



# Changes in Resting-State Spontaneous Brain Activity in Patients With Allergic Rhinitis: A Pilot Neuroimaging Study

Ziang Gao<sup>1</sup>, Xixiang Chen<sup>2</sup>, Rong Xiang<sup>1</sup>, Wei Zhang<sup>1</sup>, Lu Tan<sup>1</sup>, Wenjun Fan<sup>1</sup>, Peiqiang Liu<sup>1</sup>, Hao Lv<sup>1</sup> and Yu Xu<sup>1\*</sup>

<sup>1</sup> Department of Otolaryngology-Head and Neck Surgery, Renmin Hospital of Wuhan University, Wuhan, China, <sup>2</sup> Department of Radiology, Renmin Hospital of Wuhan University, Wuhan, China

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### \*Correspondence:

Yu Xu  
xuy@whu.edu.cn

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**Background:** Allergic rhinitis (AR) is an inflammatory disorder of the nose caused by immunoglobulin E (IgE)-mediated immune response to allergens. Apart from the typical symptoms of sneezing, itching, rhinorrhea, and nasal congestion, behavioral complications were also reported to be associated with the progression of AR, such as cognitive deficits, mood changes, memory decline, attention deficiency, poor school performance, anxiety, and depression. Recent human studies have suggested that alterations in brain function caused by allergen exposure may precipitate high levels of anxiety and emotional reactivity in asthma patients. But until now, there is no direct evidence of the relationship between brain activity and allergic rhinitis.

**Methods:** Resting-state functional magnetic resonance imaging (rs-fMRI) was used to excavate whether there remain functional changes of brain activity in AR patients. We measured the amplitude of low-frequency fluctuation (ALFF) and the z conversion of ALFF (zALFF) in 20 patients with AR and 20 age- and sex-matched healthy controls (HCs) using the rs-fMRI data.

**Results:** Compared with healthy controls, AR patients exhibited lower ALFF values in the precuneus (PCUN) and higher ALFF values in the anterior cingulate cortex (ACC). The ALFF values of these features were significantly correlated with the visual analog scale (VAS) scores, the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores, the subscales of RQLQ, and specific IgE, partly.

**Conclusion:** We found changes in resting-state spontaneous brain activity in AR patients with hypoactivity in the PCUN and hyperactivity of the ACC. The brain-related symptoms of AR might be another potential clinical intervention target for improving the life quality of AR patients. Further attention to brain activity is essential for a deeper understanding of AR.

**Keywords:** neuroimaging, allergic rhinitis, resting-state fMRI, precuneus, anterior cingulate cortex, cognition, memory

## INTRODUCTION

Allergic rhinitis (AR) is an inflammatory disorder of the nasal mucosa induced by immunoglobulin E (IgE)-mediated immune response to allergens (Cheng L. et al., 2018; Meng et al., 2019). In the past decades, AR has become a worldwide public health problem and affected up to 40% of the population. Although not life-threatening, the symptoms of AR as well as the comorbid diseases are frequently bothersome, adversely affecting work, psychological health, and quality of life, imposing a significant socioeconomic burden on both the individual and society.

The characteristic symptoms of AR are sneezing, itching, rhinorrhea, and nasal congestion (Brożek et al., 2017; Cheng L. et al., 2018; Meng et al., 2019). Apart from these typical symptoms, behavioral problems were also reported in AR patients, such as impaired quality of life (QOL), disturbed sleep, and unsatisfactory performance in school and at work (Bousquet et al., 2012; Brożek et al., 2017; Cheng L. et al., 2018; Meng et al., 2019), as well as brain-related symptoms including psychological problems, memory problems, cognition problems, concentration deficits, and mood changes (Ozdoganoglu et al., 2012; Trikojat et al., 2017). How these brain-related symptoms occur is unclear. Recent human studies have suggested that alterations in brain function could be caused by allergen exposure and might precipitate high levels of anxiety and emotional reactivity in asthma patients (Damoiseaux et al., 2012; Cui et al., 2020). Callebaut et al. (2020) found the activation of different brain regions upon nasal histamine provocation in AR patients. With an AR rat model, Yang et al. (2018) found inflammatory responses in the hippocampus region. In our previous study, neuroinflammation was also observed in the olfactory bulb in an allergic rhinitis mouse model (Lv et al., 2021). These studies suggested that there might be aberrant brain activity in the brain regions of AR patients that is responsible for the brain-related symptoms. But until now, there is no direct evidence of the relationship between brain activity and allergic rhinitis.

