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Features of the resting-state functional brain network of children with autism spectrum disorder: EEG source-level analysis

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Abstract We study the specific features of the organization of the functional brain networks of children with autism spectrum disorder (ASD) by analyzing at the source level the data obtained in the EEG experiment in the resting-state paradigm. We pay special attention to age-related changes in the characteristics of functional networks during the particularly important age period from early childhood to adolescence. The analyzed experimental groups consisted of 148 ASD children and 173 neurotypical children that were considered as a control group. In the theta band, we revealed an age-independent functional connectivity pattern, consisting of the brain areas responsible for emotions and consciousness, where the strength of connections is higher in neurotypical children compared to ASD children. Moreover, we discovered lower network global clustering in the delta + theta band in ASD children. Thus, more segregated, but more highly connected subnets are formed in the delta + theta band in neurotypical individuals compared to ASD ones. We can suggest increased control over emotions and stronger interaction between the emotional and conscious domains in neurotypical children. In the extended alpha band, we revealed an age-dependent functional connectivity pattern, demonstrating hyper-activation in the ASD group for ages below 6–7 years old and hypo-activation—for older ages. Also, we discuss the development of effective approaches to autism therapy, which should be based on the normalization of aberrant functional connections.

1 Introduction

Autism spectrum disorder (ASD) is a largely heritable neurological condition that significantly reduces the social interaction abilities of the affected individual. Its rather unclear origins attracted the increased attention of clinical scientists and caused the development of various diagnostic and therapeutic approaches. Due to the high social significance of this topic, a significant effort has been made to determine the associations between brain functioning and ASD development. Some studies indicate that ASD develops at prenatal and early postnatal stages [1, 2] and has a broad range of diagnostic ages [3], which stimulated active research of early diagnostics methods based on behavioral [4–6] as well as neurological indicators [7–9].

A considerable amount of studies are dedicated to the development of various techniques for the identification of biomarkers of ASD based on neurophysiological data analysis. Among them, fMRI draws a lot of interest. In particular, both task-related and resting-state fMRI were used in several classification systems for ASD children [10, 11]. Besides, quantitative analysis

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of fMRI provides valuable knowledge about physiological processes that take place in the central neural system of individuals with ASD [12–14]. The use of fMRI, however, is rather limited by the high cost and the fact that it is a medical technology that is intended for use in clinical conditions. Another promising technique is an analysis of EEG time series, which was also involved in the development of systems for the detection and classification of ASD-related abnormalities [15, 16] and the analysis of its spectral features [17, 18].

A promising approach to the study and diagnosis of ASD is analysis at the level of functional brain networks [19]. In this case, the brain is considered as a single system consisting of many connected interacting areas [20]. The characteristic functional connectivity patterns represent brain activity during cognitive task solving, as well as its state both in norm and in deviations. Such an approach proves to be particularly effective for detecting normal and pathological brain states, since it reveals not just disruptions in the activity of individual brain regions, but studies the features of the integrative dynamics of the brain. ASD has been linked with atypical connectivity across multiple brain systems, yet the nature of these differences in young children with the disorder is not well understood [19, 21].

Resting-state functional connectivity analysis (mainly resting-state fMRI) has proven to be a powerful tool for examining intrinsic functional brain connectivity in clinical pediatric populations [21]. Resting-state experimental paradigm offers two advantages over task-based paradigms. Firstly, it allows easier data collection from children with ASD who have difficulties with long task-based experiments [22]. Secondly, it identifies underlying intrinsic functional networks that are not confounded by differences in task performance or strategy differences. By estimating temporal correlations of the resting-state signals (e.g., BOLD or EEG signals) between functionally coupled brain regions, it is possible to identify intrinsically connected functional networks that are not confounded by cognitive tasks [23]. Many disruptions in the functioning of the functional network in ASD individuals are already apparent in the resting state of the brain. This is usually a consequence of the malfunctioning of the default mode network and the salience network in ASD people, as well as their interaction with each other and the central executive network [24]. The relationship between these networks relates to behavioral performance in the neurotypical population [25], but is not well understood in ASD.

