Fractional amplitude of low-frequency fluctuation and degree centrality in autistic children: a resting-state fMRI study

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ABSTRACT

Autism negatively affects healthy cognitive development in children. As reliable neuroimaging markers, fractional amplitude of low-frequency fluctuation (fALFF) can reflect the intensity of spontaneous brain activity, and degree centrality (DC) can reflect connectivity of whole brain at voxel-level. By combining these two markers we can study the pathological mechanism of autism from more aspects. We investigated fALFF and weighted DC differences using functional magnetic resonance imaging (fMRI) data in 24 autistic children and 24 neurotypical children. Compared with neurotypical children, autistic children showed increased fALFF in right medial frontal gyrus, right dorsal anterior cingulate cortex, and bilateral ventral posterior cingulate cortex as well as decreased fALFF in bilateral visual cortex. Compared with neurotypical children, autistic children also showed increased weighted DC in left middle temporal gyrus, left middle frontal gyrus, and bilateral ventral posterior cingulate cortex as well as decreased weighted DC in left posterior cerbellar lobe and left visual cortex. Results in our study suggest that the pathological mechanism of autism is associated with spontaneous activity and connectivity changes in many brain regions, these changes will affect the ability of theory of mind.

Keywords: Children autism, Functional magnetic resonance imaging, Degree centrality, Amplitude of low-frequency fluctuation, Theory of mind

1. INTRODUCTION

Autism spectrum disorder (ASD) was first reported by Kanner [1]. ASD is a mental and psychological disorder that has a profound influence on the cognitive development of children. ASD is considered to have a large amount of genetic heterogeneity [2]. Recent investigations have found that the total fraction of ASD attributable to genetic inheritance may be about 30-40% [3]. Therefore, other factors have a significant role in autism. Study the pathological mechanism of autism will have a profound impact on the treatment of children with autism.

Autism is mainly manifested as social interaction barriers, communication barriers, narrow interests, and stereotyped repetitive behavior [4]. These three kinds of symptom clusters are thought to be caused through different mechanisms [5]. A great deal of evidence has shown that complex social cognitive deficits contribute to these core symptoms [6]. As an ability in social cognition, theory of mind (ToM) is the ability of an individual to understand their own mental states and those of other people around them. ToM is strongly associated with individuals' social and emotional relationships with others and ability to communicate [7]. Autism is often thought to be caused by severe deficiency in this ability, many studies have shown that children with autism have poor ToM skills [8].

Autism is thought to be a brain disease. It has become ever more apparent that understanding the complex functions of the brain and the functional disorders depends on understanding the precise functional connectivity and spontaneous activity of the brain [9]. Images can be used for target detection [10, 11]. Based on neuroimaging, it has found that ToM cortical network includes the medial frontal gyrus, anterior cingulate, and right temporoparietal junction [12]. The default mode network (DMN) is also closely related to autism, it is the basis of ToM. Due to its non-task and short time, resting state functional magnetic resonance imaging (rs-fMRI) is widely used in the research of spontaneous brain functional activity [13, 14], it is posited to partly reflect the statistical history of interactions between brain regions [15]. Many studies based on fMRI have shown that individuals with autism have a large difference in the anatomy and functional activity of ToM related regions [16]. By classifying fMRI data, markedly alterative DMN related regions, superior parietal lobule, fusiform gyrus and anterior insula are found in autistic individuals [17]. In autism, an increased

functional connectivity is found in lateral parietal and anterior medial prefrontal cortex [18]. Based on a meta-analysis of morphometry studies, the cortical thickness of the cingulate cortex in children with autism has been found to be significantly different from that of children without autism [19]. By assessing their own emotional response, it is found that autistic individuals have additional activation in frontal and inferior temporal regions [20]. Brain abnormalities in autistic individuals are associated with DMN in most previous studies.

In the research reported in this paper, it is postulated that autistic children and healthy children have differences in both spontaneous activity and connectivity of brain. We aimed to compare the spontaneous brain function activities in autistic children and healthy children, and to analyze the potential abnormal degree centrality (DC) of the brain regions using rs-fMRI data.

2. MATERIALS AND METHODS

In this study, fractional amplitude of low-frequency fluctuation (fALFF) and DC are integrated into analysis. Fig. 1 illustrates the framework of this study. Firstly, all fMRI data were preprocessed, and fALFF and DC were subsequently calculated. After that t-test and multiple comparison correction were used to implement statistical analysis. Finally, many brain regions between the two groups were found to be different.