Neuroimaging techniques could help detect structural and functional brain abnormalities at an early stage. Studies incorporating structural and functional magnetic resonance imaging (MRI) can provide more comprehensive information on the underlying mechanisms of the various pathways in the pathogenesis of diseases (Dodd et al., 2012). Resting-state functional MRI (rs-fMRI) is an excellent tool for probing neural networks and has been widely used to investigate changes in the global functional network connectivity and local spontaneous neuronal activity in the brain at rest. Contrastingly, in the subjective cognitive decline (SCD) disease model, some studies have failed to find structural changes, but have reported differences in brain function, as measured by blood oxygen level-dependent functional MRI (BOLD fMRI) (Scarapicchia et al., 2019). Notably, some neuroimaging findings in Alzheimer's disease (AD) suggest that changes in brain function may actually precede changes in brain structure (Damoiseaux et al., 2012). The amplitude of low-frequency fluctuation (ALFF) is an rs-fMRI method that may serve as a surrogate for neural activity at a single-voxel level (Dodd et al., 2012; Cui et al., 2014, 2020; Yang et al., 2018; Scarapicchia et al., 2019; Callebaut et al., 2020;

Lv et al., 2021). Given that, an ALFF analysis may provide important information on the spontaneous brain activity pattern specific to AR and on the difference between AR patients and healthy controls (HCs).

In this study, our primary goal was to observe the changes in resting-state spontaneous brain activity in ALFF in AR patients, aiming to make an initial study of the mechanisms of the brain-related symptoms in AR. Taking into account that few studies to date have examined the relationship between AR and brain-related disorders in individuals with AR, and that none of the fMRI measures of BOLD variability in this group was reported, we also investigated the relationship between alterations in ALFF and clinical indexes, as well as allergy indicators, using correlation analysis for our pilot neuroimaging study.

## MATERIALS AND METHODS

### Participants

A total of 20 AR patients were recruited from the Otorhinolaryngology Department of Renmin Hospital of Wuhan University. The inclusion criteria were as follows: 18–50 years old and moderate to severe AR for more than 1 year. The diagnostic criteria for AR are according to the Allergic Rhinitis and its Impact on Asthma Guidelines (ARIA) (Brożek et al., 2017): (1) positive skin prick tests or circulating levels of allergen-specific IgE antibody  $\geq 0.7$  kU/L and (2) clinical history or identified allergen. The exclusion criteria were allergic asthma; moderate to severe atopic dermatitis; any autoimmune disorder; specific immunotherapy during the past 3 years; any severe chronic inflammatory disease; any neuropsychiatric disease; any history of brain surgery, alcohol, or drug abuse; contraindications to MR examinations; and pregnancy or breastfeeding. Demographic and clinical data such as age, gender, year of education, disease duration, visual analog scale (VAS) score, and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score of each patient were collected.

Twenty age-, sex-, and education level-matched HCs were also enrolled as a control group in the present study. All of the subjects were right-handed according to the Edinburgh Handedness Inventory.

This study was approved by the Human Research Ethics Committee of Renmin Hospital of Wuhan University (Wuhan, China). Written informed consent was given to all the participants (approval WDRY2020-K233).

