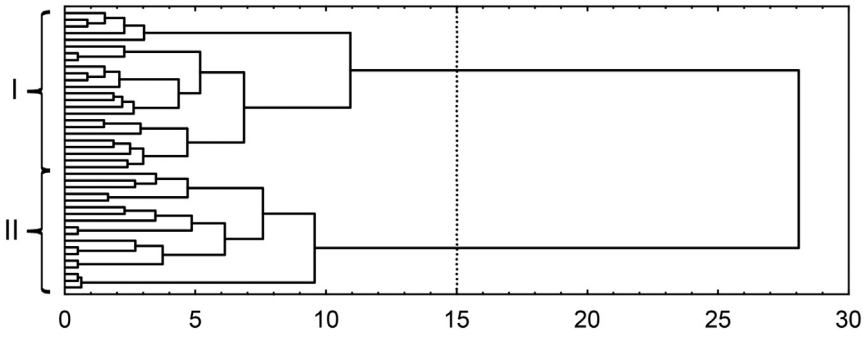

Fig. 1. Hierarchical cluster analysis using Ward's method. Notes: I, II – clusters of children were revealed based on behavioral data: I-ASD-S group; II-ASD-nonS group. X axis is the Euclidean distance in multidimensional space (on base of the 13 quantitatively estimated psychological characteristics) between children. Each line on the y axis indicates one child. Dotted line shows the distance that was applied for cluster (group) separation.

Then the children with ASD were divided into two subgroups (by the K-means analysis based on the 13 estimated values for each child): one group with "severe dysfunction" (ASD-S), including 24 patients (21 boys, age range: 4–9 years old, mean age: 5.9 ± 1.7 [SD]), and another group with "non-severe/mild dysfunctions" (ASD-nonS), including 18 patients (15 boys, age range: 4–9 years old, mean age: 6.6 ± 1.7 [SD]).

2.3. EEG registration and analysis

Children, accompanied by a caregiver, sat with their eyes opened in a separate room for EEG registration. A medical nurse was also in the room and observed the eyes-opened state. Children did not perform any specific task. The EEG was recorded using the Mitsar 21 channel EEG system (Mitsar, Ltd. St. Petersburg, http://www.mitsar-medical.com). We used nineteen silver-chloride scalp electrodes that were located according to the 10–20 international system at sites Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2. The input signals referenced to the linked ears were filtered between 1.6 and 50 Hz with a 50-Hz notch filter and digitized at a rate of 250 Hz. The ground electrode was placed on the forehead. All electrode impedances were kept below 5 kΩ. EEGs were recorded in the eyes-opened condition for at least 2 min. The quantitative data were obtained using WinEEG software (Ponomarev V.A, Kropotov Ju.D. The register for the computer programs of RF No. 2001610516, 08.05.2001).

2.3.1. EEG data filtering

The eye-blink artifacts were corrected by zeroing the activation curves of the individual ICA components corresponding to eye blinks (Vigário, 1997; Jung et al., 2000; Tereshchenko et al., 2009). In addition, epochs with excessive amplitude of filtered EEG and/or excessive faster and/or slower frequency activity were automatically marked and excluded from further analysis. The exclusion thresholds were similar to those described previously (Ponomarev et al., 2014) and were set as follow: 100 μV for non-filtered EEG, 50 μV for slow waves in the 0–2-Hz band, and 40 μV for fast waves filtered in the 20–35-Hz band. Finally, the EEG was manually inspected to verify artifact removal. No less than eight artifact-free EEG analysis epochs (approximately 30 s) were used for EEG data analysis. Before further processing, the entire array of EEG recordings was filtered at the 2–40-Hz frequency band to minimize the overlearning problem in the ICA algorithm (Sarela and Vigario, 2003).