In this paper, we study the features of functional brain networks in ASD children based on the analysis of EEG data obtained in the resting-state experimental paradigm. We focus on age-related changes in the characteristics of functional networks during the particularly important age period from early childhood to adolescence. This study is important both for advancing our understanding of the causes and mechanisms of ASD and for developing methods for diagnosing ASD in the early stages of life (especially for mild manifestations of ASD).

2 Methods

We considered two groups of subjects: the ASD group (148 children) and the neurotypical group "Typical" (173 children). All subjects were divided into four age groups: gr1 (2–4 y.o.), gr2 (4–6 y.o.), gr3 (7–9 y.o.), and gr4 (10–16 y.o.). During the EEG experiment, the individuals were instructed to sit with their eyes open and try not to make visible movements. EEG data consisted of 19-channel recordings with an average duration of about several minutes sampled at 250 Hz, while the duration of the EEG recording for each subject was determined by his ability to complete the task for as long as possible. The EEG electrodes were placed in accordance with the 10–20 international system. EEG was preliminarily cleaned of the artifacts using frequency filters and the ICA.

We conducted the source-level assessment of the functional connectivity network to identify the features of functional relationships between different physiological brain areas [26] associated with age-related changes and the development of ASD. The sources were reconstructed using a frequency-domain partial canonical coherence (PCC) method [27]. PCC is one of the most convenient for evaluating relationships between sources because it provides more flexibility for data processing. In particular, the PCC implementation directly outputs the Fourier coefficients for each dipole position separately for each epoch. An MRI image of the head and brain was used to create a head model based on the boundary element method (BEM) with three types of tissues (brain, skull, and skin) [28]. Because our dataset has no individual MRI images, and the human head and brain undergo significant changes in the age of 2–16

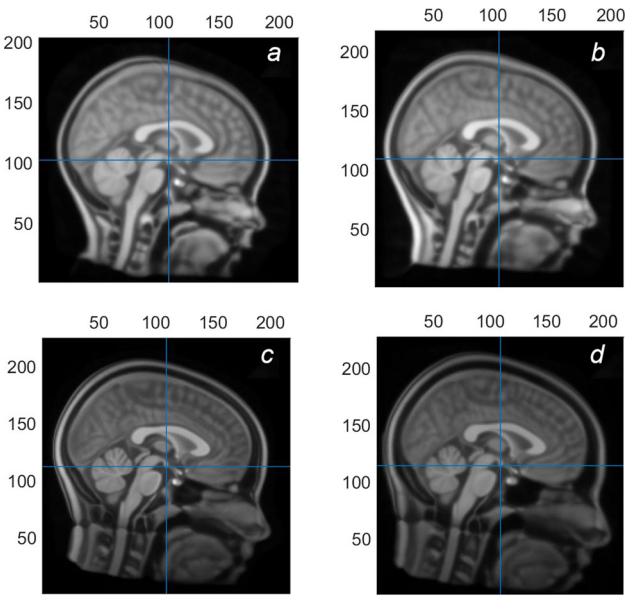

Fig. 1 The MRI images for groups gr1 (**a**), gr2 (**b**), gr3 (**c**), and gr4 (**d**) used for modeling

years, we used the public database of MRI images "Neurodevelopmental MRI Database" [29], which presents averaged MRI images for various age groups. Figure 1 shows MRI images that were selected for the considered age groups. We applied the OpenMEEG method [30] to solve the forward problem (a necessary component for source reconstruction), which has the best accuracy among all similar approaches. As a result of the PCC-based source reconstruction procedure, we obtained the power distributions of source activity in the brain on a 3D grid with $\tilde{1}0,000$ voxels (the exact number depends on the age group).