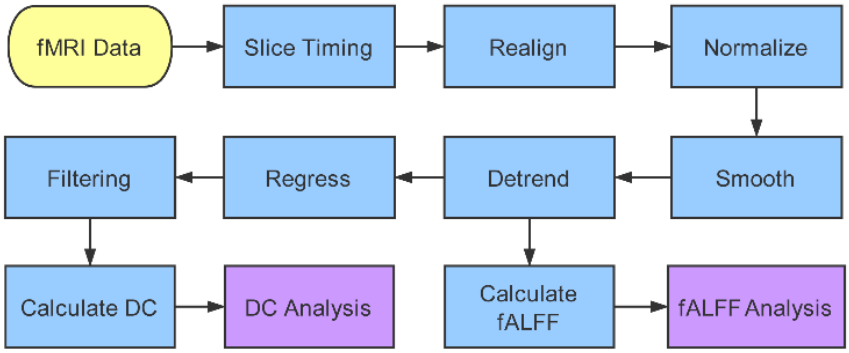

Figure 1. Framework of this study.

2.1 Participants

Data were extracted from the Autism Brain Imaging Data Exchange Project. Different imaging centers have different scanners and surroundings, these factors can have a great impact on brain function images, so we use data from a single image center. By testing the qualities of the brain function images and head movements, we chose 48 children for follow-up studies. Boys are more likely to be affected by ASD, so there were fewer data from girls, limiting the current analyses to boys [21]. All autistic children who were prescribed stimulant medications abstained from taking psychoactive medications for at least 24 hours before undergoing their MRI scans. ASD diagnosis included DSM-IV criteria applied in autism. Neurotypical children required absence of psychiatric diagnosis based on the Child and Adolescent Symptom Inventory. Exclusion criteria were full-Scale IQ below 80, as measured by the Wechsler Intelligence Scale for Children (WISC-IV), and no other neurological diagnosis based on parent report. Children with serious image artifacts and head motion were excluded. Here, 24 autistic children and 24 neurotypical children of the same age (age range, 8.9-13.9 years), handedness, and IQ were studied (Table 1).

Table 1. Participant characteristics.

	Autism	Neurotypical	P-value
No. of children	24	24	
Age (mean±SD)	11.38 (1.41)	11.32 (1.31)	0.971[a,*]

Full IQ (mean±SD)	117.67 (13.47)	117.42 (12.15)	0.962[a,*]
Males/ females	24/0	24/0	
Handedness (right/left)	18/6	18/6	
SRS_TOTAL	81.67 (39.35)	18.25 (19.17)	1.39e-4[a,*]

Test for differences between groups (two-tailed):

SRS_TOTAL total raw score of the social responsiveness scale.

[a] Two-group independent t-test.

[*] Significant difference between groups ($p < 0.05$).

2.2 FMRI data acquisition

A Siemens Trio 3-T scanner was used to acquire imaging data. Participants rested with their eyes open looking at a black screen, known to be an effective way to maintain the resting state [22]. Foam cushions placed in the space between the participant's head and the 12-channel head coil minimized head motion. Anatomic images were acquired using Siemens MPRAGE sequence: matrix = 256 × 256, 176 axial slices of 1 mm thickness, TR = 2530 ms, TE = 3.5 ms, FOV = 256 × 256 mm, flip angle = 8°, voxel size = 1.0 × 1.0 × 1.0 mm^3. Functional images were acquired using an echoplanar imaging sequence: matrix = 64 × 64, 43 axial slices of 2.5 mm thickness, TR = 2000 ms, TE = 30 ms, FOV = 192 × 192 mm, flip angle = 90°, voxel size = 3.0 × 3.0 × 2.5 mm^3.

2.3 FMRI analysis

We preprocessed all fMRI data using SPM12 and DPARSF package [23]. The first 7 volumes were discarded to stabilize the functional signal. Then functional data were corrected for slice timing and head motion. Children with sudden head movements exceeded 2 mm or 2° were excluded. All the corrected data were then spatially normalized into a standard space (MNI305) and resampled to 3-mm isotropic voxels. Children with suboptimal normalization were excluded. An isotropic Gaussian kernel of 8-mm full width at half maximum was used to spatially smooth the normalized data, and linear trends were removed. The data after removal of linear trends were used for assessment of fALFF analysis. In order to construct a voxel-wise functional network, the data after removal of linear trends then regressed out nuisance variables (consist of 24 head-motion parameters, the white matter (WM) signals and cerebrospinal fluid (CSF) signals). We did not use global signal regression because is known to lead to more negative correlations [24]. Finally, fMRI data were band-pass filtered between 0.009 and 0.08 Hz. By applying this band-pass filtering (0.009-0.08 Hz), nuisance variables were sufficiently controlled [25].

