

Characteristics of brain functional and structural connectivity in alexithymic students

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Background: Alexithymia is a multifaceted personality trait and a risk factor for several mental and physical diseases.

Methods: In this study, 21 alexithymic students and 21 nonalexithymic students were recruited from the local university and assigned to the alexithymic group and the control group, respectively. Then, the functional connectivity and the structural connectivity among the brain regions of the students were investigated using resting-state functional magnetic resonance imaging (rsfMRI), function connection (FC) analysis, and diffusion tensor imaging (DTI).

Results: The rsfMRI results revealed 14 brain regions showing significant differences in the amplitude of low-frequency fluctuations between the two groups. Comparative analysis of the FC and DTI data in these brain regions between the two groups identified altered levels of functional and structural connectivity between the following four pairs of regions in the alexithymic subjects: the right inferior temporal gyrus and the central posterior gyrus, the left temporal gyrus and the insula, and the bilateral superior frontal gyrus and the anterior cingulate gyrus.

Conclusion: Compared with single MRI analysis, the multiple MRI analysis identified more precisely the brain regions that could play a key role in the development of alexithymia.

Keywords: rsfMRI, DTI, functional connectivity, structural connectivity, alexithymia

Introduction

Alexithymia is a personality trait characterized by difficulties in identifying and describing one's own emotional feelings and external thinking style.¹ Several studies have confirmed the relationships between alexithymia and depression, anxiety, autism, and a number of other psychosomatic disorders.²⁻⁷ It has been reported that approximately 9% of people suffer from alexithymia.⁸ Clarifying the neural mechanism of alexithymia can improve the understanding about this personality trait and its relationships with psychosomatic disorders.

The development of functional magnetic resonance imaging (fMRI) in recent years has provided a precise and noninvasive technique for exploring the neuropathological basis of alexithymia. Previous studies using fMRI have suggested that alexithymia was associated with abnormal neural activity in several brain regions, including the prefrontal cortex, the cingulated cortex, the insula (INS), the amygdala, the precuneus, and the superior temporal gyrus.⁹⁻¹¹ However, some of these regions are also known to be associated with several other mental disorders such as depression, anxiety, autism, and schizophrenia.¹²⁻¹⁵ Therefore, it is necessary to identify more precisely the brain regions that play a key role in the development of alexithymia. Furthermore, these studies have suggested that alexithymia was associated with multiple brain regions rather than only a single region. Multiple brain regions must cooperate with other

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brain regions to maintain regular brain functions. Therefore, it is reasonable to hypothesize that the development of alexithymia is associated with not only the abnormal neural activity of several brain regions but also the somewhat abnormal functional or structural connectivity among these brain regions.

Function connection (FC) analysis provides a powerful method for investigating the functional connectivity among brain regions. Liemburg et al¹⁶ reported abnormal FC levels among the medial prefrontal cortex (mPFC), the occipital areas, the INS, and the anterior cingulate cortex (ACC) in individuals with alexithymia. In addition, structural connectivity is an important index that can be used to investigate the cooperative effects among the brain regions associated with alexithymia. Diffusion tensor imaging (DTI) is a highly sensitive method for measuring the structural integrity of the white matter tracts that connect the brain regions. A study using DTI conducted by Ho et al¹⁷ suggested that the superior longitudinal fasciculus, a primary white matter tract that connects the frontal, occipital, parietal, and temporal lobes, showed a significant correlation with alexithymia. These studies have partly supported the abovementioned hypothesis. Unfortunately, the study conducted by Liemburg et al¹⁶ investigated only the brain regions in the default network, and that of Ho et al¹⁷ focused only on the corpus callosum and the superior longitudinal fasciculus.

To verify the abovementioned hypothesis and identify more precisely the key brain regions associated with alexithymia, the present study was conducted to investigate the functional and structural connectivity features between each brain region showing abnormal neural activity in subjects with alexithymia. First, we identified all the brain regions that exhibited abnormal neural activity in alexithymic individuals using resting-state fMRI (rsfMRI). Then, we examined the FCs between each of these regions and the other regions of the entire brain using FC analysis. Finally, we examined the structural features of the FCs showing abnormal levels in alexithymic individuals using DTI analysis. Holistic knowledge about the functional and structural connectivity of the brain regions associated with alexithymia will contribute toward an in-depth understanding of the neural nature of this multifaceted personality trait, ie, alexithymia.