2.3.2. Group independent component analysis (gICA)

The simplest mixture model, $X(t) = AS(t)$, is assumed in the case of ICA, where the output $X(t)$ is $n \times 1$ vector of measured potentials (n = number of electrodes) at time point t ($t = 1,\ldots,T$), A is $n \times n$ mixing matrix (where columns of A matrix are the IC topographies) and $S(t)$ is $n \times 1$ vector of independent components. If A is invertible, then the sources $S(t)$ can be estimates as $S(t) = W\,X(t)$, where $W = A - 1$ is an unmixing matrix. The InfoMax algorithm was used to obtain estimates of the unmixing matrix W. We used a C++ implementation of the InfoMax algorithm, which is part of WinEEG software and was practically identical to the procedure *runica* from the package EEGLAB (Delorme and Makeig, 2004); however, there were two simple changes. The stopping weight change was reduced from 10-6 (default value) to 10-7. In addition, the maximum number of iterations was increased from 512 (default value) to 3000.

The adjustments that were made to the InfoMax algorithm gave a more accurate estimation because of the increase in the number of iterations. The whole set of individual EEG recordings in all children (excluding the epochs containing artifacts) was concatenated into one combined time series, which was used for assessment of the W matrix, and the corresponding matrix A was calculated as the inverse of W ($A = W - 1$). The signals for each individual EEG recordings were computed as $s(t) = Wx(t)$. Following the recommendations given in an earlier published article (Ponomarev et al., 2014), the number of signals (components) was chosen to be equal to the number of electrodes (i.e., 19). Further, these components will be denoted as ICF3, ICF8, etc., in accordance with the position of the maximum on its topography. The reliability analysis of the ICA decomposition was carried out using the methods based on a random split-half of the group of subjects (see Ponomarev et al., 2014 for details). The results of this analysis were similar to those described in Ponomarev et al. (2014).

2.3.3. Spectral and statistical analysis

Spectral analysis was performed for the raw (linked-ears reference) EEGs and for the gIC, separately. For each individual and for each independent component (or each EEG channel), power spectra were computed as follows. The 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). Power spectra with < 8 averaged epochs were eliminated from further analysis. The grand average power spectra were computed for each independent component (or each EEG channel) and for each group (control subjects and patients), separately. The absolute power (squared microvolt) was computed for the theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30) frequency bands and was transformed using the decimal logarithm for normalization. The theta/alpha and theta/beta power ratios were also investigated. The theta/alpha ratio can be used as an index of brain maturation and development (Farber et al., 1990), while the theta/beta ratio might be prognostic for attention dysfunction (see Arns et al., 2013).

Further, ANOVA was applied for pairwise comparison of groups for each gIC (or electrode), separately. The differences at $p < 0.01$ were considered relevant, but the Bonferroni correction (5 spectral estimations × 19 gICs × 3 groups) was applied to determine formal statistical significance at $p < 0.05/285 = 0.0002$. To quantify the effect sizes of the differences in the EEG spectral characteristics, the Cohen's d statistic was computed. MANOVA was used to evaluate significant differences within the three groups of children (Control, ASD-S and ASD-nonS groups) for chosen gICs.

The gIC 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 Zürich, Switzerland (http://www.uzh.ch/keyinst/loreta.htm). For theoretical issues of this method

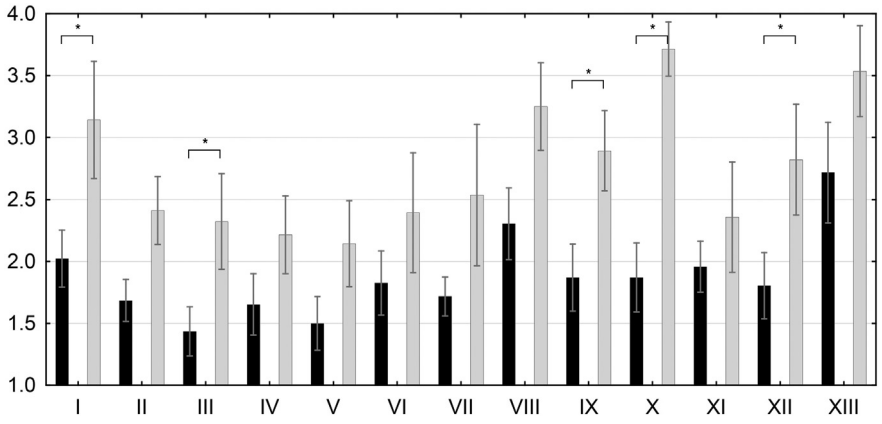

Fig. 2. Mean mental functions development scores in the ASD-S and ASD-nonS groups of children. Notes: black columns–ASD-S group; gray columns–ASD-nonS group. Y axis–averaged values of explored function developmental levels (min = 1, max = 4). X axis–evaluated characteristics: I–contact with specialist in examination situation, II–social development (social interactions), III–attention, IV–working efficiency, V–behavior, VI–cognitive interest, VII–performance of the instructions, VIII–perception, IX–reasoning, X–speech production, XI–speech comprehension, XII–calculating abilities, XIII–self-care skills. Y axis–average values of estimations. Whiskers denote a 0.95 confidence interval. The differences with $p < 0.001$ are marked with asterisk (*).