2.4 FALFF calculation

To directly identify the differences of brain activity in each brain region, we estimated the amplitude of the brain activity using fALFF analysis. ALFF is the most direct way to reflect local brain activity in resting state [26]. Compared with ALFF, fALFF effectively reduces the effects of noise in the ventricular system and large vessels [27]. fALFF analysis was performed using DPARSF. A gray matter brain template was used here. After removal of linear trends, the time series for each voxel were transformed to a frequency domain, and the square root was calculated at each frequency of the power spectrum. The sum of amplitude across 0.009-0.08 Hz was divided by the sum across the entire frequency range [27]. The data were transformed to Z-values with Z-Standardization.

After each fALFF map was controlled for age, sex, handedness and IQ. By means of single-sample two-tailed t-tests, significant functional data were obtained for each group; and GRF criteria were used for multiple comparison correction with a voxel-level threshold of $p < 0.05$ and a cluster-level threshold of $p < 0.05$, corresponding to $z > 1.96$ and cluster size > 78 voxels. Then they were used for group-level random effects analysis to determine if differences in fALFF between the autism group and neurotypical group. Two-sample two-tailed t-tests was computed to determine the overall differences between the two groups; and Gauss random field (GRF) criteria was used for multiple comparison correction with a voxel-level threshold of $p < 0.05$ and a cluster-level threshold of $p < 0.05$, corresponding to $z > 1.96$ and cluster size > 76 voxels.

2.5 DC calculation

We used weighted DC to observe the connection in their brains. DC is based on voxelwise functional connectivity, it can capture correlations with whole brain network. A gray matter brain template was used here. Firstly, time series of each voxel was extracted. Then we construct a correlation matrix, r_{xy} in correlation matrix represents the Pearson correlation of two corresponding voxels' blood oxygenation level dependent signals. Correlation in each voxel was then transformed to Z-score by using Fisher's r-to-z transformation to improve normality. We computed positive correlations and use threshold r=0.25 to remove weak correlations caused by noise [28]. The final correlation between two voxels was defined as follows:

$$\begin{cases} 0, r_{xy} < r \\ z_{xy}, r_{xy} < r \end{cases}$$

where z_{xy} is Z-score for r_{xy}. The average correlation between one voxel and all other voxels constitutes its DC. Finally, each weighted DC map was transformed to Z-values with Z-Standardization.

After each weighted DC map was controlled for age, sex, handedness and IQ. By means of single-sample two-tailed t-tests, significant functional data were obtained for each group; and GRF criteria were used for multiple comparison correction with a voxel-level threshold of $p < 0.05$ and a cluster-level threshold of $p < 0.05$, corresponding to $z > 1.96$ and cluster size > 88 voxels. Then they were used for group-level random effects analysis to determine if differences in fALFF between the autism group and neurotypical group. Two-sample two-tailed t-tests was computed to determine the overall differences between the two groups; and GRF criteria was used for multiple comparison correction with a voxel-level threshold of $p < 0.05$ and a cluster-level threshold of $p < 0.05$, corresponding to $z > 1.96$ and cluster size > 80 voxels.

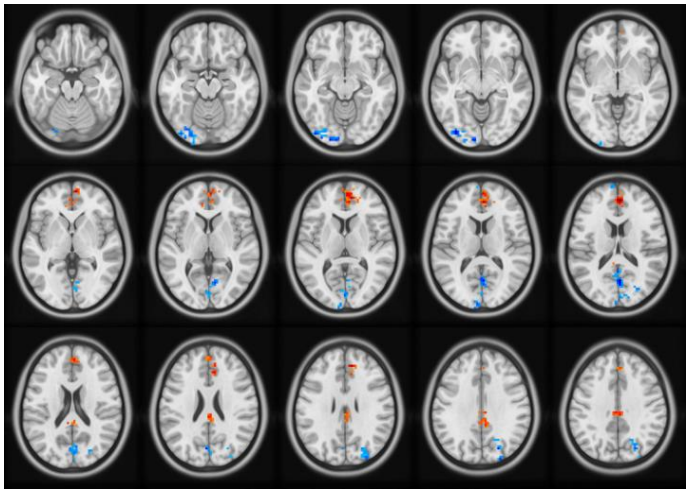

Figure 2. Significant differences between autistic children and neurotypical children.

