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Original scientific paper

Causal connectivity abnormalities of regional homogeneity in children with attention deficit hyperactivity disorder: a rest-state fMRI study

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Abstract

The present study aimed to investigate individual differences of causal connectivity between brain regions in attention deficit hyperactivity disorder (ADHD) which was a psychiatric disorder. Resting-state functional magnetic resonance imaging (R-fMRI) data of typically-developing controls (TDC) children group and combined ADHD (ADHD-C) children group were distinguished by the support vector machine (SVM) with linear kernel function, based on regional homogeneity (ReHo), amplitude of low frequency fluctuation (ALFF) and fractional ALFF (FALFF). The highest classification accuracy yielded by ReHo was 90.91 %. Furthermore, the granger causality analysis (GCA) method based on the classified weight map of regions of interesting (ROIs) showed that five causal flows existed significant difference between TDC and ADHD-C. That is, the averaged GCA values of three causal connections (i.e. left VLPFC → left CC1, right PoCG → left CC1, and right PoCG → right CC2) for ADHD-C were separately stronger than those for TDC. And the other two connections (i.e. right FEF → right SOG and right CC1 → right SOG) were weaker for ADHD-C than those for TDC. In addition, only two causality flows (i.e. left VLPFC → left CC1 and right PoCG → right CC2) presented that their GCA values were positively correlation with ADHD index scores, respectively. Our findings revealed that ADHD children represented widespread abnormalities in the causality connectivity, especially involved in the attention and memory related regions. And further provided evidence that the potential neural causality flows could play a key role in characterizing individual's ADHD.

Keywords

ADHD; ReHo; GCA; SVM; fMRI

Introduction

Attention deficit hyperactivity disorder (ADHD) was a mental disorder with age-inappropriate symptoms, which was mainly characterized by poor sustained attention, impulsiveness (ADHD-I), and hyperactivity (ADHD-H). Many functional neuroimaging studies had been carried out to discover the pathologies underlying the disorder. Convergent evidences have demonstrated that ADHD induced abnormalities both in brain structure (i.e. reduced volume and cortical thickness in frontal, anterior cingulate cortex [1], amygdala [2], hippocampus [3], cerebellum [4, 5] and occipital [6, 7]) and brain function (i.e. functional connectivity alterations among frontal-occipital, temporo-occipital [8, 9], and frontal-striatal circuits networks [10, 11]). Recently, resting-state functional magnetic resonance imaging (R-fMRI) has attracted increasing attention for mapping large-scale neural network function and dysfunction. Seed-based methods were used to detect network alterations of ADHD patients, especially the abnormalities in default mode network and visual network [12]. Although, these studies provided valuable insights into the pathological mechanism of ADHD, some significant limitations were clearly found. Firstly, the obtained information was limited to the selected regions of interest (ROIs) through seed-based methods and made it difficult to examine functional connectivity patterns on a whole-brain scale [13]. Secondly, traditional group-level statistical methods were not able to provide evidence for evaluating the discriminative power of the identified connections at the individual level [14].

Pattern analysis based on the group level statistical methods can complement seed-based and univariate statistical analyses, which helped researchers discover diagnostic markers of disease and provide additional help for clinical diagnosis. The causal connection such as Granger causality analysis (GCA) reflected the directional flow of information between brain regions [15]. The causal relationship and adjustment patterns between different activation regions could be observed using GCA, which provided new insights for ADHD.

Taken together, we studied the causal connectivity of brain regions in combined ADHD (ADHD-C) children group using multivariable variable GCA methods. Firstly, we used machine learning methods to distinguish ADHD-C children and typically-developing controls (TDC) children for the purpose of obtaining a more convincing difference in brain regions. Secondly, we calculated the classified weight map and the ROIs (seeds) were selected according to the peak points of the weight map. Then on the basis of GCA, a network analysis was conducted. Finally, we studied the correlation between ADHD index scores and GCA values. The results of this study can provide strong support for the cognitive process of ADHD-C.