We used coherence [31] to evaluate the coupling strength between the sources, which allows us to exclude false connections due to the field spread. In the first stage, the connectivity matrix for all dipoles (voxels) in the brain volume was determined. Then, we carried out the parcellation procedure using the Brainnetome brain atlas [32] designed to study activation and functional connectivity in the brain, dividing each hemisphere into 123 zones based on the structural and functional characteristics of these zones. As a result, we obtained a 246x246 matrix containing measures of functional connections between 246 anatomical regions of the brain.

To highlight significant functional connections and network patterns that significantly change between groups, we used a network modification of nonparametric cluster testing—NBS [33]—and the false discovery rate (FDR) approach [34], which allows addressing the multiple comparisons problem at the network level. FDR is more sensitive to focal effects at the level of isolated connections, while NBS is more powerful in the detection of distributed networks covering many connections between brain regions. We considered the influence of two factors: the Diagnosis factor (ASD or Typical) and the Age group factor (gr1-4), as well as their interaction (Diagnosis * Age group).

To analyze the direction of the effect between groups, the connection strength was averaged over all the links included in the corresponding identified cluster.

In our study, we considered the following frequencies of interest (FOIs):

- δ + lower θ-ranges (2–6 Hz),
- extended α-range(6–13 Hz),
- β-range (13–30 Hz).

To describe the global properties of the entire functional brain network, we evaluated the global clustering coefficient (when the clustering coefficient is high, the graph is densely grouped around several nodes; when it is low, the connections in the graph are relatively evenly distributed among all nodes) and network efficiency (an indicator of how efficiently information is distributed in the network, calculated as the average inverse length of the shortest path in the network) [35, 36]. We also used a two-way ANOVA to analyze the influence of the selected factors on these network characteristics.

3 Results

Using the NBS and FDR, we revealed the influence of the Diagnosis factor on the functional connections in the θ-band. In particular, a network pattern was determined (see Fig. 2), where the connections vary significantly between the ASD and Typical groups. Analysis of the effect direction demonstrated (Fig. 2b) that the connectivity strength in this pattern is higher in the Typical group compared to ASD. The revealed network structure includes the following areas of the brain:

- right superior frontal gyrus, dorsolateral region 8 (A8dl), responsible for social consciousness;
- left orbital gyrus, medial area 14 (A14m), responsible for emotions (mainly fear) and consciousness;
- right superior frontal gyrus, medial area 9 (A9m), responsible for consciousness (mainly associated with attention), inhibition of motor activity and emotions;
- left cingulate gyrus, rostroventral region 24 (A24rv), responsible for emotions.

The results indicate that neurotypical children have a higher level of integration in the identified subnetwork than children with ASD, which suggests a stronger interaction between the brain areas responsible for emotions and consciousness in the Typical group. Moreover, the θ-rhythm is usually the integrative rhythm in the human brain. We suggest increased control over emotions and stronger interaction between the emotional and conscious domains in neurotypical children. We assume that the strengths of functional connections in the identified network pattern can be used as a biomarker of a person's predisposition to ASD.

We revealed that the interaction of the factors Diagnosis and Age group does not affect the coupling strength in this subnet (see Fig. 3). One can be see that for all age groups (gr1–gr4), the strength of connections is higher in the Typical group compared to ASD.

Statistical analysis using the FDR revealed another network pattern in the extended α-band (see Fig. 4), in which the coupling strength is influenced by the interaction of the factors Diagnosis and Age group. In the first and second age groups, these connections are stronger for the ASD group, and in the third and fourth—for the Typical group. The revealed network structure includes the following areas of the brain:

- right orbital gyrus, area 13 (A13), responsible for a whole range of emotions (from fear to sadness and happiness);
- left lower parietal lobe, rostrodorsal region 40 (A40rd), responsible for working memory, attention, observation, imagination and movement, and spatial perception;
- left cingulate gyrus, rostroventral region 24 (A24rv), responsible for emotions;