Methods

Subjects

All participants were recruited from among college students who participated in a freshmen mental health examination in 2015. All subjects were right-handed and had no history of

brain injuries, substance abuse, or mental disorders. Those with contraindications to MRI scans or had consumed any psychotropic medications within 6 months before this study were excluded. Eligible alexithymic participants were randomly chosen, telephonically contacted, and assigned to the alexithymic group (Alex group). The eligible non-alexithymic participants, who matched the alexithymic participants in terms of age and sex, were randomly chosen, telephonically contacted, and assigned to the control group (Cont group). A total of 21 participants in the Alex group (age =18.33±1.06 years, eleven males and ten females) and 21 participants in the Cont group (age =18.62±1.07 years, eleven males and ten females) were recruited in this study. The study protocol was approved by the Research Ethics Review Board of Hangzhou Normal University. All subjects provided written informed consent in accordance with the Declaration of Helsinki.

Psychological measurements

The situation of alexithymia, depression, and anxiety of these participants was accessed, respectively, using the Chinese version Toronto Alexithymia Scale-20 (TAS-20), Self-Rating depression Scale (SDS), and Self-Rating Anxiety Scale (SAS). TAS-20 was used to assess the status of alexithymia. TAS-20 has 20 entries, with scores of 1–5 corresponding to “highly disagree” to “highly agree”, and the score of the scale was the sum of the scores of each entry. The subjects with a TAS-20 score >60 were assigned to the Alex group, and those with a score <52 were included in the Cont group.¹⁸ SDS and SAS both include 20 items. The standardized score is obtained by the integral part of 1.25-fold of the total score of 20 items. Subjective depression was defined as a standard SDS score ≥50. Subjective anxiety was defined as a SAS score ≥53. Therefore, all data of the participants with SDS score ≥50 or SAS score ≥53 should be excluded.

MRI measurements

All MRI scan processes were performed with a 3T whole-body MR imager (GE MR750, GE Healthcare, Chicago, IL, USA). The rsfMRI were acquired: sequence = gradient recalled echo-echo planar images (GRE-EPI), axial slices, 43 slices, repetition time (TR)/echo time (TE) =2,000/30 ms, field of view (FOV) =220×220 mm, resolution =64×64, flip angle (FA) =90°, total scan time =480 seconds. Participants were instructed to simply rest with their eyes closed, not to think of anything in particular, and not to fall asleep. The 3D T1-weighted images were acquired: sagittal slices, 180 slices, TR/TE =8,100/3, resolution =256×256,

FOV =256×256, thickness/gap =1/0 mm, FA =8°, total scan time =305 seconds. Lastly, DTI was acquired: Spin-Echo Echo-Planar Imaging sequence, 67 axial slices, TR/TE =8,600/minimum, FOV =192×192, matrix =128×128, num shots =1, slice thickness =1.5 mm. Diffusion direction: TENSOR, 30 directions, *b*-value=1,000 s/mm², NEX (number of excitation)=2, number of T2 images =4, voxel size =1.5×1.5×1.5 mm³, total scan time =593 seconds.

Data processing and statistical analysis

Based on the MatLab 2011b (MathWorks, Natick, MA, USA), data preprocessing was performed using Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/>), the Data Processing Assistant for Resting-State fMRI (DPARSF, <http://www.restfmri.net>), and the rsfMRI data analysis toolkit (REST, <http://www.restfmri.net>).^{19,20} The images were corrected for slice-time differences, realigned for head motion correction, coregistered to T1, and spatially smoothed, according to a previous study's suggestion.²¹ The amplitude of low-frequency fluctuation (ALFF) map was calculated. The ALFF values of the whole brain gray matter regions of the subjects in the Alex group and the Cont group were voxel-by-voxel-based compared using the independent *t*-test of REST software to obtain the brain regions with significant differences ($P < 0.01$, AlphaSim correction, cluster size > 21). The result was displayed using xjView software (<http://www.alivelearn.net/xjview/>).

The brain regions showing a significant difference on ALFF were selected as the region of interest (ROI) (diameter =5 mm), with the Montreal Neurological Institute coordinates shown in Table 1. The time series correlation coefficient between each ROI and each voxel in the whole brain was calculated by REST. After Fisher's *z*-transformation, the FC map of each ROI and the whole brain was obtained. The FC values of each ROI and the entire brain of the subjects in the Alex group and the Cont group were compared using the independent *t*-test of REST software to obtain the pairs of brain regions with significantly different FC values ($P < 0.01$, AlphaSim correction, cluster size > 21).^{22,23} The result was visualized with the BrainNet Viewer (<https://www.nitrc.org/projects/bnv/>).²⁴ For each individual dataset, the FC values of these pairs of brain regions were extracted using REST. The FC values of the two groups were compared using Independent-Samples *t*-test by SPSS statistical software version 19.0 (IBM Corporation, Armonk, NY, USA).