3. RESULTS

3.1 FALFF analysis result

The major regions in which autism group showed increased fALFF were right ventromedial prefrontal cortex (vmPFC), right dorsal anterior cingulate cortex (dACC) and bilateral ventral posterior cingulate cortex (vPCC). Autism group showed decreased fALFF in bilateral visual cortex (see Fig. 2). Specific information of group differences is shown in Table 2.

Table 2. Group differences in fALFF between autistic children and neurotypical children.

	BA	Size (Voxels)	Side	Peak T value	Coordinates (MNI)		
					x	y	z
Visual cortex	17,18,19	136	L	-4.4437	-36	-87	-9
Visual cortex	17, 18, 19	114	R	-5.2335	3	-66	15
vmPFC	10	97	R	4.0847	6	60	1
dACC	32	51	R	4.5373	3	48	15
vPCC	23	16	L	3.8716	-1	-24	39
vPCC	23	40	R	3.6660	3	-24	31

3.2 DC analysis result

The major regions in which autistic group showed increased weighted DC were left middle temporal gyrus (MTG), left vmPFC and bilateral vPCC. Autism group showed decreased weighted DC in left visual cortex (see Fig. 3). This pattern is somewhat consistent with results in fALFF. Specific information of group differences is shown in Table 3.

Table 3. Group differences in weighted DC between autistic children and neurotypical children.

	BA	Size (Voxels)	Side	Peak T value	Coordinates (MNI)		
					x	y	z
MTG	21	36	L	5.3450	-54	9	-30
vmPFC	10, 11	36	L	4.0478	-12	45	-6
Visual cortex	17, 18, 19	68	L	-4.2858	-3	-84	-12
vPCC	23	38	L	4.0206	-9	-42	27
vPCC	23	35	R	3.6229	12	-39	33

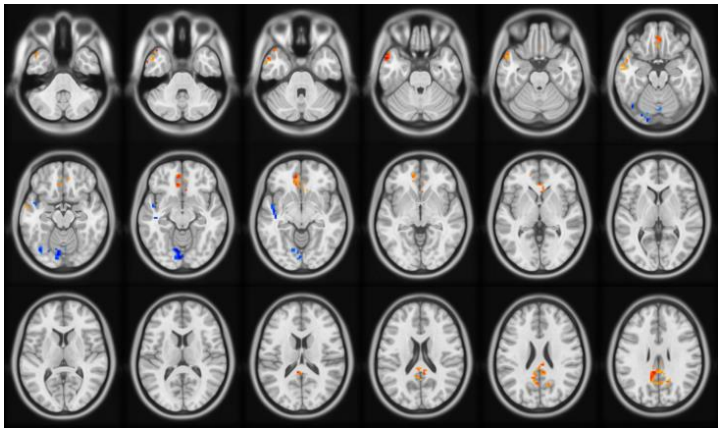

Figure 3. Two-sample t-tests comparing weighted DC of autism and neurotypical groups.

4. DISCUSSION

In this study, we studied changes of spontaneous brain activity and functional connectivity in autistic children compared with neurotypical children. Children were rigorously screened so they would better reflect the current age of the actual situation, but the sample size was relatively small. We compared the differences in brain activity and connectivity between autistic children and neurotypical children by using fALFF and DC. There are two main results: 1) Compared with neurotypical group, autism group showed increased fALFF in right vmPFC, right dACC and bilateral vPCC as well as decreased fALFF in bilateral visual cortex. 2) Compared with neurotypical group, autism group showed increased weighted DC in left MTG, left vmPFC and bilateral vPCC as well as decreased weighted DC in left visual cortex. Almost all of these abnormal parts of the brain are an important hub of the ToM cortical network. The current results converge with prior evidence of altered ToM [29, 30], further indicating that the abnormalities in the ToM cortical network are likely to be an important factor in the social cognitive impairment observed in children with autism.

Our study found increased fALFF and degree values in vmPFC in autistic children. vmPFC is connected with MTG, ACC and PCC. vmPFC is related to higher-order brain function, which is involved in emotional regulation, decision-making and self-control. Decision-making dysfunction may cause autistic children to make repeated decisions, which is consistent with the behavior of autistic children. Emotional dysfunction will make autistic children lose control of their emotions.