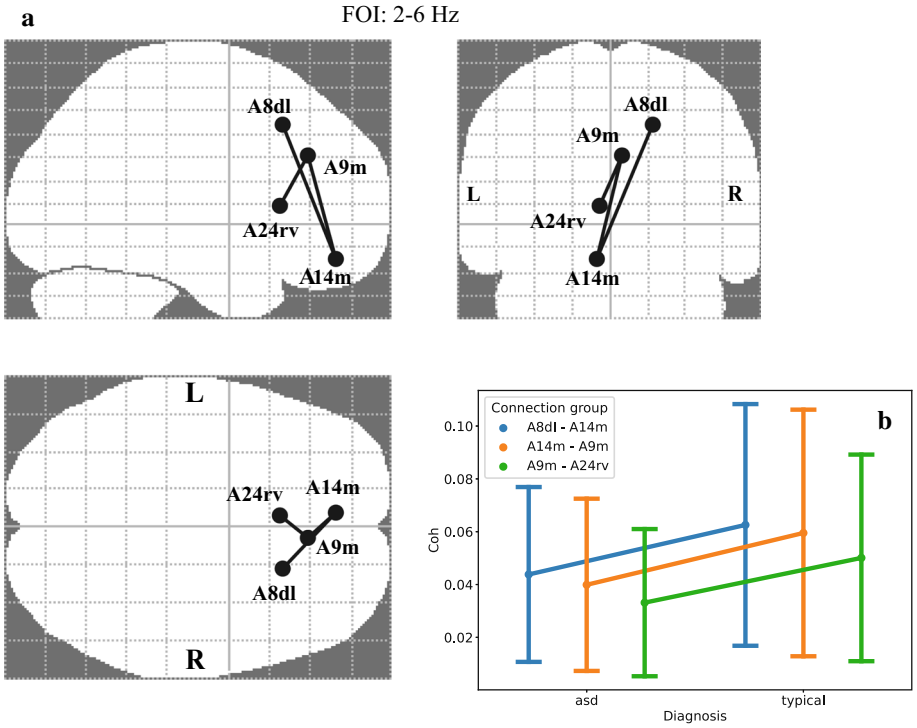

Fig. 2 **a** The functional connectivity in the coronal, axial, and sagittal projections of the brain in the θ range (2–6 Hz) assessed via NBS and FDR. The presented connections differ significantly between ASD and Typical groups: (connection 1, f-value = 17) right superior frontal gyrus, dorsolateral area 8 (A8dl)—left orbital gyrus, medial area 14 (A14m); (connection 2, f-value = 18.3) A14m—right superior frontal gyrus, medial area 9 (A9m); (connection 3, f-value = 19.2) A9m—left cingulate gyrus, rostroventral area 24 (A24rv); **b** The difference in coherence of the connections between ASD and Typical groups: mean ± SD

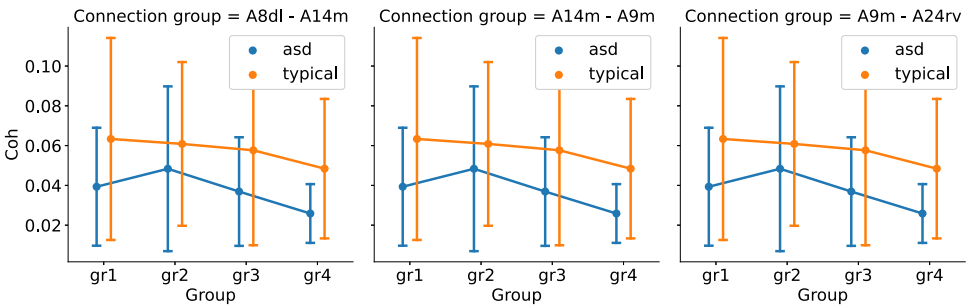

Fig. 3 The difference in coherence measure of the connections between the age groups gr1–gr4 for ASD and Typical groups: mean ± SD

- right superior parietal lobe, lateral region 5 (A5l), responsible for shape perception, movement execution, imagination and observation, attention, working memory, and spatial perception;
- left superior frontal gyrus, medial area 10 (A10m), responsible for explicit memory, consciousness, and emotions.