The DTI data were processed using the Pipeline for Analyzing Brain Diffusion Images (PANDA, <http://www.nitrc.org/projects/panda/>) and DTI Studio (<https://www.mristudio.org/>).

Table 1 Brain regions showing significant differences on ALFF between the Alex group and the Cont group

Brain regions (BA)	Voxel size	Peak MNI coordinate			Peak t value
		X	Y	Z	
Alex < Cont					
PreCG	30	-24	-18	66	-4.0067
ACC	24	0	0	30	-3.4135
PostCG	43	54	-12	21	-4.4691
INS	23	-30	-27	21	-3.6573
Thalamus, left	92	-15	-24	15	-4.4737
Primary visual cortex (V1)	24	24	-69	12	-3.7334
HIP	22	-18	-42	3	-3.3616
Putamen, left	60	-30	0	-3	-4.1590
Putamen, right	52	30	-6	-3	-4.0324
Alex > Cont					
SFG_R	21	18	66	6	3.6904
SFG_L	37	-21	60	0	4.0344
ITG_R	66	63	-48	-9	4.7707
ITG_L	22	-57	-63	-12	4.0419
OFC_R	21	45	48	-15	3.4859
Parahippocampal gyrus	99	24	-30	-36	3.8754

Note: $P < 0.01$, AlphaSim correction, cluster size > 21 .

Abbreviations: ACC, anterior cingulate cortex; Alex, alexithymia group; ALFF, amplitude of low-frequency fluctuations; Cont, control group; HIP, hippocampus; INS, insula; ITG_L, inferior temporal gyrus, left; ITG_R, inferior temporal gyrus, right; MNI, Montreal Neurological Institute; OFC_R, orbitofrontal cortex, right; PreCG, precentral gyrus; PostCG, postcentral gyrus; SFG_L, superior frontal gyrus, left; SFG_R, superior frontal gyrus, right.

The DTI data processing included transferring Digital Imaging and Communications in Medicine to Neuroimaging Informatics Technology Initiative, image registration, normalizing, and smoothing. Maps of FA were computed from the DTI data. Based on the FC analysis results, the FA values were extracted using the Fiber Assignment by Continuous Tracking algorithm.²⁵ Data normality of FA in the two groups was assessed by the Kolmogorov–Smirnov test. Data showing a normal distribution were summarized by mean \pm SD, and data showing a nonnormal distribution were summarized by median values. The FA values of the two groups were compared using Independent-Samples *t*-test by SPSS. Differences were considered to be significant at a two-sided *P*-value of 0.05. The result was visualized by BrainNet Viewer.

Results

Comparative analysis of ALFF between the two groups

The results of the amplitude of ALFF analysis showed that the neural activities of nine brain regions were significantly lower, and the neural activities of six brain regions were significantly higher in the Alex group than those in the Cont group (Table 1, Figure 1).