### MRI Acquisition Data Preprocessing

Scanning of this study was performed at the Radiology Department of Renmin Hospital of Wuhan University (Wuhan, China) using a 3-T MR scanner (Discovery MR 750 W System; GE Healthcare, Milwaukee, WI, United States) with an eight-channel head coil. Structural T1-weighted images were acquired with the following parameters: 192 slices, repetition time/echo time = 8.5/3.3, thickness = 1.00 mm, no intersection gap, acquisition matrix =  $256 \times 256$ , field of view =  $240 \times 240$  mm<sup>2</sup>, and flip angle = 12°. Echo planar images (EPIs) were acquired with the following parameters: 40 slices, repetition

time = 2,000 ms, echo time = 25 ms, thickness = 3.0 mm, gap = 1.2 mm, acquisition matrix =  $64 \times 64$ , flip angle =  $90^\circ$ , field of view =  $240 \times 240 \text{ mm}^2$ , and voxel size =  $3.6 \times 3.6 \times 3.6 \text{ mm}^3$  during an 8-min scanning time. Three EPI series were collected from all participants, and they underwent MRI scans with their eyes closed, but not sleeping.

## Functional MRI Data Acquisition and Preprocessing

Resting-state functional images were preprocessed through Statistical Parametric Mapping SPM12<sup>1</sup> and the toolbox for Data Processing Assistant and Analysis for Brain Imaging<sup>2</sup> software.

Steps could be briefly generalized as follows: (a) Remove the first 10 time point functional images to achieve equilibrium because of lack of adaptation to the scanning environment and unstable initial MRI signal. (b) The intra-volume temporal mismatch and intervolumetric spatial displacement were subsequently corrected. EPIs were normalized to the Montreal Neurological Institute (MNI) standard space and resampled to a resolution of  $3 \times 3 \times 3 \text{ mm}^3$ . Normalized images were smoothed spatially with a  $6 \times 6 \times 6 \text{ mm}^3$  full width at a half maximum Gaussian kernel. Denoising methods were applied, including bandpass filtering and nuisance covariate regression (linear trend, Friston 24-parameter head motion parameters, white matter signal, cerebrospinal fluid, and global signal). Subjects with head motion that exceeded the maximum displacement of 2 mm at each axis and an angular motion of  $2^\circ$  for each axis ( $x$ ,  $y$ ,  $z$ , pitch, roll, and yaw) were excluded from further analysis. Using this criterion, seven AR subjects and three control subjects were excluded, which resulted in 20 AR and 20 control subjects.

## Amplitude of Low-Frequency Fluctuation

The BOLD time series for each voxel was first converted to the frequency domain using fast Fourier transform. The square root of the power spectrum was subsequently computed and averaged across the specified frequency range (0.01–0.08 Hz) at each voxel. The averaged square root was considered the ALFF. Finally, this value was transformed using Fisher's  $z$  transformation amplitude of low-frequency fluctuations ( $z\text{ALFF}$ ) and used for subsequent group-level analysis. Calculations were performed using REST software version 1.8<sup>3</sup>. Then, the mean ALFF value was extracted by averaging the ALFF values over all voxels for each individual.

## Statistical Analysis

Demographic and clinical data such as age, gender, year of education, disease duration, VAS score, and RQLQ score were analyzed using the Statistical Package for the Social Sciences version 26.0 (IBM Corporation, Armonk, NY, United States) between the two groups. The two-tailed  $t$ -test was performed for variables and the statistical threshold set at  $p < 0.05$ .

The two-sample  $t$ -test was used to compare the  $z\text{ALFF}$  values in each voxel of the two groups (two-tailed, voxel-level:

$p < 0.01$ ; Gaussian random field theory correction, cluster-level:  $p < 0.05$ ). Pearson's correlation analysis was used to investigate the relationship between the mean ALFF values in different brain regions and clinical performance for AR patients. Spearman's correlation analysis was employed to investigate the

**TABLE 1** | Demographic and clinical characteristics between allergic rhinitis (AR) patients and the healthy control (HC) group.