Note that these areas have a quite particular functionality, while the areas of the subnet, which are affected only by the Diagnosis factor, belong to more general, high-level behavioral domains.

Statistical analysis of global network characteristics revealed the influence of the Diagnosis factor on the global clustering coefficient in the $\delta + \theta$-range. It is higher in neurotypical children compared to the ASD group in all age groups (see Fig. 5). This means that the level of segregation in neurotypical participants is higher than in children with ASD. From the point of view of network topology, this means that in the Typical group, separate subnets are formed with high connectivity strengths and the number of connections between elements within them (as, for example, the subnet found in the $\delta + \theta$-range for the Diagnosis factor effect). In other words, the more segregated characteristic network "Typical" has a higher ratio of local links to global links than a less segregated "ASD". We found no significant effects on network efficiency.

4 Discussion

The focus of the current study was to investigate if there exists a difference in functional connectivity structure between autistic (ASD) and typically developing (TD) children and if this change has any correlation with age. Our study provides evidence of weaker connectivity in the theta band in the frontal and limbic lobes of individuals with autism, in addition to lower network clustering in the delta+theta band. Thus, we revealed in the delta+theta band the more segregated, but more

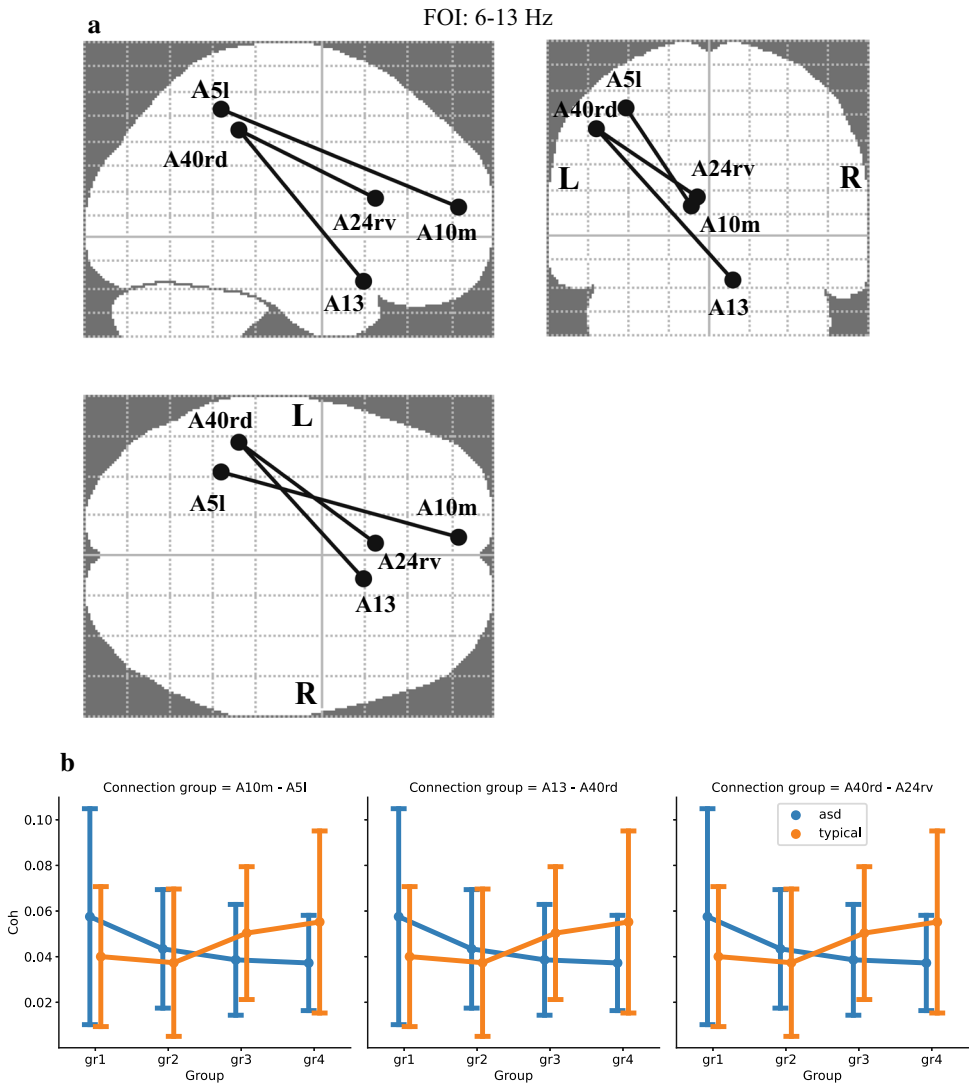