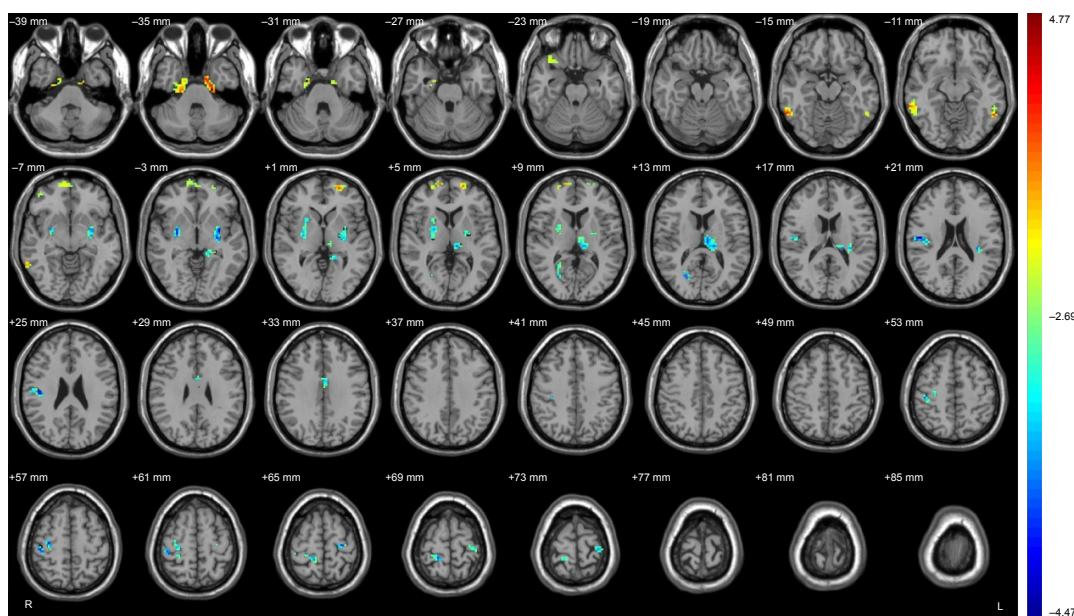


Figure 1 Brain regions showing significant differences on ALFF between Alex and Cont group.

Notes: $P < 0.01$, AlphaSim correction, cluster size > 21 ; red and yellow color means Alex $>$ Cont; blue and green color means Alex $<$ Cont.

Abbreviations: Alex, alexithymia group; ALFF, amplitude of low-frequency fluctuations; Cont, control group.

Comparative analysis of functional connectivity between two groups

The results of the analysis showed significantly different FC values of 14 pairs of regions, including inferior temporal gyrus (right) (ITG_R) and postcentral gyrus (preCG), ITG_R and V1, ITG_R and Putamen (left), ITG_R and Putamen (right), ITG_L and INS, superior frontal gyrus (right) (SFG_R) and postcentral gyrus (postCG), SFG_R and INS, orbitofrontal cortex (right) (OFC_R) and Putamen (left), Putamen (right) and INS, ITG_L and SFG_L, SFG_R and ACC, SFG_L and ACC, OFC_R and PostCG, OFC_R and hippocampus in the Alex group, compared with those in the Cont group (Table 2, Figure 2).

Comparison analysis of functional connectivity between two groups

The results revealed significantly different FA values of four pairs of regions, including the ITG_R and PostCG, ITG_L and INS, SFG_R and ACC, and SFG_L and ACC in the Alex group, compared with those in the Cont group (Table 3, Figure 2).

Discussion

Based on previous studies, this was the first study to compare the neurological activity of each brain region of subjects with and without alexithymia in the resting state. The results showed an altered neural activity in 15 regions (Table 1) in

Alex group compared with that in Cont group. Previous neuroimaging studies have also demonstrated abnormal activities in these 15 brain regions in subjects with alexithymia.^{9,26,27} Therefore, using these brain regions as the ROIs, this study indicated that the FC levels between 14 pairs of brain regions (Table 2) in the Alex group were found to be significantly different from those in the Cont group. It was notable to observe that all the brain regions involved in the altered

Table 2 Fourteen pairs of regions showing significant differences on FC between the Alex group and the Cont group

Brain regions	Alex	Cont	t value	P-value
ITG_R-PostCG	0.243±0.054	0.625±0.061	-4.527	<0.001
ITG_R-V1	0.038±0.016	0.105±0.035	-5.09	<0.001
ITG_R-Putamen_L	0.024±0.011	0.12±0.041	-4.06	0.001
ITG_R-Putamen_R	0.013±0.044	0.119±0.042	-3.421	0.002
ITG_L-INS	0.339±0.048	0.721±0.041	-3.416	0.002
SFG_R-PostCG	0.116±0.047	0.206±0.035	-3.687	0.001
SFG_R-INS	0.283±0.044	0.314±0.047	-3.824	0.001
OFC_R-Putamen_L	0.201±0.051	0.234±0.044	-3.177	0.002
Putamen_R-INS	0.53±0.073	0.592±0.064	-3.568	0.001
ITG_L-SFG_L	0.465±0.047	0.398±0.052	4.46	<0.001
SFG_R-ACC	0.639±0.046	0.341±0.039	3.499	0.002
SFG_L-ACC	0.524±0.050	0.341±0.044	4.271	0.001
OFC_R-PostCG	0.071±0.061	0.12±0.041	4.022	0.001
OFC_R-Hippocampus	0.427±0.075	0.337±0.065	4.127	0.001

Abbreviations: ACC, anterior cingulate cortex; Alex, alexithymia group; Cont, control group; ITG_L, inferior temporal gyrus, left; ITG_R, inferior temporal gyrus, right; OFC_R, orbitofrontal cortex, right; PreCG, precentral gyrus; PostCG, postcentral gyrus; SFG_L, superior frontal gyrus, left; SFG_R, superior frontal gyrus, right.