Materials and methods

Subjects

Forty right-handed subjects with TDC (mean age =9.61; 29 males, 11 females; mean index =45.11) and twenty-six right-handed subjects with ADHD-C (mean age = 9.8, 15 males, 11 females; mean ADHD index = 73.04) were investigated in the current study. Children with comorbidities were not included in the study. All data were obtained from the ADHD dataset of New York University (http://fcon_1000.projects.nitrc.org/indi/adhd200/).

Data acquisition and analysis

Functional images were acquired on a SIEMENS TRIO 3-Tesla scanner. Functional images were obtained axially using Echo planer imaging (EPI) sequence (TR= 2000ms, TE= 15ms, 33 slices, Slice thickness= 4.0mm, FOV= 24 ×24 cm^2, flip angle= 90°, resolution= 256×256). The acquire time of functional imaging was 360 seconds. To facilitate the localization of functional images, high-resolution T1-weighted was spoiled gradient-recalled whole-brain volume (TR= 2530ms, TE= 3.25ms, slices= 256, thickness/gap =1.33.0/0mm, FOV=256×256mm^2, resolution=256×256, flip angle=7°).

Data pre-processing was carried out using Data Processing Assistant for Resting-State fMRI (DPARSF) [16], which was based on Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit [17]. Pre-processing was performed as follows: 1) removal of the first ten volumes and slice timing correction; 2) the functional images were spatial normalized to Montreal

Neurological Institute (MNI) space applying the unified segmentation parameters; 3) The linear trend, head motion parameter (measured by Friston-24 model), white matter (WM), and cerebrospinal fluids (CSF) signals were further regressed out as nuisance covariates; 4) After removing of linear trend, band-pass filtering (0.01-0.08 HZ) was performed on the time course of each voxel for further Regional homogeneity (ReHo) analysis. The ReHo was calculated according to the described procedure in Zang et al. [18]. Moreover, the spatial smoothing (FWHM = 6 mm) was conducted after ReHo calculation as described by previous studies. In addition, the calculation process of ALFF and FALFF could be explained by the work of Zuo [19].

Feature extraction, classification and GCA brain network analysis

For each participant, the corresponding whole brain parameters have been calculated as above. We used the REST toolbox (version 1.8. http://www.restfmri.net/forum/REST V1.8) to compare the difference between different brain images (i.e. ReHo, ALFF and FALFF) of ADHD-C group and TDC group. Two-sample t-tests (two-tailed, P<0.05) and multiple comparisons with Gaussian Random Field (GRF) Theory (voxel-level p = 0.01, cluster-level p =0 .05, two-tailed) were applied for statistical testing. Based on the results of correction, the voxel values in differential brain regions were used as feature for classification. The support vector machine (SVM) classifier with linear kernel function was used to evaluate discrimination of ADHD-C from TDC. The accuracy, sensitivity (SE) and specificity (SP) were estimated by leave-one-out cross-validation (LOOCV) to assess the performance of the classifier. In order to further study the causal relationship between differential brain regions of ADHD-C , ROIs were constructed based on peak points of the weight map [20] and the information flow between brain regions of two groups was analysed by GCA [21]. Finally, we investigated the correlation between significant GCA values and ADHD scale scores in two groups. The whole processing step was shown in Figure 1.