Fig. 4 **a** The functional connectivity in coronal, axial, and sagittal projections of the brain in α-range (2–6 Hz) assessed via FDR. The presented connections differ significantly both between ASD and Typical groups and gr1–gr4 groups: (connection 1, f-value = 14.3) right orbital gyrus, area 13 (A13)—left lower parietal lobe, rostrodorsal area 40 (A40rd); (connection 2, f-value = 14.9) A40rd—left cingulate gyrus, rostroventral area 24 (A24rv); (connection 3, f-value = 15.2) right superior parietal lobe, lateral area 5 (A5l)—left superior frontal gyrus, medial area 10 (A10m). **b** The difference in coherence measure of the connections between the age groups gr1–gr4 for ASD and Typical groups: mean ± SD

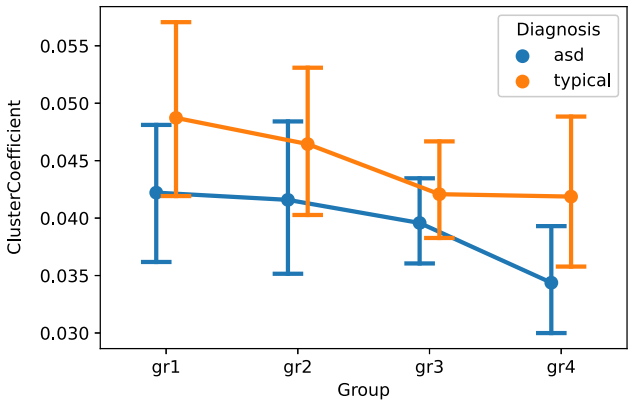

Fig. 5 The difference in clustering coefficient between the age groups gr1–gr4 for ASD and Typical groups in δ+θ-range: mean ± SD

highly connected subnets in TD individuals as compared to ASD children. The current study also demonstrates that there is no apparent relationship between "Diagnosis" and "Age" that can affect the functional connectivity in the theta band.

Instead of functional connectivity MRI (fcMRI), we used EEG for analysis. This approach makes it possible to identify the features of the functional interaction between different physiological areas of the brain due to age-related changes and the development of cognitive impairment. Though resting-state fcMRI is a preferred method among researchers, problems associated with the temporal resolution, which further lead to difficulty in separating neuronal activity from hemodynamics, and construction of stable images from a large number of independent samples at the expense of resolution loss [37–41], make it less favorable in this study.

