Altered Cerebellum Spontaneous Activity in juvenile Autism Spectrum Disorders Associated with Cognitive Functions

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Research

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Abstract

Background

Autism Spectrum Disorders (ASD) is a neurodevelopment disorder. The cerebellum has been reported to be one of the key regions involved in ASD. However, the associations between the cerebellum and clinical traits remain unclear.

Methods

Here we performed Amplitude of Low Frequency Fluctuations (ALFF) analysis to detect the alterations of brain spontaneous activity in ASDs and explore the associations between spontaneous brain activity and clinical traits.

Results

Compared with normal controls, cerebellum crus 2 showed significantly weaker average ALFF values. Other regions such as left cerebellum 6, cerebellum vermis 4 5, putamen, SMA and thalamus showed increased mean ALFF values. In ASD patients with SRS total score T above 59, the mean ALFF values of cerebellum vermis 4 5 was significantly correlated with SRS total score T ($r=0.175, P=0.031$), SRS cognition score T ($r=0.169, P=0.036$) and SRS motivation score T ($r=0.176, P=0.028$).

Conclusions

These findings were not observed in other brain regions and in normal controls. Our study suggests a role of cerebellum in cognitive impairments in ASD and supports a mechanistic basis for the targeted treatment of ASD disorders.

Trial registration

Not applicable.

1 Introduction

Autism spectrum disorder (ASD), characterized by the persistent existence of deficits in social cognition, communication and restricted, repetitive patterns of sensory-motor behaviors, is a cluster of mental disorders of the neurodevelopmental type (Association, 2013; Lord, et al., 2018). Approximately one in 161 children worldwide suffered from ASD (Elsabbagh, et al., 2012). The pathophysiology of ASD remains unknown despite enormous studies available, including neuroimaging studies. To date, temporal and frontal lobe, thalamus and basal ganglia, basal ganglia, the limbic system, as well as cerebellum etc. have been reported to be affected in ASD (Hampson and Blatt, 2015; Maximo and Kana, 2019; Pascual-Belda, et al., 2018). Among these brain regions involving in ASD, the cerebellum was one of the most studied brain regions.
The cerebellum has for a long time been thought as one important brain region functioning in motor learning and coordination (De Zeeuw and Ten Brinke, 2015; Manto, et al., 2012). There is accumulating evidence supporting the cerebellum as one of the key brain regions involved in ASD. Genetic factors in ASD were estimated to be approximately 80% (Bai, et al., 2019). Meanwhile, a few of risk genes have been recognized to be related to cerebellum abnormality in ASD (Aldinger, et al., 2013; Wang, et al., 2019). Moreover, the ASD patients showed alterations in cerebellum volume and Purkinje Cell density (Skefos, et al., 2014; Webb, et al., 2009). The resting-state brain functional connectivity (FC) analysis also showed altered cerebro-cerebellar and within-network of cerebellum FCs in ASD (Khan, et al., 2015; Stoodley, et al., 2017). These findings from genetic, anatomical and neuroimaging studies strongly suggest that the cerebellum plays an important role in neuropathophysiological mechanisms of ASD. However, the small sample size in most ASD studies limited the reliability of these findings. Results from different studies were not exactly consistent. More importantly, few studies focused on the associations between brain regions and clinical traits (e.g., cognition, communication, motivation) in ASD.

The question how the cerebellum in ASD is associated with clinical symptoms has been a matter of interest in recent studies. A previous neuroimaging study has indicated that reductions of gray matter in ASD children in cerebellar lobule VII (Crus I/II) correlated with the severity of symptoms in social interaction and communication (D'Mello, et al., 2015). Regional Homogeneity (ReHo) analysis found that the ReHo value in cerebellum in ASD is significantly correlated to clinical trait scored by Social Communication Questionnaire (SCQ) (Dajani and Uddin, 2016). Some other studies, however, failed to detect the correlations between FC or spontaneous activity of cerebellum and symptoms of ASD (Carper, et al., 2015; Padmanabhan, et al., 2013). Therefore, the relationship between cerebellum and symptoms of ASD remains to be clarified.

The aim of the present study was to explore the associations between spontaneous activity of cerebellum and the clinical traits of ASD. For that purpose, we applied Amplitude of Low Frequency Fluctuations (ALFF) analysis on resting state functional magnetic resonance imaging (fMRI) to explore the spontaneous brain activity divergences between ASD patients and healthy controls. Then, the ALFF values of region of interest (ROI), used to depict the spontaneous activity were extracted, and their correlations with symptoms of ASD were analyzed. Finally, the probable relations between cerebellum-thalamus circuits and clinical traits were detected.