see (Pascual-Marqui, 1999, 2002).

We used non-parametric Spearman's correlation analysis to investigate the relationships between the psychological (cognitive function scores) and physiological data (the spectral characteristics in the revealed gICs). The spectral power of gICs in the theta, alpha and beta bands and theta/alpha and theta/beta power ratios were correlated with the psychological characteristics. The correlations were adjusted for multiple comparisons as evaluations were made for all 13 cognitive and social functions and spectral characteristics of 19 gICs ($5 \times 13 \times 19$), and a Bonferroni correction was applied for the multiple comparisons ($p < 0.05/1235 = 0.00004$); additionally, correlation coefficients higher or equal to 0.5 (middle correlation level) were considered.

3. Results

3.1. Psychological data

Both subgroups of children with ASD had a developmental delay compared to the age norm and had significant differences in their cognitive function development (Fig. 2).

As we can see in Fig. 2, the mental functions in the group with severe autistic dysfunction (ASD-S) were lower than in the group of children with less impairment (ASD-nonS). The most prominent differences between the groups were obtained for “contact with the specialist in the examination situation” (I), “attention” (III), “reasoning” (IX), “speech production” (X) and “calculating abilities” (XII), with a level of significance of $p < 0.001$ by means of Mann-Whitney test.

3.2. Physiological data

The EEG data from the groups of children with different severities of cognitive and social interaction dysfunctions (ASD-S, ASD-nonS) were compared to the EEG data from the control group of children (Control) that exhibited normal mental, speech and social interaction development. Significant differences in the gICs and EEG spectral power were obtained in the theta and beta frequency bands using ANOVA for pairwise group comparisons.

The theta frequency band comparison between the ASD-S and Control group of children using ANOVA revealed gIC spectral power differences localized in the frontal (ICF3, ICF4, ICF8 components), parietal (ICP3, ICPz), right temporal (ICT6) and occipital (ICO1, ICO2) cortex areas (Table 1), and the size effects of the differences ranged from 0.69 to 1.09 by Cohen's d. A comparison of the raw EEG spectral power using ANOVA revealed differences in the F8, Pz, T4, T5, T6, O1, and O2 sites, with size effects ranging from 0.67 to 0.89 by Cohen's d.

The beta frequency band comparison between the ASD-S and Control group of children using ANOVA revealed differences that were localized in the frontal (ICF3), parietal (ICPz), right and left posterior temporal (ICT5, ICT6) and right occipital (ICO2) cortex areas, and the size effects of the differences ranged from 0.63 to 1.35. Using ANOVA, a comparison of the raw EEG spectral power in the corresponding electrode positions revealed differences in the F4, Pz, T6, and O2 sites, with size effects ranging from 0.65 to 0.9 by Cohen's d. The evaluated size effects for the common regions of differences between the ASD-S and Control group were similar or had higher values for gIC than the size effects during the spectral power analysis without ICA decomposition of the EEG signal. Therefore, the use of the ICA decomposition results seemed to be more reasonable. In general the spectral EEG and gIC analyses revealed qualitatively comparable results (differences of EEG and gIC spectral power in the same frequency bands with the approximately same localization and with the same direction of changes), but the statistical importance of differences in a case of the gICA was a little bit higher as well as the effect size (that was also slightly higher). Therefore further we discuss the data obtained by means of the gIC analysis.

The gIC differences between the ASD-nonS and Control group of children in the theta and beta frequency bands were observed and were localized to ICF3 for both bands and the right occipital (ICO2) cortex in the beta frequency band. The differences in the gIC spectral power in the ASD (ASD-S, ASD-nonS) groups versus the Control group of children are presented in Table 1.