There is a general consensus among previous studies that used EEG that a difference is present among functional connectivity of ASD and TD subjects, however, the high heterogeneity of experiments makes it nearly impossible to state that its either hypo-connectivity or

hyper-connectivity [42–49]. Nevertheless, our result of weaker connectivity in the theta band is in line with previous resting-state fcMRI studies of the brain [50–53]. Brain regions that showed weaker connectivity: right superior frontal gyrus; dorsolateral area 8 (A8dl), right upper frontal gyrus; medial area 9 (A9m), left orbital gyrus; medial area (a14m) and left cingulate gyrus; rostroventral region 24 (a24rn) are solely responsible for social cognition, emotions control, and motor activity inhibition. Not only the emotional and social behavior expressed by individuals suffering from autism validate these findings, but also these findings provide an explanation of the neural features underlying development features in ASD subjects. Interestingly, several machine learning approaches find almost the same regions that contribute the most to an autism diagnosis [54–56]. It must be noted that medication and camouflaging techniques [57] employed by some autistic individuals were not considered in this study.

It came to our account that the interaction of the factors "Diagnosis" and "Age" does not affect the strength of the connectivity in the theta band and the TD group has higher connection strength as compared to ASD in all age groups. A high diversity of parameters in previous studies makes it difficult to interpret how age alters the connectivity structure [58–63]. To the best of our knowledge, this is the first EEG study evaluating the effect of age on connectivity strength in the theta band.

We, however, observed a unique connectivity pattern in the extended alpha band where the strength of connections is influenced by the interaction of "Diagnosis" and "Age". This connectivity pattern is stronger in the first two groups of ASD as compared to TD and is dominated by TD in the third and fourth groups. It may reflect age-related changes in the mechanisms of ASD development. This peculiar pattern was found in the frontal, parietal, and limbic lobes, which are generally responsible for emotions, memory, attention, imagination, spatial perception and consciousness. The presence of abnormal alpha waves in autistic subjects has long been a matter of discussion among researchers [64–69], and further work needs to be done to investigate the factors that led to this pattern.

At present, the developmental influence on functional brain connectivity in ASD is one of the hot topics in ASD research [19, 21, 70–74]. Usually, functional connectivity studies have focused on a single age group (e.g., childhood, adolescence, or adulthood) or combined age groups. There are some studies [21] considering age-related alternations of functional networks in ASD subjects. The principal conclusion here is that functional connectivity atypicalities in the disorder are not uniform across the life span. Hyper-connectivity is more characteristic of young children (early childhood) with ASD compared to TD, while hypo-connectivity may begin to emerge in adolescence and persist into adulthood [21, 75]. Nevertheless, the division into large age cohorts in most studies does not allow a more or less precise definition of the range of ages when such a transition from the functional connectivity pattern of hyper-activation to the pattern of hypo-activation occurs. Particularly important here is a detailed consideration of the childhood age cohort, when major changes in the brain occur. From this perspective, our work complements the existing knowledge about age-related changes in functional networks in ASD subjects. The patterns revealed in the alpha band, firstly, confirm the age transition of functional connectivities in ASD from hyper-activation to hypo-activation and, secondly, show that the transition seems to occur in the 6–7 years old range. The obtained results can lead to a more nuanced understanding of atypicalities of functional brain connectivity in ASD.

From the analysis of clusters in the delta and theta range, we found out the network is less segregated in the ASD group. [76, 77] are in line with our results, expressing higher segregation in the default mode network of TD individuals. Further analysis showed that the more segregated networks in TD groups have a higher ratio of local links to global connections. [60, 77] found out that ASD subjects have higher inter-network connectivity as compared to intra-network connectivity. Yerys et al. urged that this poor segregation is consistent with an excitation or inhibition imbalance model of ASD [76]. From these results, it can be concluded that poorer segregation in ASD subjects is a possible cause for them showing impaired cognitive and behavioral functions. The inability to perform high-level functions and processing high-level information are some examples of further impairment caused by this poor segregation.

Nowadays, the development of classifiers for identifying ASD subjects by biomarkers at the level of a functional network using machine learning methods is an urgent problem with promising prospects [78–82]. Such classifiers appear to be particularly useful in cases of mild symptoms of ASD and early childhood when objective indicators of autism may be lacking [83]. It is especially important here to take into account the age of an individual since it has been shown that specific functional connectivity patterns are transformed with age [75]. From this perspective, the revealed in our study patterns of functional connectivity is a step toward developing biomarkers for objectively identifying children with ASD. We suggest that specific networks can distinguish children with ASD from TD children and predict symptom severity in children with ASD [75, 81].