2 Materials And Methods

Participants

The data included in present study were acquired from the Autism Brain Imaging Data Exchange II (ABIDE II, http://fcon_1000.projects.nitrc.org/indi/abide/abide_II.html) (Di Martino, et al., 2017) dataset collected by 19 independent sites. We downloaded the whole dataset including 1114 subjects with resting-state functional magnetic resonance imaging (fMRI) data and their phenotypic data. Then, juvenile ASD patients (aged less than or equal to 18 years) were selected for the study. Age- and sex-matched healthy
subjects were included as controls. The clinical severity of ASD was scored using the Social Responsiveness Scale (SRS) (T scores) (Constantino, 2013) where available and included five subscales: awareness, cognition, communication, motivation, mannerism.

**Data preprocessing**

The scan protocols of the resting state fMRI vary across the 19 sites. Therefore, we preprocessed the neuroimages site by site using standardized pipeline with corresponding parameters. The pre-processing steps included removing the first four volumes, slice-timing correction, motion realignment, spatial normalization using the EPI template to the stereotactic space of the Montreal Neurological Institute (MNI) with voxel size of $3 \times 3 \times 3$ mm. Then, nuisance covariates including head motion parameters and linear trends were regressed out from the BOLD signals. Finally, we performed temporal bandpass filtering (0.01–0.08 Hz) across time series. These steps were conducted using a MATLAB toolbox Data Processing & Analysis for Brain Imaging (DAPABI) (Yan, et al., 2016).

**Amplitude of Low Frequency Fluctuations (ALFF) analysis**

After data preparation, the ALFF analysis on each subject's data was performed using DAPABI (Yan, et al., 2016). The ALFF analysis on fMRI data has been widely applied to measure the magnitude of the energy from Blood oxygenation level dependent (BOLD) signal intensity and indirectly depict the intensity of regional spontaneous brain activity (Deng, et al., 2016; Lu, et al., 2014; Tu, et al., 2015) in resting state. Such relative activity of the local brain area is caused by the rhythmic activity of brain region functionally related to other brain regions. Power spectra of the time series were calculated and the sum of amplitudes within the low frequency band (.01-0.08 Hz) was computed for each voxel. Then the square root was obtained at each power spectrum frequency. The ALFF value of each voxel was taken as average square root across the interest band and was divided by the mean ALFF value within the brain mask to obtain a standardized value (Yu-Feng, et al., 2007). The location assignments of ALFF differences between ASDs and NCs were done by using Anatomical Automatic Labeling template 2 (AAL2) (Rolls, et al., 2015).

The ALFF values of regions of interest (ROIs) were extracted to characterize the spontaneous activity of ROIs. The ALFF values of ROIs for each subject were extracted to depict spontaneous brain activity.

**Correlation analysis**

To explore the associations between clinical severity and brain spontaneous activity, Pearson correlation analysis between the extracted ALFF values of ROIs and SRS T scores were performed.

**Statistical analysis**

To test the spontaneous brain activity differences between ASDs and NCs, we carried out ALFF analysis and used two-sample $t$ test and two tailed threshold free cluster enhancement (TFCE) correction with Permutation Analysis of Linear Models (PALM) permutation test ($P < 0.005$, number of permutations...
1000) (Chen, et al., 2018; Winkler, et al., 2016). The edge cluster connectivity criterion, rmm = 5, cluster size >= 50 voxels.

The relationship between ALFF values or FCs and SRS T scores, depicted by Pearson correlation were analyzed with false discovery rate (FDR) correction. And we used two-sample t-test with FDR correction to compare ASDs and NCs with respect to ALFF values of each region, respectively. We computed Cohen's d for each variable to depict the effect size between two groups. Only those FDR adjusted P values lower than 0.05 were considered significant.

3 Results

Sample Composition

1114 subjects were included from 19 sites. 399 ASD patients (336 males, 63 females) and 441 normal controls (NCs, 298 males, 143 females) aged less than or equal to 18 years. To decrease the sample sex bias between two groups, we randomly included (Matlab randperm function) 361 ASD patients (298 males, 63 females) and 361 HCs (298 males, 63 females) in the latter ALFF analysis. No age differences were observed in the two groups. The mean and SD of Social Responsiveness Scale total T scores in ASDs and NCs is 76.67 ± 13.42 and 43.89 ± 6.38 respectively. The detailed demographic and id lists of the participants are shown in Supplementary Table 1 and Supplementary Table 2.