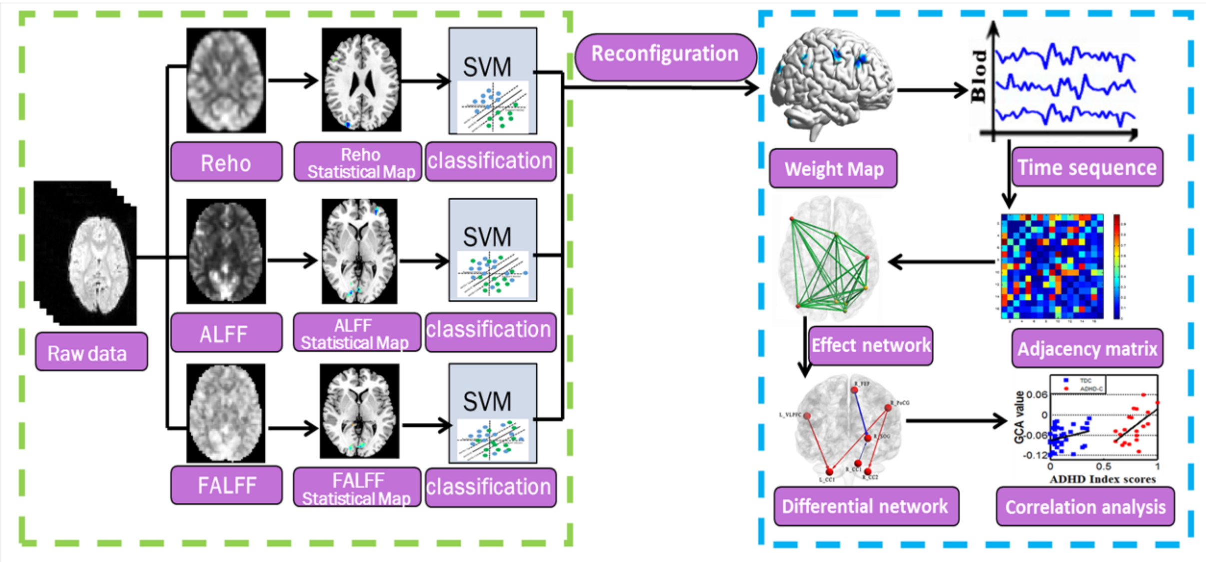

Figure 1. The main steps of data analysis including basic data preprocessing, parameter feature calculation (ReHo, ALFF, FALFF), feature selection, classification, ROIs selection, network construction, GCA network analysis and ADHD scale analysis.

Results

By two-sample t-tests and multiple comparison correction, the differential brain regions were used as the features for classification. The classification results were shown in Table 1 which indicated that the ReHo yielded a higher classification rate than other features (accuracy: 90.91 %, sensitivity: 92.5 %, specificity: 88.46 %). Receiver operating characteristic curve (ROC) was a comprehensive index reflecting the continuous variables of sensitivity and specificity. Hence, The ROC curve of ReHo was presented in Figure 2, and it revealed the relationship between sensitivity and specificity by the method of composition. In this study, AUC (area under the curve) was equalled to 0.94.

Table 1. Classification results using different imaging feature

SVM_Method	Metrics	Accuracy	Sensitivity	Specificity (%)
Linear Kernel	ReHo	90.91	92.5	88.46
	ALFF	66.67	72.5	57.69
	FALFF	74	87.5	53

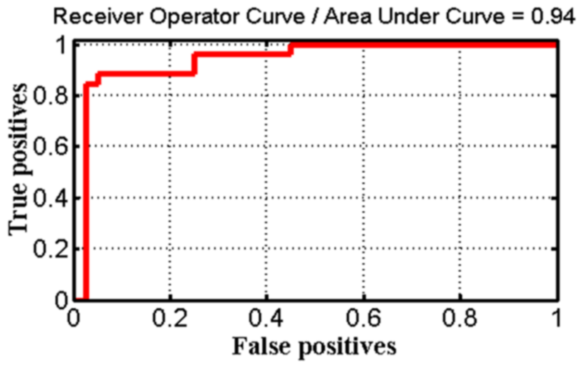

Figure 2: The ROC curve based on the ReHo value.

Differentiated regions

The significant activated regions of ReHo revealed by two-sample t-tests and multiple comparison correction were showed in Figure 3. Compared with the TDC group, the activation of left middle occipital gyrus (MOG), right superior occipital gyrus (SOG), bilateral frontal eye field (FEF), bilateral crus I of cerebellar (CC1) and right crus ll of cerebellar (CC2) was greater in ADHD. However, the decreased activation of the left ventrolateral prefrontal cortex (VLPFC), right middle frontal gyrus (MFG), right postcentral gyrus (PoCG) and right temporo-parietal junction (TPJ) was found in ADHD.