Characteristics	HC (n = 20)	AR (n = 20)	p-value
Age (years)	32.3 ± 9.1	37.1 ± 8.3	0.104
Male/female (n)	9/11	9/11	–
Education (years)	15.2 ± 1.6	14.2 ± 3.7	0.291
VAS scores	–	46.6 ± 12.5	–
Overall	–	7.9 ± 2.2	–
Sneezing	–	7.3 ± 2.3	–
Rhinorrhea	–	7.2 ± 2.9	–
Itching	–	6.1 ± 2.9	–
Congestion	–	7.7 ± 2.7	–
Eye itching	–	6.0 ± 1.6	–
Lacrimation	–	4.8 ± 2.3	–
Impact on life	–	7.6 ± 2.3	–
RQLQ scores	–	95.5 ± 28.9	–
Activity limitation	–	10.3 ± 3.9	–
Reading	–	3.2 ± 1.8	–
Practice	–	2.9 ± 1.7	–
Social activities	–	4.2 ± 1.7	–
Sleep disturbance	–	9.9 ± 5.8	–
Difficulty getting to sleep	–	3.4 ± 2.1	–
Wake up during the night	–	2.9 ± 2.2	–
Restless	–	3.7 ± 2.2	–
Non-nasal/eye symptoms	–	22.6 ± 10.0	–
Fatigue	–	3.7 ± 2.0	–
Thirsty	–	3.0 ± 2.2	–
Productivity degradation	–	2.9 ± 1.9	–
Tired	–	3.4 ± 2.0	–
Attention deficit	–	3.5 ± 1.4	–
Headache	–	2.9 ± 1.8	–
Exhausted	–	3.4 ± 2.0	–
Practical problems	–	13.4 ± 5.4	–
Have to carry tissues	–	4.4 ± 1.9	–
Need to rub nose/eyes	–	4.5 ± 1.9	–
Need to blow nose	–	4.5 ± 1.8	–
Nasal symptoms	–	16.4 ± 5.1	–
Congestion	–	4.7 ± 1.7	–
Rhinorrhea	–	4.5 ± 1.7	–
Sneezing	–	4.6 ± 1.5	–
Postnasal drip	–	2.7 ± 2.1	–
Eye symptoms	–	10.3 ± 5.3	–
Eye hyperemia	–	2.2 ± 2.0	–
Lacrimation	–	2.9 ± 1.8	–
Eye ache	–	1.7 ± 1.4	–
Eye itching	–	3.6 ± 1.5	–
Emotional function	–	11.2 ± 4.8	–
Depression	–	1.5 ± 1.5	–
Impatient or restless	–	3.2 ± 1.7	–
Irritable	–	2.7 ± 2.2	–
Embarrassed	–	3.9 ± 1.8	–

VAS, visual analog scale; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

<sup>1</sup><http://www.fil.ion.ucl.ac.uk/spm/>

<sup>2</sup><http://rfmri.org/dpabi>

<sup>3</sup>[www.restfmri.net](http://www.restfmri.net)

**TABLE 2** | Two-sample *t*-test differences between AR patients and HCs using the ALFF method.

Brain region	R/L	No. of voxels	MNI (x, y, z)			Peak
AR < HC						
PCUN	L	105	0	-66	36	-5.1729
AR > HC						
ACC	L	61	-6	39	-6	4.7576

AR, allergic rhinitis; HCs, healthy controls; ALFF, amplitude of low-frequency fluctuation; FWE, family-wise error; R/L, right/left hemi-cerebrum; MNI, Montreal Neurological Institute; PCUN, precuneus; ACC, anterior cingulate cortex.  $p < 0.01$ , cluster level;  $p < 0.05$ , FWE correction.

correlation between the ALFF *z*-values in the precuneus (PCUN) and specific IgE. Partial correlation analyses were performed in the comparisons above, excluding the effects of gender, age, and years of education. A *p*-value < 0.05 was considered to represent a significant difference.