In all of the abovementioned independent components, the EEG spectral power in the theta and beta frequency bands was higher in the ASD children than in the normally developing children. There were no significant differences in the gIC spectral power in the theta and beta frequency bands between the ASD-S and ASD-nonS groups of children.

MANOVA confirmed the differences between the Control and ASD groups of children in the eight analyzed independent components in the theta frequency band (Wilks' Lambda = 0.66974, $F(16, 206) = 2.85$, $p < 0.01$) and the five analyzed independent components in the beta frequency band (Wilks' lambda = 0.675, $F(10, 174) = 3.77$, $p < 0.0001$). The topographies of the gICs and corresponding power spectra are presented in Fig. 3. Importantly, the ICF3 component reflected the activity distributed over the scalp surface with a slight amplitude increase in the frontal lobe.

There were no differences in the theta/alpha or theta/beta ratios of the spectral power in each gIC at the $p < 0.01$ level between the ASD-S and ASD-nonS groups or between the ASD-nonS and Control groups. The theta/alpha power ratios differed only between the ASD-S and Control groups at $p < 0.01$ at the ICF3, ICF8, ICT4, ICT5, ICT6, and ICO2 locations ($p > 0.05/285$). The identified differences in the theta/alpha ratio appeared to be caused by the enhanced values of the theta power observed in the subjects with ASD. The aforementioned ratio values of spectral power in the gICs did not reveal additional or more pronounced differences for the group comparisons.

Table 1
Significant differences in the gIC theta and beta band spectral power between the groups of children with autism and the Control group.

Comparisons	Theta 4–8 Hz	ICF3	ICF4	ICF8	ICP3	ICPz	ICT6	ICO1	ICO2
ASD-S versus CONTROL	F [1,93] =,	**20.31**	10.36	14.38	7.89,	9.96	**17.71**	9.37	8.18
	p <	**0.00002**	0.002	0.0003	0.006	0.002	**0.0001**	0.003	0.005
	Size-effect	**1.09**	0.79	0.80	0.69	0.79	**1.08**	0.74	0.72
ASD-nonS versus CONTROL	F [1,87] =,	12.29	–	–	–	–	–	–	–
	p <	0.0007							
	Size-effect	0.92	–	–	–	–	–	–	–

	Beta 13–30 Hz	ICF3	ICF4	ICT5	ICP3	ICPz	ICT6	ICO1	ICO2
ASD-S versus CONTROL	F [1,93] =,	**16.9**	–	7.4	–	8.7	12.4	–	7.3
	p <	**0.0001**		0.007		0.004	0.0007		0.008
	Size-effect	**0.95**	–	0.63	–	1.35	0.95	–	0.70
ASD-nonS versus CONTROL	F [1,87] =,	11.0	–	–	–	–	–	–	10.1
	p <	0.002							0.002
	Size-effect	0.84	–	–	–	–	–	–	0.88

Notes: showing results with $p < 0.01$; Bonferroni-corrected threshold of significance at $p < 0.0002$ marked in bold.

3.3. Correlations between the psychological data and the EEG spectra data

The correlation analysis revealed an inverse relationship between the cognitive and social function development and the theta power, theta/alpha ratio and theta/beta ratio in most of the areas where differences between the ASD and Control groups were obtained (Fig. 3). As shown in Table 2, the greatest number of correlations was observed for the function of "attention".

The correlations for the analyzed theta power and the theta/alpha and theta/beta ratios for the attention function were inversed. That corresponds to an enhanced theta power along with a reduction in the alpha or beta frequency bands in individuals with attention dysfunction and delays in central nervous system development (Barry et al., 2003; Hobbs et al., 2007). The most pronounced inverse relationships for "attention" and the physiological data (values of theta spectral power and the theta/alpha and theta/beta ratios) were revealed for the gIC in the parietal cortex (ICPz, ICP4 and ICP3). Notably, there were middle-level inverse correlations between the theta/alpha ratio and other cognitive characteristics, such as "contact with the specialist in the examination situation", "behavior", "attention", "perception" and "working efficiency". The obtained results demonstrated an inverse correlation between the explored psychological characteristics and the level of slow-wave activity in the posterior associative and temporal cortices.