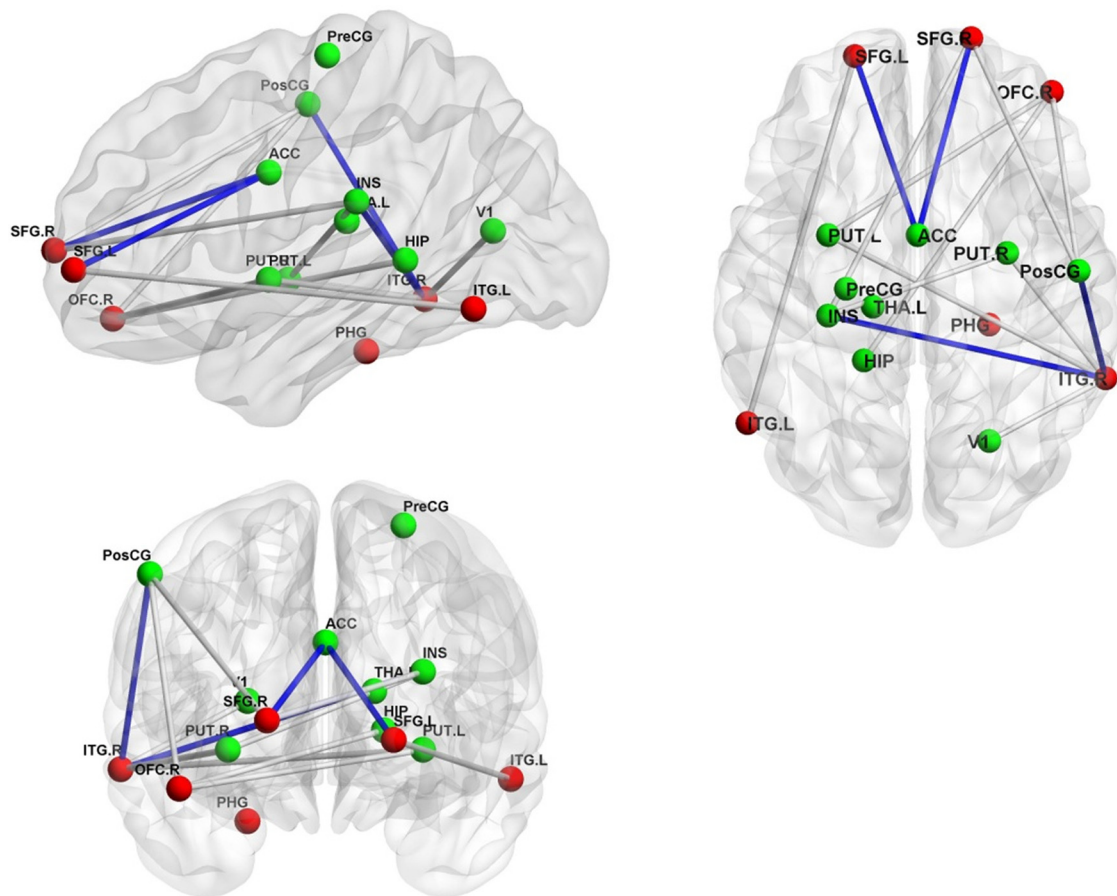


Figure 2 The pairs of regions showing the significant differences on FC or FA between the Alex group and the Cont group.

Notes: Red ball means Alex > Cont on ALFF; green ball means Alex < Cont on ALFF; gray line means the difference on FC between the Alex group and the Cont group is statistically significant; blue line means the difference on FA between the Alex group and the Cont group is statistically significant.

Abbreviations: ACC, anterior cingulate cortex; Alex, alexithymia group; ALFF, amplitude of low-frequency fluctuations; Cont, control group; HIP, hippocampus; INS, insula; ITG.L, inferior temporal gyrus, left; ITG.R, inferior temporal gyrus, right; PHG, parahippocampal gyrus; PreCG, precentral gyrus; PostCG, postcentral gyrus; PUT.L, PUTAMEN, left; PUT.R, Putamen, right; SFG.L, superior frontal gyrus, left; SFG.R, superior frontal gyrus, right; THA.L, thalamus_L; V1, primary visual cortex; OrbPFC.R, orbitofrontal cortex, right.

functional connectivity belonged to the 15 regions showing significant altered neural activity in this study. This implies that the functional connectivity results accurately identified all the brain regions that are actually associated with alexithymia. Finally, based on these 14 pairs of brain regions, the structural connectivity results demonstrated lower levels of structural connectivity between four pairs of regions (Table 3)