We believe that identifying abnormalities in the functional networks of ASD subjects is the key to developing effective approaches to autism therapy, which should be based on the normalization of aberrant connections. This concept is supported by modern research [83]. Yamada et al. concluded that successful normalization of the individual's functional connectivity pattern using functional connectivity-based neurofeedback would lead to a reduction in psychiatric symptoms [84]. Pineda et al. hypothesized that neurofeedback produces positive behavioral changes in ASD children by normalizing the aberrant connections within and between neural

circuits [85]. Neurofeedback exploits the brain's plasticity to normalize aberrant connectivity patterns apparent in the autistic brain. Later, Pineda et al. revealed that EEG-based neurofeedback training produces normalization in behavioral and electrophysiological measures of high-functioning autism [86].

Basically, the functional connectivity normalization can be achieved by different types of neurofeedback (functional-connectivity-based neurofeedback, fMRI-based neurofeedback, EEG-based, etc.) [84–87], music therapy [83, 88, 89], hormonal therapies with oxytocin or vasopressin receptor antagonists [83, 90, 91], transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) of the brain [92–95]. Notably, oxytocin modulates the functional connectivities known for social threat processing and emotion regulation, suggesting a neural mechanism by which oxytocin may have a role in the therapy of ASD [90]. Functional neuroimaging studies reported increased activation in brain regions involved in the processing of social information and reward processing in ASD patients after oxytocin administration [96, 97]. In turn, TMS and tDCS are effective non-invasive techniques for the modulation of brain regions' activity and connections between them. Consequently, TMS and tDCS are perspective approaches for the purposes of the normalization of the individual's functional connectivity pattern during ASD therapy. Recently, some progress has been made here [92–95]. However, further studies are necessary for defining target areas in the brain for TMS/tDCS to improve therapy performance. The results of the present research suggest potential target areas.

The present study suffers from the following limitation. We used the template MRI scan instead of individual scans and low-density EEG electrode placement, which can lead to errors of up to several centimeters in the source localization procedure [98]. However, the use of statistical tests at the group level allows us to identify the areas (as well as connections between them) in which differences between groups (ASD vs. Typical) are most pronounced, with the size of these areas appearing to be significantly smaller than the possible error of source localization procedure. Nevertheless, it should be kept in mind that the results of source localization for an individual subject may be unrepresentative due to high localization errors, so it is not recommended to draw any conclusions from them.

5 Conclusions

In this study, we focused on the investigation of the differences in functional connectivity structure between ASD and TD children and on the possible correlations with age. Our study provides evidence of weaker connectivity in the theta band in the frontal and limbic lobes and lower network clustering in the delta+theta band of ASD individuals for all age cohorts (2–16 y.o.). Thus, we revealed in the delta+theta band the more segregated but more highly connected subnets in TD individuals compared to ASD children. We observed a unique connectivity pattern in the extended alpha band where the strength of connections is stronger in the first two age cohorts of ASD subjects (2–6 y.o.) and is dominated by TD subjects in the third and fourth cohorts (7–16 y.o.). The revealed connectivity patterns consist mainly of the brain areas responsible for emotions, consciousness, and attention. Aberrations in functional connections between them in ASD children are a possible cause for them showing impaired cognitive and behavioral functions. We assume that the strengths of functional connections in the identified network patterns can be used as a biomarker of a person's predisposition to ASD. We believe that identifying abnormalities in the functional networks of ASD children is the key to developing effective approaches to autism therapy, which should be based on the normalization of aberrant connections.

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by SK, NS, EP, MSK, OM, OS, GP, and AH The first draft of the manuscript was written by SK and EP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availibility statement The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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