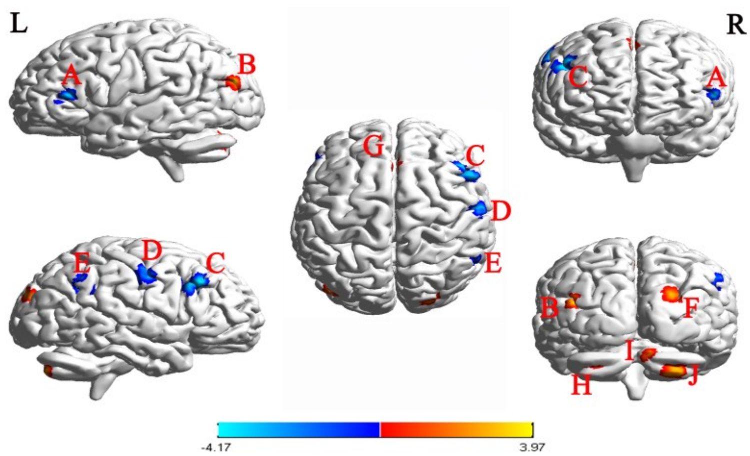

Figure 3. Regions with significant activation of ReHo map. (A) VLPFC, ventrolateral prefrontal cortex; (B) MOG, middle occipital gyrus; (C) MFG, middle frontal gyrus; (D) PoCG, postcentral gyrus; (E)TPJ, temporo-parietal junction; (F) SOG, superior occipital gyrus; (G) FEF, frontal eye field; (H) left CC1, crus I of cerebellar; (I) CC2, crus ll of cerebellar; (J) right CC1, crus I of cerebellar. Warm and cold colors indicated the increased and decreased activation of regions related to ADHD-C respectively. Here, thresholds with voxel-wise were set at p < 0.01, and thresholds with cluster-wise of Gaussian Random Field (GRF) were set at p<0.05. And cluster size >20 voxels. L: left, R: right.

Classified weight map based on ROI

The classified weight map based on ROI was shown in Table 2. The regions with significant contribution to classify the TDC group from ADHD-C group were right PoCG, right TPJ, right MFG and left VLPFC. While the regions contributed to distinguish ADHD-C group from TDC group were bilateral FEF, bilateral CC1, right CC2, right SOG and left MOG. The peak coordinates of these regions were shown in Table 2. Overall, the differences of brain regions between two groups were mainly concentrated on the frontal lobe, occipital lobe, and cerebellum, which was consistent with the previous study [22].

Table 2. The weight map of ROI regions

Label	Hemisphere	Weight (%)	Voxel	MNI_coordinate
TDC>ADHD				
PoCG	R	11.76	49	(54,-12,33)
TPJ	R	8.17	42	(54,-54,30)
MFG	R	7.18	62	(54,21,27)
VLPFC	L	6.37	37	(-54,36,6)
ADHD>TDC				
FEF	R	16.71	25	(9,18,48)
CC2	R	15.61	40	(30,-78,-42)
CC1	L	11.10	32	(-27,-72,-30)
CC1	R	10.67	32	(9,-78,-24)
MOG	L	7.58	29	(-39,-84,18
SOG	R	4.85	45	(27,-87,15)