4. Discussion

The results of the present study demonstrated the sensitivity of the

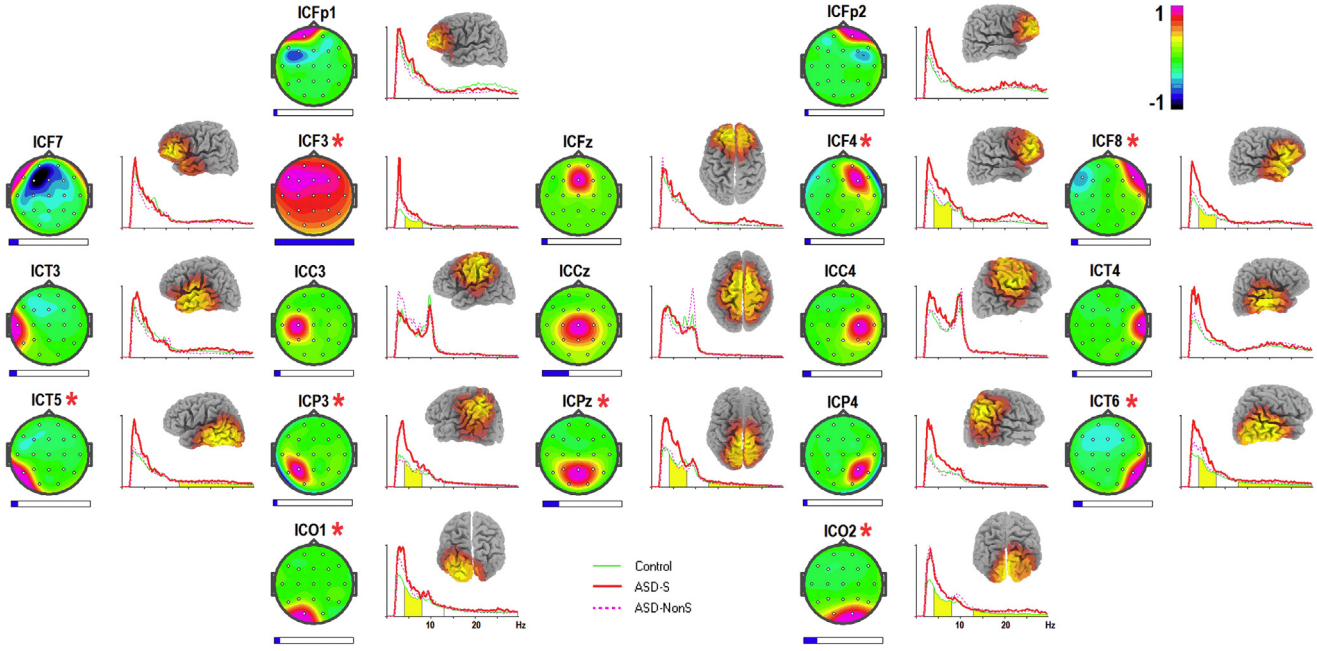

Fig. 3. Grand averaged gIC power spectra in the resting state with eyes opened for the subgroups of children with ASD (S, nonS) and the Control group of children. Notes: X axis–frequency in Hz, Y axis–amplitude spectra in standard units (each component has different normalization scale). ICF3, ICF8, etc. are the topographies of independent components named according to the nearest electrode. sLORETA images of the topographies are presented above each spectral graph. Horizontal bars below the maps partially filled with blue indicate the ratio of the power of components relative to each other. The gICs that differed significantly between the ASD and Control groups in the theta or beta frequency bands are marked with asterisk (*). We do not display the localization of the sources for ICF3 because sLORETA can give biased results in the case of multiple or widely distributed sources (Wipf et al., 2010). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
The correlations between cognitive function development and the EEG indexes (theta gIC power, theta/alpha ratio, theta/beta ratio) in the group of children with ASD.