## RESULTS

### Demographic and Clinical Data

There were no significant differences in age or sex between the HC and AR groups ( $p > 0.05$ ; see **Table 1**). **Table 1** provides the demographics of the samples and the VAS and RQLQ scores.

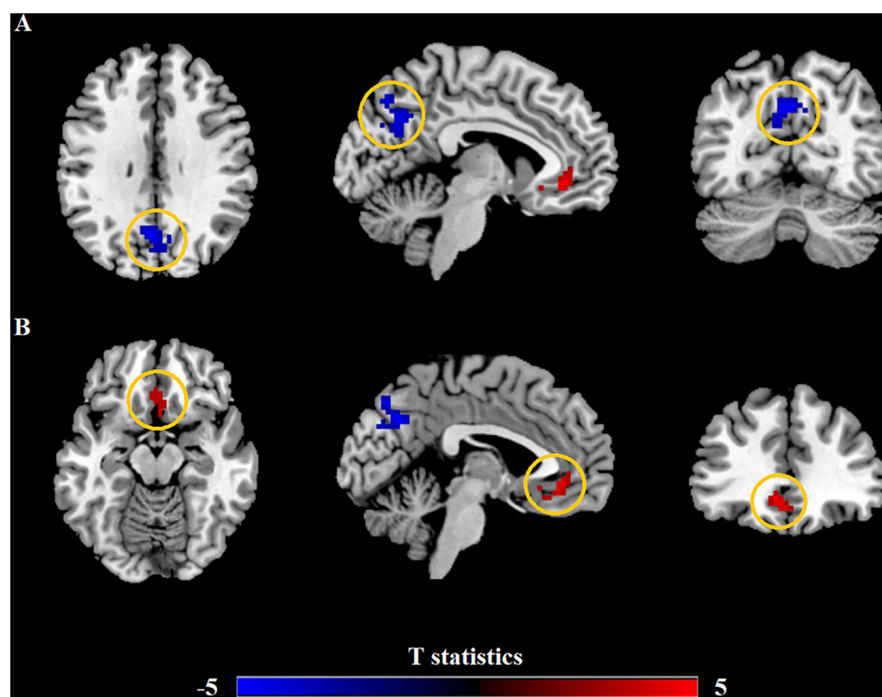
### ALFF Alterations Between AR Patients and HCs

Relevant information of the mean ALFF values is shown in **Table 2** and the visual images shown in **Figure 1**. Our findings revealed that AR patients showed significantly lower ALFF values in the PCUN and significantly higher ALFF values in the anterior cingulate cortex (ACC) compared to the HCs. The average ALFF *z*-values of the altered brain regions are shown in **Figure 2**, and the difference was statistically significant.

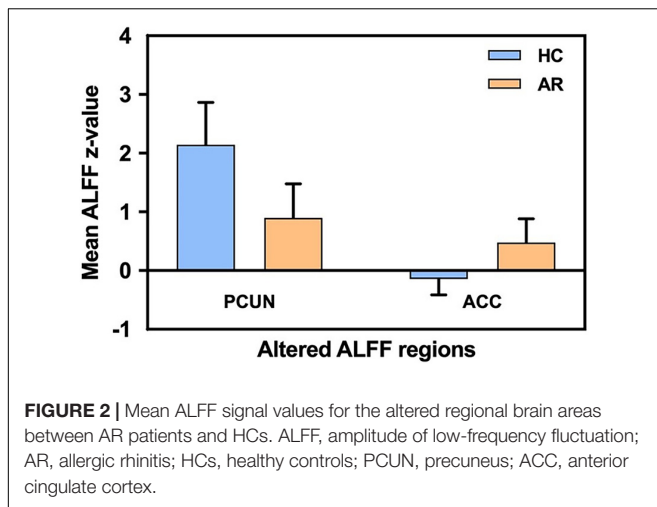
### Correlation Results

Correlation analysis revealed that the mean ALFF values in the PCUN displayed significant positive correlations with the VAS ( $r = 0.562$ ,  $p = 0.019$ ) and RQLQ ( $r = 0.623$ ,  $p = 0.008$ ) scores. Moreover, the ALFF values in the PCUN also had significant positive correlations with the RQLQ subscale of non-nasal/eye symptoms ( $r = 0.683$ ,  $p = 0.003$ ) and emotional function ( $r = 0.647$ ,  $p = 0.005$ ), as shown in **Figure 3**. There was no significant correlation between the ALFF values in the PCUN and other subscales ( $p > 0.05$ ).