Granger causality analysis based on ROI

In order to further study the relationships between these differential brain regions, the ROIs were selected according to the peak points of weight map. Each ROI was centered at the peak point of weight map with a radius of 8 mm. Accordingly, 10 ROIs were taken from the weight map and the directed adjacency matrix was calculated with GCA method (model order: p = 1). Two-sample t-tests was carried out for the adjacency matrix of two groups (p<0.05, FDR corrected). As a result, there were five significant causal flows (left VLPFC → left CC1, right PoCG → left CC1, right PoCG → right CC2, right FEF → the right SOG, right CC1 → right SOG) for ADHD-C and TDC groups. The average values of five significant causal flows were reported in Figure 4(A) and Figure 4 (B) revealed the difference via the averaged GCA values of five causal flows in ADHD-C minus those in TDC. The mean GCA values of three causal flows (i.e. left VLPFC → left CC1, right PoCG → left CC1, and right PoCG → right CC2) were positive and greater in ADHD group than in TDC group, while the other causal connectivity (i.e. right FEF → right SOG and right CC1 → right SOG) was negative. The positive causal effect meant an excitatory effect, whereas the negative causal effect represented an inhibitory effect [23]. Notably, these results revealed that the symptoms of ADHD may be caused by the dysfunction from frontal cortex to the cerebellum.

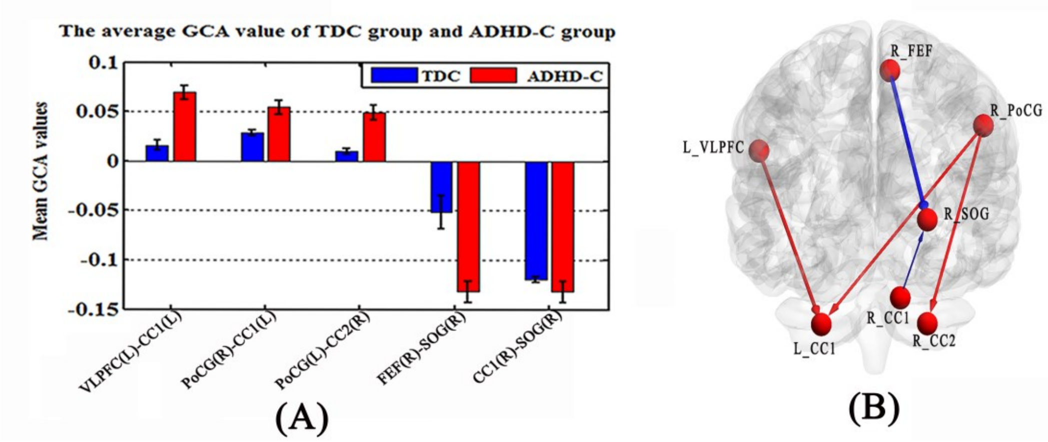

Figure 4: The significant causal flows discovered by GCA in ADHD-C and TDC groups. (A) The mean GCA values of five significant causal flows in two groups. (B) The causal flow differences obtained by the mean GCA values of ADHD-C minus that of TDC. The red edge represented positive difference of ADHD-C compared to TDC group. The blue edge represented the negative difference compared to TDC.

Correlation between the mean GCA value and ADHD index scores

Furthermore, the correlation was analysed between GCA value and the ADHD index scores. ADHD index scores were positively correlated with GCA values of left VLPFC → left CC1 and right PoCG → right CC2 only in ADHD group (see Figure 5).