Indexes	Contact with specialist in examination situation	Behavior	Attention	Perception	Working efficiency
Theta power	–	–	**ICPz, −0.6, 0.00004** **ICP4, −0.61, 0.00002**	–	–
Theta/alpha	ICT4, −0.56, 0.0001	ICT5, −0.52, 0.0005	ICP3, −0.56, 0.0001 ICPz, −0.5, 0.0007 **ICP4, −0.62, 0.00001** ICO1, −0.53, 0.0004	ICCz, −0.57, 0.0001	ICT5, −0. 5, 0.0008
Theta/beta	–	–	**ICP3, −0.6, 0.00004** ICPz, −0.52, 0.0005 ICP4, −0.54, 0.0003	–	–

Notes: gICs indexes, correlation coefficients (Rs ≥ |0.5|) and p values are presented in each column. The correlation coefficients with p*1235 < 0.05 after adjusting for multiple comparisons (by means of Bonferroni correction) are marked in bold.

applied gICA approach in the analysis of the EEG data and identified EEG markers of cognitive and communicative dysfunctions in children with ASD. The severe ASD group of children showed a lower developmental level than the non-severe ASD group. The most disturbed functions within the ASD-S group were “attention” and “behavior” (# III and V on Fig. 2), which could be related to a lack of goal-directed behavior in these children. These children were not able to pay attention to tasks or stimuli, demonstrating “field behavior” that might be related to dysfunctions in the executive system of the frontal cortex. The cognitive and social function development (“contact with the specialist in the examination situation”, “attention”, “behavior”, “perception” and “working efficiency”) in the whole group of children with ASD exhibited inverse relationships with the gIC power in the theta frequency band and the theta/alpha and theta/beta power ratios. Attention, which demonstrated the most inverse correlations with EEG activity in different brain areas, is the basic function that participates in and supports the efficiency of all higher cognitive processes. Individuals with ASD often demonstrate attention disturbances expressed as a specific deficit in filtering out or inhibiting distracting task-irrelevant information (Christ et al., 2007; Christ et al., 2011; Adams and Jarrold, 2012). There are theories of ASD focused on the specificity of attention and information processes in children with autism: the weak central coherence theory (Frith and Happé, 1994) and intense world theory (Markram and Markram, 2010). In our study, the attention scores were inversely related to low-frequency EEG activity and its ratios mainly in the parietal cortex. The theta spectral characteristics (power and its ratios) in the identified gICs seemed to correspond to the severity of the behavioral disturbances in the examined group of children with ASD.

4.1. ASD-S group versus the Control group

The ASD-S group was characterized by an increase in the low (theta) and high-frequency (beta) EEG activity in the eyes-opened condition compared to the EEG activity in the Control group. A higher spectral power of the slow-wave and high-frequency EEG activity was observed in many cortex regions in both hemispheres in gICs with both local and widespread topographies.

The prevalence of slow-wave activity outside of age norms in eyes-opened EEGs of children is usually considered an abnormality that may be related to mental retardation, developmental delay, and neurological dysfunctions (Bresnahan and Barry, 2002; Kulandaivel and Holmes, 2011). The EEGs of children with ASD are characterized by various abnormalities, including a large amount of epileptiform activity (Akshoomoff et al., 2007; Yasuhara, 2010), greater delta activity and reduced alpha activity (Bashina et al., 1994), reduced mu rhythm suppression and the absence of mu rhythm asymmetry (Oberman et al., 2005; Stroganova et al., 2007; Palau-Baduell et al., 2011). Children with a global developmental delay have been shown to have more frequent EEG abnormalities, such as low background EEG activity or epileptiform activity, than children with only specific language impairments (Kim et al., 2014). The psychological data on the ASD-S group of children support the idea of global cognitive and behavioral dysfunctions.

The observed increase in the gIC spectral power in the high-frequency band (beta) seemed to also be a marker of dysfunction in the ASD-S group of children. An increase in the spontaneous high-frequency EEG activity has been correlated with the degree of developmental delay in children with ASD (Orekhova et al., 2007, 2008). The increase in EEG power in the high-frequency bands (i.e., gamma band) could be considered an indicator of an excitatory/inhibitory imbalance, leading to over-irritation due to the abnormal development of the GABAergic system in autism (Hussman, 2001; Rubenstein and Merzenich, 2003).