The mean ALFF values in the ACC displayed significant positive correlations with the VAS score ( $r = 0.572$ ,  $p = 0.016$ ) and the RQLQ subscale of practical problems ( $r = 0.571$ ,  $p = 0.017$ ), as shown in **Figure 4**. However, no significant correlation was observed between the mean ALFF values in the ACC and other subscales of the RQLQ score ( $p > 0.05$ ).



**FIGURE 1** | Differences in the amplitude of low-frequency fluctuation (ALFF) between allergic rhinitis (AR) patients and the healthy control (HC) group. **(A)** The AR group showed significant lower ALFF values in the left precuneus (PCUN, in blue) compared with the HC group. Clusters in blue also included part of the right PCUN (16 voxels) and bilateral cuneus (25 voxels). **(B)** The AR group showed significant higher ALFF values in the left anterior cingulate cortex (ACC, in red) compared with the HC group. Clusters in red also included part of the bilateral medial orbital superior frontal gyrus (16 voxels), bilateral rectus (16 voxels), and bilateral olfactory (8 voxels).  $p < 0.01$ , cluster level;  $p < 0.05$ , family-wise error (FWE) correction.

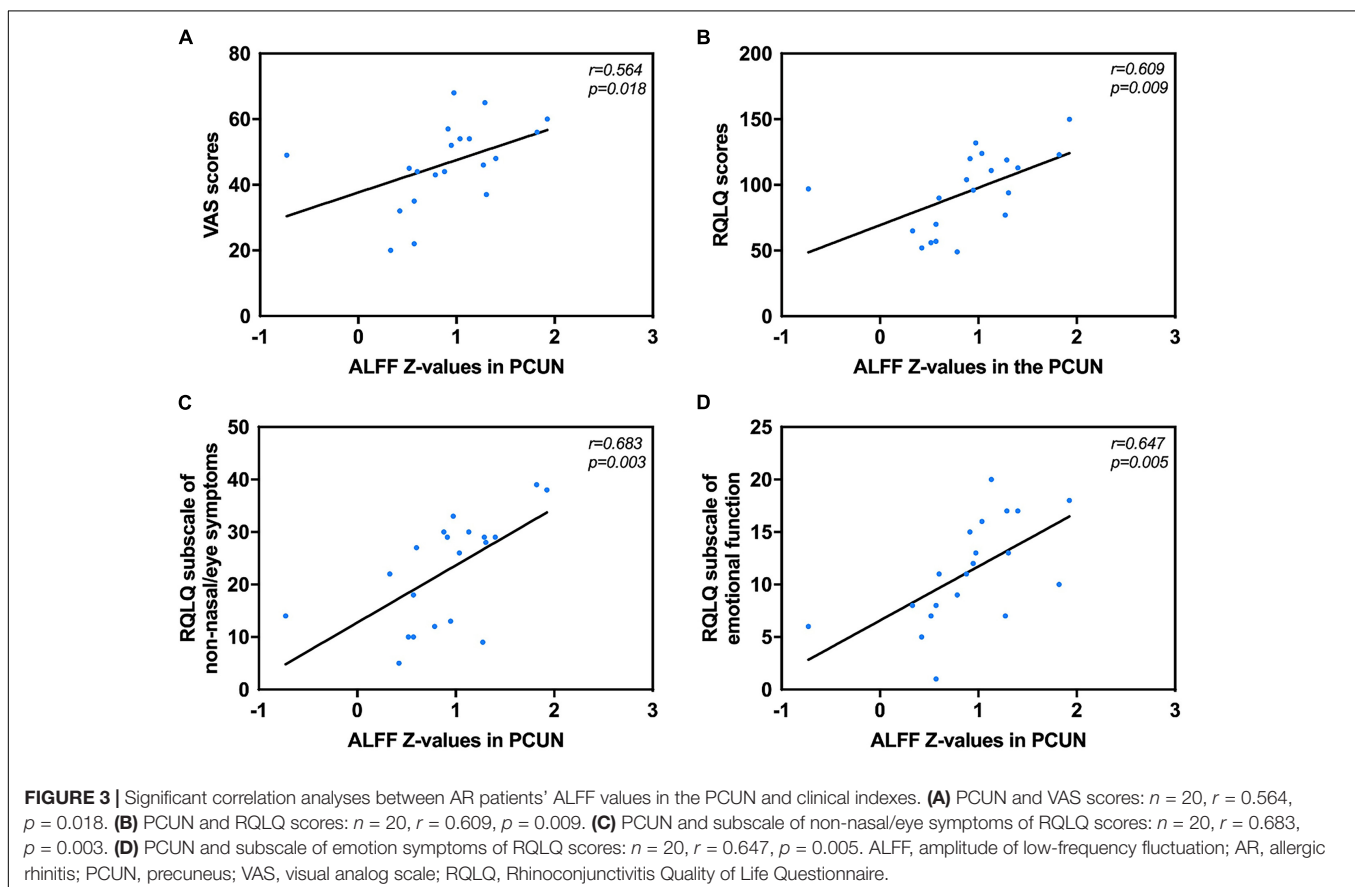


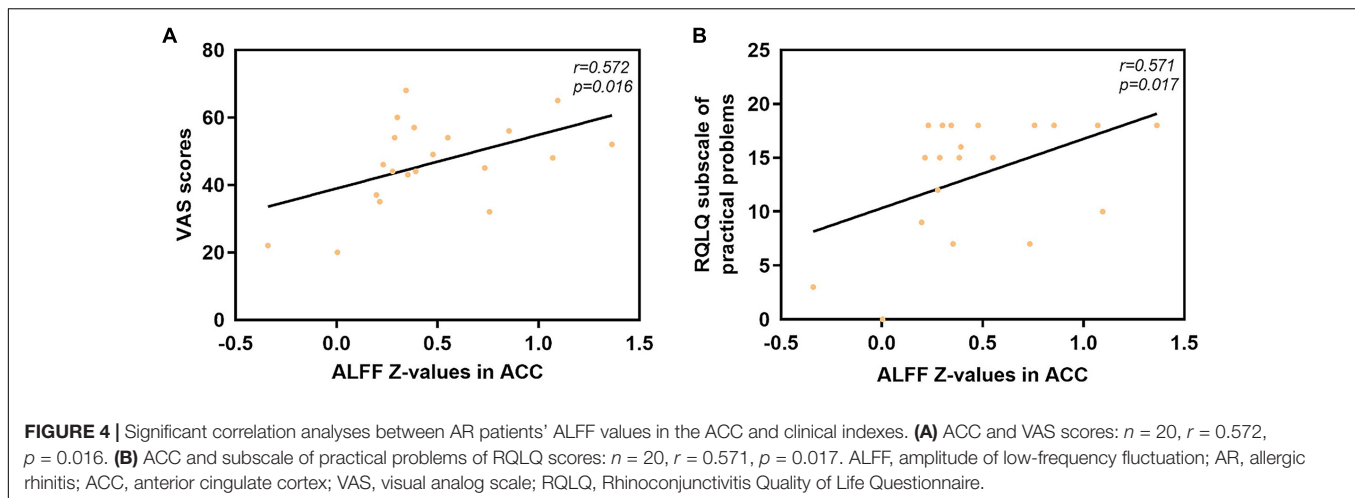
We also analyzed the fMRI results and the indexes of allergy. We found significant positive correlations between AR patients' ALFF in the PCUN and the specific IgE results ( $r = 0.743$ ,  $p < 0.001$ ), as shown in **Figure 5**. However, the correlation analysis between disease duration and the ALFF values in the PCUN and ACC showed insignificant results (PCUN:  $r = 0.254$ ,  $p > 0.05$ ; ACC:  $r = 0.022$ ,  $p > 0.05$ ), as shown in **Figure 6**. Additionally, we also performed a multivariate linear regression