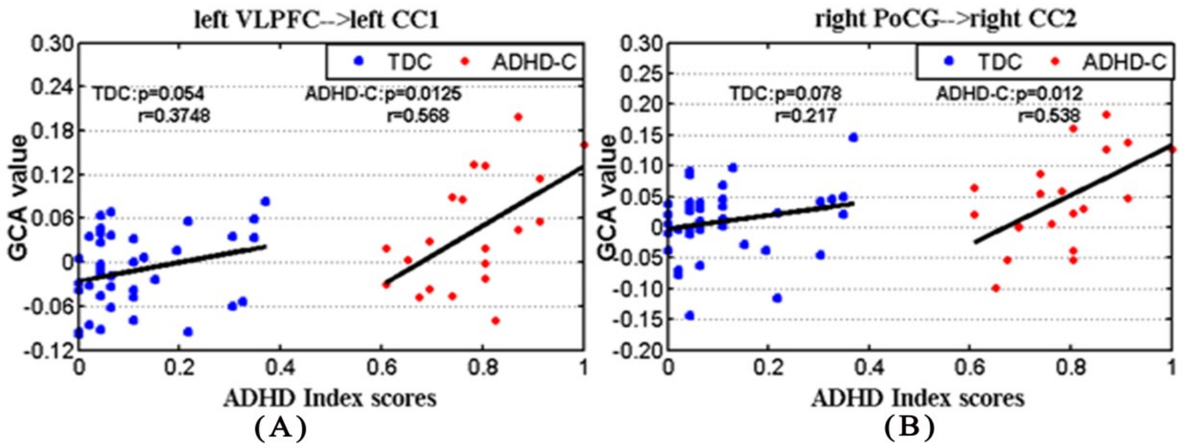

Figure 5: Granger causal influence between regions as functions of ADHD index scores in two groups. (A) left VLPFC → the right CC1; (B) right PoCG → the right CC2. Here, the significant correlations were observed only in ADHD-C group.

Discussion

In this paper, we tried to implement classification for both TDC and ADHD-C children without any other complication illness. We found that the highest classification rate (90.91 %) was captured by ReHo values. the sensitivity and specificity of the model were evaluated as well. The GCA analysis demonstrated that the information flow of ADHD group from left VLPFC to left CC1, right PoCG to left CC1 and right PoCG to right CC2 was enhanced compared to TDC group. However, the information flow from right FEF to the right PoCG and right CC1 to the right PoCG was reduced in ADHD-C group. These regions were mainly concentrated on the frontal, parietal, and cerebellum, which were included in attention network. This may suggest that the etiology of ADHD may be the dysfunction from frontal cortex to the cerebellum.

It was noted that the attention network model was composed of three sub-networks: alertness, orientation and execution control. These sub-networks were both independent and organic in anatomy and function and this view has been supported by empirical researches in different fields [24]. Alertness was defined as achieving and maintaining an alert state and orientation was required when stimuli occurred outside the current focus of attention. The executive control was defined as resolving conflicts between responses [25]. As an important part of attention network, alertness was considered as the basis for maintaining cognitive function. The role of alertness was to maintain preparation or wake-up state to accept information transmission [26]. Some studies found that the alert system was associated with the thalamus, prefrontal lobe, and parietal lobe [27, 28]. Attention orientation was responsible for selecting information from a large number of sensory inputs, and the main function was to shift attention to stimulus that need to be chosen or concerned. Attention orientation could be divided into external orienting and internal orienting: external orienting was usually accompanied by eye movements which directed attention towards target stimulation, while internal orientation involved more paid attention of individuals to internal signals usually without obvious eye movements [25]. Attention orienting was thought to be achieved by a network composed of the right temporo-parietal cortex and the right inferior frontal gyrus, which was modulated by the cholinergic system. The executive control was mainly responsible for monitoring and resolving conflicts between stimuli or reactions [26], which was related to the activities of the anterior cingulate gyrus, the lateral prefrontal cortex, and the right frontal gyrus.

In our study, the abnormalities of left VLPFC, right PoCG, right TPJ, left MOG, right SOG, bilateral FEF and cerebellum were found in ADHD-C group. These regions were mainly included in attention network. It was often assumed that neural activity in subcortical regions was modulated in a “top-down” fashion to facilitate processing of stimuli at attended locations. In particular, the parietal and frontal regions of the right hemisphere were regarded as the source of top-down bias [29, 30]. Our results showed that compared to the TDC group, the left VLPFC, right MFG, right PoCG and right TPJ were supressed in ADHD-C, while the activations of left MOG, right SOG and cerebellar region were increased. The strength of the causal connection from left VLPFC to left CC1, right PoCG to left CC1 and right PoCG to right CC2 was enhanced in ADHD-C group. The cerebellum was emerging as a key structure in several neuropsychiatric disorders, particularly in ADHD [31, 32]. Previous studies have shown that cerebellum mainly involved in motion control and advanced cognitive processes such as learning, attention shifting, visual spatial processing, working memory and emotion management [33-36]. The increased amount of information flowing into the cerebellum may explain the enhanced activation of our study. The VLPFC and PoCG of the alert network were suppressed, which may suggest that ADHD-C patients could not remain a preparation and waken state to accept information transmission and the attention was poorly sustained. Taken together, the decreased activation of VLPFC and PoCG may reflect that ADHD-C patients suffer from the defects in maintaining a preparation and waken state. In this way, the cerebellum was more active for the higher demands of receiving and storing information. This idea was also evidenced by the increased granger influences from left VLPFC to left CC1, right PoCG to left CC1 and right PoCG to right CC2.