The obtained results are very similar to the U-shaped profile of abnormal EEG activity that was previously suggested (Wang et al., 2013) to be a marker for ASD that stressed the role of the delta and gamma EEG bands. In our EEG study, the U-shaped profile for children with ASD was related to higher spectral power of gICs in the theta and beta frequency bands than the spectral power in the Control group. The pronounced differences in the theta and beta frequency bands in the ASD-S group of children were observed in the frontal, parietal, posterior temporal and occipital cortices. Based on the cognitive and behavioral dysfunctions observed in the ASD-S group of children, the higher spectral power activity in the frontal and temporal cortex may be related to impairments in the higher level integrative and executive functions of the frontal lobes and goal-directed activity in such patients. Some data suggests a correlation between the degree of intellectual impairment in autism with the amount of pathological EEG activity in the frontal and central cortex regions, such as in the system of mirror neurons, particularly in Broca's areas (Yasuhara, 2010). Structural magnetic resonance imaging (MRI) studies support the data showing developmental impairments in the frontal and temporal brain areas in children with autism (Cascio et al., 2013).

The increase in EEG spectral power in the low-frequency band in the occipital and parietal areas might be related to impairments in external information processing and abnormalities in sensory integration in the group of children with autism (Russo et al., 2010; Marco et al., 2011). In a large number of event-related potential (ERP) studies, differences in the ERPs in children and adults with autism were observed during the perception of simple auditory and visual stimuli and in response to more complicated stimuli containing emotionally or socially important information. In an ERP study (Sokhadze et al., 2009), the group with autism showed prolonged latencies to novel stimuli in the frontal and parietal cortical areas, particularly in the right hemisphere. In a group of children with ASD, the process of visual perception of socially important information also differed from the control group in a previous study (Wong et al., 2008). Children with ASD who have severe cognitive and social behavior dysfunctions may be assumed to exhibit an impairment in the systems connected with perception, processing and the analysis of sensory information, as well as the control of goal-

directed activity. These dysfunctions could be reflected in the resting-state EEG by the prevalence of low theta activity in the occipital, parietal and frontal cortices and greater beta activity in the frontal, parietal and posterior temporal areas in ASD groups than in the Controls. The values of the gIC power in the theta EEG frequency band and the theta/alpha and theta/beta ratios in the posterior cortex were related to the cognitive and social dysfunction in the entire group of children with ASD (Table 2). These observations confirmed the hypothesis that abnormal EEG activity is a marker of the severity of cognitive dysfunction.

The obtained data corresponds to results of previous studies. As previously reported (Kozhushko et al., 2014b), the values of the EEG IC spectral power in low-frequency bands were significantly higher in the frontal and temporal cortex areas in children with severe mental development impairments (including ASD) than in the control group. In the ASD-S group in the present study, similar effects were noted along with additional effects in the parietal and occipital cortices (ICP3, ICPz, ICO1, and ICO2). The increased slow-wave activity observed in these areas in the ASD-S group of children support the idea of a general slowing of EEG activity related to the systemic developmental impairments in ASD.

4.2. ASD-nonS group versus the Control group: the common ASD groups features

gIC spectral power differences that characterized the ASD-nonS group compared to the Control group were obtained in both the theta and, with less effect, beta frequency bands, which presumably represent widespread synchronous activity across the entire cortex with a maximum amplitude in the frontal areas (ICF3, Fig. 2). According to the gICA model, the ICF3 component had a widespread topography and describes some part of the EEG activity that is synchronous in all of the electrode sites; however, the ICF3 component is more pronounced in the frontal areas. As higher spectral power was revealed for both ASD groups in this IC in the low and high-frequency bands, the ICF3 component appears to be some type of common widespread activity that is distinct in the ASD group of children compared to that in the Control group. This finding corresponds to the widespread hyperconnectivity revealed by functional MRI (fMRI) in children with ASD compared to that in typically developing children (Supekar et al., 2013). To some extent it also corresponds with the larger diameter of the networks in children with ASD compared to those in typically developing children indicate enhanced long-range connectivity revealed by EEG functional connectivity analysis (Malaia et al., 2016). We can suppose that there is widespread synchronous activity in the cortex or the existence of a common source for this enhanced activity in children with ASD. Considering the topographies of the local gICs that differed between the ASD and Control groups, we hypothesized that these reflected abnormal functioning of specific cortical areas involved in perception, social cognition and reasoning in children with ASD.