ALFF changes of cerebellum regions between ASDs and NCs

To test the spontaneous brain activity differences between ASDs and NCs, ALFF analysis was performed. Six clusters were obtained and the locations were assigned by using AAL2 template. Significant differences were located in extensive cerebellar regions involving two clusters: cluster 1(cerebellum_crus2_R, cerebellum_crus2_L) and cluster 2 (cerebellum 4 5 L, cerebellum 6L and vermis 4 5). However, these two clusters in ASDs showed different changes in ALFF value. The regions of cluster 1 in ASDs showed decreased ALFF value than those in NCs while cluster 2 in ASDs showed increased ALFF value (Fig. 1, Table 1). It should be noted that other brain regions were observed to also show dramatical changes in ASD. These regions included supplementary motor Area (SMA), cingulum mid, thalamus, basal ganglia (caudate, putamen) and occipital regions, etc (Fig. 1, Table 1).
Table 1
Brain regions showing significant differences on ALFF analysis between ASD patients and healthy controls*.

<table>
<thead>
<tr>
<th>Clusters</th>
<th>Peak MNI coordinate</th>
<th>Peak intensity</th>
<th>Cluster size</th>
<th>BA</th>
<th>Structure(voxels)</th>
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*Two sample *t* test and two tailed TFCE correction with PALM permutation test were used (P < 0.005, number of permutations 1000). The locations were assigned by using a Matlab tool Xjview. Edge cluster connectivity criterion, rmm = 5, cluster size >= 50 voxels. The surface view maps were shown in Fig. 1.
<table>
<thead>
<tr>
<th>Clusters</th>
<th>Peak MNI coordinate</th>
<th>Peak intensity</th>
<th>Cluster size</th>
<th>BA</th>
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<td>Occipital_Inf_L(84)</td>
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<td>48</td>
<td>12</td>
<td>5.51</td>
<td>85</td>
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|          |        |       |       |      | \
|          |        |       |       |      | Frontal_Inf_Tri_L(24) |

*Two sample t test and two tailed TFCE correction with PALM permutation test were used (P < 0.005, number of permutations 1000). The locations were assigned by using a Matlab tool Xjview. Edge cluster connectivity criterion, rmm = 5, cluster size >= 50 voxels. The surface view maps were shown in Fig. 1.

ALFF values of spontaneous brain activity was correlated with Clinical trait

Considering that four subregions of cerebellum (cerebellum crus 2, left cerebellum 4 5, left cerebellum 6, cerebellum vermis 4 5), putamen, SMA and thalamus showed significantly altered ALFF in ASDs, we hypothesized that these changes in ALFF, depicting the spontaneous brain activity might be associated with clinical traits. Therefore, to examine the relationship between alteration of ALFF and clinical trait, Pearson correlation analyses were performed between SRS T scores including SRS total T score, SRS awareness T score, SRS cognition T score, SRS communication T score, SRS motivation T score and SRS mannerisms T score and mean ALFF values of these ROIs. ROIs regions including left cerebellum crus 2, left cerebellum 4 5, left cerebellum 6, cerebellum vermis 4 5, putamen, thalamus and SMA were defined using AAL2 template (Rolls, et al., 2015). The mean ALFF values of each ROI for individuals were extracted from corresponding ALFF results.

We noted that in juvenile ASD patients with SRS total T scored above 59 (n = 258), the mean ALFF value of cerebellum vermis 4 5 was significantly correlated with SRS Total T (r = 0.175, P = 0.031, FDR correction), SRS cognition T (r = 0.169, P = 0.036) and SRS motivation T (r = 0.176, P = 0.028), These
Findings from comparisons of ALFF values between ASDs and NCs

To explore the ALFF trends in ASDs, we further compared the mean ALFF values of ROIs between ASDs and NCs. The sample was same as the ALFF analysis. It was noted that the ASD group showed increased ALFF values that of NCs in left cerebellum 6 ($P = 0.001$, $t = 3.209$, Cohen’ $d = 0.239$), cerebellum vermis 4 5 ($P = 0.039$, $t = 2.071$, Cohen’ $d = 0.154$), putamen ($P < 0.01$, $t = 3.339$, Cohen’ $d = 0.249$), thalamus ($P < 0.001$, $t = 4.355$, Cohen’ $d = 0.325$) and SMA ($P < 0.001$, $t = 4.530$, Cohen’ $d = 0.338$). However, the mean ALFF values of left cerebellum crus 2 in ASD patients were lower than that of NCs ($P < 0.001$, $t=-4.165$, Cohen’ $d=-0.310$). The two groups presented no significant differences in the ALFF values of left cerebellum 4 5 (Fig. 3).