Autistic children are thought to have social cognitive dysfunction associated with ToM [31], they have difficulty understanding other individuals' mental state and behavior. We found decreased fALFF and degree values in bilateral visual cortex in autistic children. We can obtain a lot of information from the outside world, and the information obtained by vision occupies a large proportion in all sensory information. As an important region of the brain, visual cortex is responsible for processing visual information. Ventral flow pathway of visual cortex is associated with object recognition and long-term memory. Dorsal flow pathway of visual cortex is involved in controlling the direction of eye's attention. Lesions in visual cortex will make autistic children unable to correctly recognize the facial expressions of other individuals, thus affecting their ToM.

Because of impaired advanced cognitive function, the total performance of autistic children is often unreasonable when reading other individuals' facial expressions. Confronted with different cognitive tasks, autistic children with damage in dACC have communication barriers. In a previous study, the head of ACC was found to participate in emotion-related processes, and dACC was related to cognition. The functional connectivity between ACC and other brain regions and the abnormal activation of ACC were the characteristic manifestation of impaired autism brain network [32]. Our study found increased fALFF values in right dACC in autistic children. In summary, these results suggest dACC is closely related to the symptoms of autism, and its abnormal activation and connectivity are associated with cognitive impairment.

MTG contains neurons with many different functions, which means that its own function is also variegated. MTG is not only involved in language processing and understanding but also participates in many other functions, such as action observation, processing of complex sounds, logical reasoning, and dynamic recognition of facial expressions [33]. Our study found increased degree values in left MTG in autistic children. Previous results have shown that MTG is one of the most important hubs of the brain for recognition of facial expressions [34], and it is also implicated in ToM processing. By studying how the brain activity supporting autobiographical memory, prospection, and ToM, a study showed that autobiographical memory, prospection, and ToM shared a common pattern in neural activity, and MTG is one of the most important parts of the brain [35]. Lesions in MTG may affect language comprehension ability and facial expression recognition ability of autistic children, and then they will cause communication disorder.

Even if we do not participate in any task, our brain will persistent activate. When we are in resting state, activation of DMN is very remarkable. As one of the major brain networks, DMN is considered related to many mental diseases. Hubs of DMN are precuneus/PCC, mPFC and bilateral parietal cortex [36]. Our study found alterative degree and fALFF values in bilateral PCC and bilateral mPFC in autistic children, these are all hubs of DMN. DMN is not only the neural basis of self, but also the basis of ToM. Lesions in DMN are closely related to core symptoms of autism. Lesions in DMN will make autistic children difficult in social communication.

We found decreased fALFF in dACC in autistic children, but we did not found significant altered DC in dACC in autistic children. Mirror neurons are involved in empathic reaction, and they are presented in dACC. When a child is involved in empathic reaction, dACC in the brain will be actived. Empathy defect in autistic children can reflect why just fALFF in ACC was found the significant difference in autistic children.

In our current study, we found changed spontaneous activity and connectivity in autistic children compared with neurotypical children. Results in our study indicate that the mechanism of autism is associated with changed spontaneous activity and connectivity in many brain regions. DMN is remarkably changed in autistic children compared with neurotypical children, these changes will affect the ability of ToM. As the most important brain regions, if their functions are handicapped and they are not able to normally receive sensory information from other brain regions, these dysfunctions will affect social cognition, language cognition, emotional cognition, and so on. Therefore, we believe that autism is not only related to abnormal functional connectivity, the abnormality of both brain spontaneous activity and connectivity constitute the physiological mechanism of autism. Our study will require improvement in future studies. The number of subjects was relatively small due to data quality and age, sex differences between two groups.

5. CONCLUSION

In conclusion, this study demonstrated that spontaneous activity and connectivity are abnormal in autistic children. fALFF and DC were integrated into analysis with the same subjects. Thus we studied the pathological mechanism of autistic children from more aspects. Compared with neurotypical children, autistic children showed increased fALFF in right vmPFC, right dACC, and bilateral vPCC as well as decreased fALFF in bilateral visual cortex. Compared with neurotypical children, autistic children also showed increased weighted DC in left MTG, left vmPFC, and bilateral vPCC as well as decreased weighted DC in left visual cortex. Results in our study suggest that the physiological mechanism of autism is associated with changed spontaneous activity and connectivity in many brain regions, these changes will affect the ability of ToM. Future work will include the study of adult autism and explore changes in brain of autistic individuals during their growth process.

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