The neurons of FEF were associated with the inhibition of saccade production. The activation of FEF decreased rapidly when the stop-signal was given in a stop-signal paradigm, while it increased for fixation [37]. In addition, the FEF has been implicated in responding preferentially to attended stimuli and exerted the top-down shifts of attention to bias the processing of task-related information as evidenced by a number of studies [38]. The occipital cortex (right superior occipital gyrus) regulated by top-down control was mainly recruited during diverse tasks (i.e. auditory, visual and tactile modalities) and played an important role in visual-spatial attention, working memory. Compared to the TDC group, the decrease in the strength of the causal connection between FEF and SOG suggested that FEF may reduce control over occipital cortex in ADHD-C. This reduced top-down control may suggest that ADHD-C had a deficit in biasing the processing of behaviorally relevant objects and filtering the irrelevant information [39]. This interpretation was evidenced by neurophysiological studies. For example, attention deficit hyperactivity disorder has suffered from behavioral deficits such as a poor sustained attention, impulsiveness and hyperactivity, which explaining the reduced top-down control from symptoms [40]. Attention reorienting was reflected by the activation of fronto-striatal-insular network and reduced functional connectivity of the ADHD children in the fronto-striato-parieto-cerebellar network was reported by Rubia [41, 42]. Furthermore, the decreased fronto-parietal connectivity was found when ADHD conducted the working memory and interference suppression task [43, 44]. The inputs from the cerebellum were thought to reflect the frequency and timing of events. Furthermore, the cerebellum was involved in bottom-up neural systems and send bottom-up signal to posterior cortical systems for enabling the objects perceived selectively [45]. fMRI studies have indicated that the abnormality of cerebellum was related to attentional impairments such as autism, attention deficit hyperactivity disorder [46, 47]. The decreased granger causality of between cerebellum and occipital cortex may suggest that ADHD-C had deficient in sensory tracking related to attention [48]. This consistent with the idea that ADHD had difficulty in representing transiently relevant information for attention and memory. The decreased functional connectivity was found in cerebellum and superior parietal lobule compared to the controls when ADHD patients conducted a working memory task [49]. The decreased granger influence from FEF to SOG and from cerebellum to SOG may be responsible for the dysfunction of attention orienting in ADHD.

In summary, we speculated that the core symptoms of ADHD might derive from abnormal functions of alert network and orientation network from the GCA analysis.

Conclusion

We concluded that ADHD-C children had a frontal lobe - occipital - cerebellar abnormality derived from the R-fMRI study of ReHo. The classification analyses were done for distinguishing the ADHD-C patients from the TDC group. The highest classification rate (90.91%) was captured by the ReHo with the 92.5% sensitivity and 88.46% specificity. Compared to the TDC group, the attention networks were significant suppressed, whereas the cerebellar region activated which was revealed by two-sample t-tests. On the basis of GCA analysis, the strength of the causal connection from left VLPFC to left CC1, right PoCG to left CC1 and right PoCG to right CC2 was enhanced, while the connection from right FEF to the right SOG and right CC1 to right SOG were weakened. These results suggested that ADHD have abnormal functions in alert network and orientation network for maintaining preparation state and attention. However, the cerebellum activated more for compensation mechanism. In conclusion, the above findings supported the hypothesis that ADHD patients were disordered in the loop of frontal lobe to the cerebellum.

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