Medication effect and ALFF values of ROIs

Considering that medication might have potential impacts on spontaneous brain activity of ROIs, we divided the ASDs into two groups according to their medication status. We found that the ALFF differences between ASDs with medications ($n = 84$) and ASDs without medication ($n = 172$) did not survive after FDR adjusted.

Reproducibility

We assessed reproducibility through a simple strategy. We randomly selected (with Matlab) another two sex- and age-matched groups and carried out ALFF analysis. The results of ALFF analysis remained the same with same settings as previous analysis (Supplementary Fig. 1). Then, we defined the ROIs based on AAL2 atlas, not based on our own ALFF clusters.

4 Discussion

In the present study, we applied ALFF analysis to detect the alterations of spontaneous brain activity in ASDs and explored the associations between spontaneous brain activity and clinical trait. The different ALFF pattern can be related to different brain spontaneous activity patterns of the ASDs and NCs. The regions with different ALFF pattern were used as ROIs to investigate if the ALFF was related to the clinical severity of ASD. For that purpose, Pearson’s correlation analysis was employed to demonstrate the probable correlations between spontaneous brain activity and clinical traits. Furthermore, subgroup analysis of ASDs suggested that spontaneous activity of the brain might be impacted by medication status. Finally, ALFF analysis with another randomly selected sample produced a similar ALFF map,
which confirmed the high reproducibility of the present study. The combined findings are expected to provide evidence for a functional role of cerebellum in ASD from the functional imaging level.

Based on our findings from functional imaging data, we confirmed the important role of cerebellum in ASD, which is in accordance with previous fMRI studies (Itahashi, et al., 2015; Jack, et al., 2017). Importantly, the decreased ALFF values of cerebellum crus 2 and increased ALFF values of cerebellum 4 5 and cerebellum vermis 4 5 in ASD patients might suggested that the subregions of cerebellum have heterogeneous roles in ASD. That means the dysfunction of ASD might be partly attributed to the enhanced brain spontaneous activity in cerebellum 4 5, cerebellum vermis 4 5, cerebellum 6 and declined brain spontaneous activity in cerebellum crus 2. The subsequent correlation analysis supported this assumption: the ALFF of cerebellum vermis 4 5 was positively correlated with SRS total score T. Interestingly, we noted that the spontaneous activity of left cerebellum crus 2 was negatively related to SRS motivation score T in NCs, which might be caused by decreased spontaneous activity of left cerebellum crus 2 in ASDs. These findings support a mechanistic basis for the targeted treatment of ASD related disorders. Excessive or insufficient spontaneous activity of subregions in cerebellum could induce disorder in ASD.

As we expected, the cerebellum spontaneous activity was associated with clinical severity and functional deficits, which is in good agreement with earlier ALFF analysis (Guo, et al., 2017) and task-dependent fMRI study (Murphy, et al., 2017). Specifically, we found that SRS cognition score T was only positively related to cerebellum vermis 4 5, which were not obtained in NCs. This result, has not been presented in previous studies, indicated that excessive spontaneous brain activity in the cerebellum subregion: vermis 4 5 might play a key role in the changes of cognitive function in ASDs. Notably, the ALFF changes of other ROIs such as cerebellum 4 5 in ASD patients were not significantly correlated with any clinical trait scored with SRS, though cerebellum 4 5 showed a significantly increased ALFF in ASDs, compared with NCs. This result further supported the notion that no single pattern could be drawn to characterize the role of cerebellum in ASD.

The present findings about the role of cerebellum subregions in cognitive function were in accordance with previous studies. Clinical study has confirmed that patients with cerebellum lesions might experience cerebellar cognitive affective syndrome (Argyropoulos, et al., 2020). The abnormal cerebellum activity has also been found in other disease with cognitive impairment such as Parkinson's Disease (Solstrand, et al., 2020). However, the organization of cognitive function was still an unsolved issue. The cerebellum crus 2 has been found to send and receive projections to (from) prefrontal area 46 (Bostan, et al., 2013). In addition, imaging studies have indicated that some subregions of cerebellum might functionally couple networks of the cerebral cortex (Buckner, 2013). Our results confirmed this speculation: the left Cerebellum Crus 2 showed decreased spontaneous activity, while the left cerebellum 6 and cerebellum vermis 4 5 showed increased spontaneous activity, compared with NCs. Notably, only the spontaneous activity of vermis 4 5 was found to be significantly correlated with SRS cognition score T. These findings indicated that different patterns might be drawn for different subregions of cerebellum
in cognitive function. We speculated that the anatomically and functionally heterogeneity together play a role in the cognitive function of cerebellum.