Local differences, which characterize the less severe ASD group, were revealed in the visual perception areas in the right hemisphere (in the beta frequency band) and were also observed for the ASD-S group. These differences could be related to difficulties in perception, i.e., objects, faces and their emotional meaning, leading to problems in social interactions, where this type of information is important. Support for the abnormalities in specific perceptional neural substrates of the right occipital cortex comes from data from Pei et al. (Pei et al., 2014), which demonstrated a reduction in the steady-state visually evoked potential (SSVEP) amplitude in the right hemisphere in patients with ASD compared to that in control subjects.

The data obtained in our research suggest that regardless of the severity of the cognitive dysfunctions, the areas of prominent distinctions between the ASD and Control groups of children were related to the frontal cortex. Dysfunctions in the frontal cortical areas usually correspond to deficits in higher executive functions and speech processing. Various abnormalities of speech and language comprehension and production have been observed in autism, even if the patients' mental abilities were normal, which may be related to disturbances in the development and connectivity of the corresponding cortical areas (Sharda et al., 2014). In accordance with these hypotheses, stimulations of the corresponding areas could improve clinical outcomes in patients with ASD. A previous study (Amatachaya et al., 2015) demonstrated that anodal transcranial direct current stimulation (tDCS) applied to the left frontal cortical area (electrode F3 according to the 10-20 system) led to an improvement in speech perception, which supports our previously obtained results (Kozhushko et al., 2014a).

On one hand, the obtained data on the two groups of children with ASD with differing cognitive and social behavioral dysfunction severity confirm a similar tendency as was observed in common groups of development disorders, an increase in slow-wave EEG activity with increased developmental dysfunction (Machinskaya and Kurgansky, 2013; Kozhushko et al., 2014b). On the other hand, the topographies of the gIC spectral power differences and the observed effects of increased power in the slow-wave (4–7 Hz) and high-frequency (13–30 Hz) bands in the ICF3, ICPz, ICT6, and ICO2 cortex areas could be considered to be promising EEG markers of the disturbances observed in the development of ASD. Thus, our data partly support the suggestion of a U-shaped profile of abnormal EEG activity with increases in the low and high-frequency spectral power patterns and a reduction in the alpha frequency in patients with ASD (Wang et al., 2013). However, our data cannot support the last part of this assumption because we did not obtain differences in the alpha spectra for both groups of children with ASD; however, we can stress that the theta/alpha power ratio was inversely correlated with the greatest number of examined psychological functions. Importantly, increases in both the theta and beta gIC spectral power are very similar to the markers for ASD. The differences in both ASD groups compared to the Controls corresponded not only to a significant increase in the gIC theta and beta power in the frontal cortex but also to an increase in the gIC beta power in the right occipital cortex, which may also be considered to be one of the EEG features of ASD.

The identified increase in the low and high-frequency spectral power of local EEG activity isolated by gICA that characterized the ASD-S group was related to areas that participate in regulating behavior, perception and emotional reactions. More numerous and widely distributed independent sources of slow activity were observed in the group of children with severe developmental delay and social behavioral impairments than in those characterized as the non-severe ASD group. This difference suggests an overall slowing of the EEGs, which may be the basis of a systemic immaturity of mental functions and characterize not only a temporal developmental delay but also mental retardation, as these more severe disturbances lack the necessary “acceleration” of cortical rhythmic activity and mental processes during ontogenesis (Lebedinsky, 2003). The inverse correlations of the developmental level of the explored cognitive functions and the slow-wave gIC spectral power observed in this study are in agreement with that assumption.

5. Conclusions

The EEG investigation showed differences in the gIC spectral power in the theta and beta EEG frequency bands for two groups of ASD children with differing cognitive and communicative dysfunction severity compared to the EEG activity in the Control group. More number of gIC spectral power differences were observed between the ASD-S and Control 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 correlation analysis also stressed a particular role for the parietal cortex in the severity of the cognitive dysfunctions in children with ASD and demonstrated inverse relationships between the slow-wave spectral power values, its ratios to other bands, and the level of cognitive functions.

The whole group of children with autism was characterized by higher power in both the theta and beta frequency bands in the 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.

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