Table 3 Brain regions showing significant differences on fractional anisotropy between the Alex group and the Cont group

Brain regions	Alex group	Cont group	t value	P-value
ITG_R-PostCG	0.362±0.0037	0.378±0.0046	-2.386	0.022
ITG_L-INS	0.049±0.0034	0.187±0.0053	-2.181	0.035
SFG_R-ACC	0.189±0.0054	0.369±0.0053	-2.688	0.010
SFG_L-ACC	0.517±0.0039	0.536±0.0053	-2.933	0.006

Abbreviations: ACC, anterior cingulate cortex; Alex, alexithymia group; Cont, control group; INS, insula; ITG_L, inferior temporal gyrus, left; ITG_R, inferior temporal gyrus, right; PostCG, postcentral gyrus SFG_L, superior frontal gyrus, left; SFG_R, superior frontal gyrus, right.

in the Alex group. Both the functional connectivity and the structural connectivity of the four pairs of brain regions in the Alex group were significantly different from those in the Cont group, indicating that the uncooperative condition of the four pairs of brain regions could most probably be the neural basis underlying the development of alexithymia.

The human ITG is a part of the visual conduction pathway and is primarily responsible for visual processing.²⁸ The PostCG is also known as the primary body sensory cortex and is responsible for receiving and organizing sensory information from the entire body. The INS has a wide range of fiber connectivity to other brain regions and is primarily responsible for body and visceral sensation, self-pain perception, visceral movement, and autonomic nervous control.^{29,30} Pollatos and Gramann³¹ reported functional hyperactivity of ITG in a subject with hyperalexithymia. In addition, several studies have confirmed that the core symptom of

alexithymia (blunted feeling) is related to the impaired function of the superior temporal gyrus.^{32,33} A few studies have also confirmed that alexithymia (difficulties identifying and describing one's own emotions) is associated with impaired interoception.^{34,35} Ernst et al³⁶ also demonstrated the association of interoceptive awareness and alexithymia with neurotransmitter concentrations in the INS and the ACC.³⁶ Furthermore, a few clinical surveys and neuroimaging studies have suggested that alexithymia was associated with functional or structural impairments in the INS.^{37–39} Therefore, it is reasonable to suggest that the mechanism of alexithymia is associated with the dysfunction of the ITG, the PostCG, and the INS.

The SFG is primarily involved in the regulation of fine body movements and a variety of cognitive functions such as working memory, scenario memory, and attention.^{40,41} In addition, the SFG belongs to the default network and holds a wide range of fiber connectivity to other regions in the default network, such as the cingulate gyrus.⁴² The ACC is an important component of the cerebral limbic system and is primarily involved in several complex body and visceral motor functions and pain responses.^{43,44} Moreover, the ACC belongs to the default network and is responsible for the integration of various information inputs into the brain and the regulation of various complex cognitive processes by coordinating with other regions in the default network.^{43,45} Several previous studies have suggested the relationship between the dysfunctions of SFG and ACC and alexithymia.^{46–48} The present study has further demonstrated that the abnormal functional and structural connectivity between the bilateral SFG and ACC may be involved in the key mechanism underlying the development of alexithymia.

Interestingly, this study indicated the low-level structural connectivities between the four pairs of brain regions in the Alex group. The FC values between the bilateral ITG and the PostCG/INS were also lower in Alex group than those in the Cont group. However, the FC values between the bilateral SFG and ACC were higher in the Alex group than those in the Cont group. This inconsistency implies that a low-level structural connectivity induces a high- or low-level functional connectivity and that neither high- nor low-level FC presents a concordant or good functional connectivity.

Conclusion

This study analyzed the functional connectivity and the structural connectivity between the brain regions associated with alexithymia, primarily using rsfMRI, FC analysis, and DTI. Based on the data obtained from the multiple analysis methods, the abnormal functional and structural connectivity

was precisely identified between the bilateral ITG and the PostCG/INS and between the bilateral SFG and ACC associated with alexithymia. A limitation of this study is the small sample size. To clarify the neural mechanism of alexithymia, more subjects will be recruited in a further study to delineate the relationship of alexithymia with the functional and structural connectivity between these four pairs of brain regions in the future.

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Author contributions

Dai Han designed and managed the imaging data selection and analysis. Yantong Fang wrote the first draft of the manuscript. Yantong Fang, Mei Li, Minjun Mei, and Xiaofei Sun undertook the psychology measurement and statistical analysis. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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