Besides cerebellum, some other brain regions including SMA, thalamus and putamen were also found to show significant changes in ALFF. According to previous studies, these brain regions might function in the form of functional circuits, such as cortico-basal ganglia-thalamic circuits (Nair, et al., 2013; Schuetze, et al., 2016). To explore the relations between FC of these regions and clinical traits, we have calculated the functional connectivity between the six ROIs (results not shown). However, we did not find significant associations between functional connections of ROIs and clinical traits. Therefore, further studies are needed to investigate how these brain regions showing significant changes of ALFF, interact with each other in ASDs.

In subgroup analysis, it was noted that ASD patients with medication and ASD patients without medication showed no differences in brain spontaneous activities of ROIs after critical FDR correction, which means that the targets of drugs present used might be not linked to the ROIs including cerebellum, thalamus and SMA. However, there was study found that medication use might affect brain FC in ASDs (Linke, et al., 2017). Considering that the significant changes of brain spontaneous activity in ASDs, regulating brain spontaneous activity might be one important treatment mechanism of ASD medications. However, longitudinal studies should be devoted to investigating whether ALFF changes over the course of ASD treatments.

**Conclusion**

In conclusion, in this functional imaging approach based on ALFF analysis and Pearson’s correlation analysis, we were able to demonstrate that ASD patients showed significantly alterations in spontaneous activity of cerebellum regions involving cerebellum crus 2, cerebellum 4 5, cerebellum 6 and cerebellum vermis 4 5. Moreover, the changes of spontaneous activities of cerebellum vermis 4 5 were significantly correlated with cognitive functions in ASD. Our study suggests a role of cerebellum in cognitive impairments in ASD and supports a mechanistic basis for the targeted treatment of ASD related disorders.

**Abbreviations**

ASD: Autism spectrum disorder; ALFF: Amplitude of low frequency fluctuations; ReHo: Regional homogeneity; fMRI: Functional magnetic resonance imaging; ROI: Region of interest; SRS: Social Responsiveness Scale; SMA: Supplementary motor Area; FC: Functional connectivity;

**Declarations**

**Acknowledgments**
We thank the Special Training Program for Young Scientific and Technological Talents of Southwest Medical University 2020-2022 for sponsorship of Jianghai Ruan. The authors acknowledge members of the Autism Brain Imaging Data Exchange and the International Neuroimaging Data-sharing Initiative for their efforts to aggregated and organized phenotypic and imaging data.

Authorship contribution statement

Jinglun Li: Data curation, Methodology, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. Xiu Chen: Conceptualization, Methodology, Data curation, Writing - original draft. Ruwen Zheng: Conceptualization, Data curation, Writing - review & editing. Ai Chen: Conceptualization, Methodology, Writing - review & editing. Yan Zhou: Methodology, Data curation, Formal analysis. Jianghai Ruan: Conceptualization, Methodology, Supervision, Writing - original draft, Writing - review & editing, Funding acquisition.

Funding

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Availability of supporting data

The used data are open available at database ABIDE II (http://fcon_1000.projects.nitrc.org/indi/abide/abide_II.html). The ID of subjects used in the study are listed in Appendix 1.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Southwest Medical University (Luzhou, China).

Consent for publication

Not applicable.

Competing interest

The authors declare that they have no Conflict of Interest.

References


Figures
Figure 1

Surface view of regions showing altered ALFF in ASD group, compared to NC group. A ALFF differences between ASDs and NCs in cerebellum. B ALFF differences between ASDs and NCs in brain regions except cerebellum. Two sample t test and two tailed threshold free cluster enhancement (TFCE) correction with Permutation Analysis of Linear Models (PALM) permutation test were used (P<0.005, number of permutations 1000). The color bar represents the range of t values. L, left. R, right. The detailed locations assignments were shown in Table 1.

Figure 2
Pearson's correlation analysis between ALFF of cerebellum vermis 4 5 and clinical traits in ASD patients. The correlations between ALFF of cerebellum vermis 4 5 and SRS total score T(A), and SRS cognition score T (B), and SRS motivation score T. The included ASD patients in this analysis were those patients within the included samples with a SRS total score T higher than 59 (n=258). The r in each image indicated the Pearson's correlation coefficient r of corresponding variables. Significant correlations were not observed in other ROIs of ASD patients or in NC group (Supplementary table 2 and 3).*P values have been adjusted with false discovery rate (FDR) correction.

Figure 3

Comparisons of the mean ALFF values for each ROI between ASDs and NCs. Two sample t test with FDR correction were used for the comparisons. The d values indicated the effect size Cohen’s d. * P<0.05 after FDR adjusted, **P<0.01 after FDR adjusted, ***P<0.001 after FDR adjusted.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1.docx