analysis on ALFF z-values in the PCUN ( $F = 41.150$ ,  $R^2 = 0.864$ ) and ACC ( $F = 24.383$ ,  $R^2 = 0.787$ ), as shown in **Table 3**.

## DISCUSSION

Brain-related symptoms are an important part of AR. By the statistics of the keyword search results in PubMed and Google Scholar databases, we found that several brain-related symptoms in AR have been mentioned frequently, especially in recent years, as shown in **Figure 7**. Epidemiologic studies showed that a diagnosis of major depressive disorder is 1.7 times higher in AR patients compared to that in non-allergic subjects (Cuffel et al., 1999; Hurwitz and Morgenstern, 1999). Despite anxiety and depression, disorders relating to cognition, attention, and memory in AR are also common clinically. A cross-sectional study found that allergic rhinitis was associated with loss of energy and concentration difficulty (Robles-Figueroa et al., 2020). Kremer et al. illustrated that AR was related to a significantly impaired psychological wellbeing and perceived impaired cognitive functioning (Kremer et al., 2002). Pollen-allergic AR patients delivered an increased amount of total errors in specific measurements of spatial working memory during the pollen season compared to those in the control group (Papapostolou et al., 2020). It has been shown that untreated allergic patients experience a subtle slowed speed of cognitive





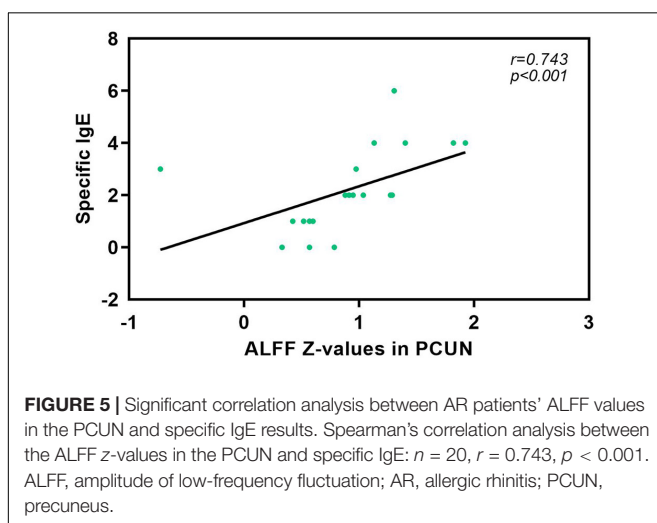
processing (Marshall et al., 2000). Moreover, recent studies have proposed that pediatric allergic airway disease was associated with declines in cognitive function and school attendance (Yamasaki et al., 2020). As for attention deficits, AR is also reported to be closely related to attention-deficit hyperactivity disorder (ADHD) in previous studies (Brawley et al., 2004; Melamed and Heffron, 2016; Yang et al., 2016; Feng et al., 2017; Miyazaki et al., 2017; Wang et al., 2018; Chen et al., 2019; Guo et al., 2020). Children with ADHD were found to be more likely to have AR than are their counterparts (Miyazaki et al., 2017). Brain-related symptoms like cognitive impairment (CI), mood changes, and attention deficits also exist in other allergic diseases such as asthma and atopic dermatitis. It is worth mentioning that CI was largely observed in adults with asthma (Rhyou and Nam, 2020). Additionally, patients with vasomotor rhinitis also suffer from psychological damage (Zheng et al., 2020).

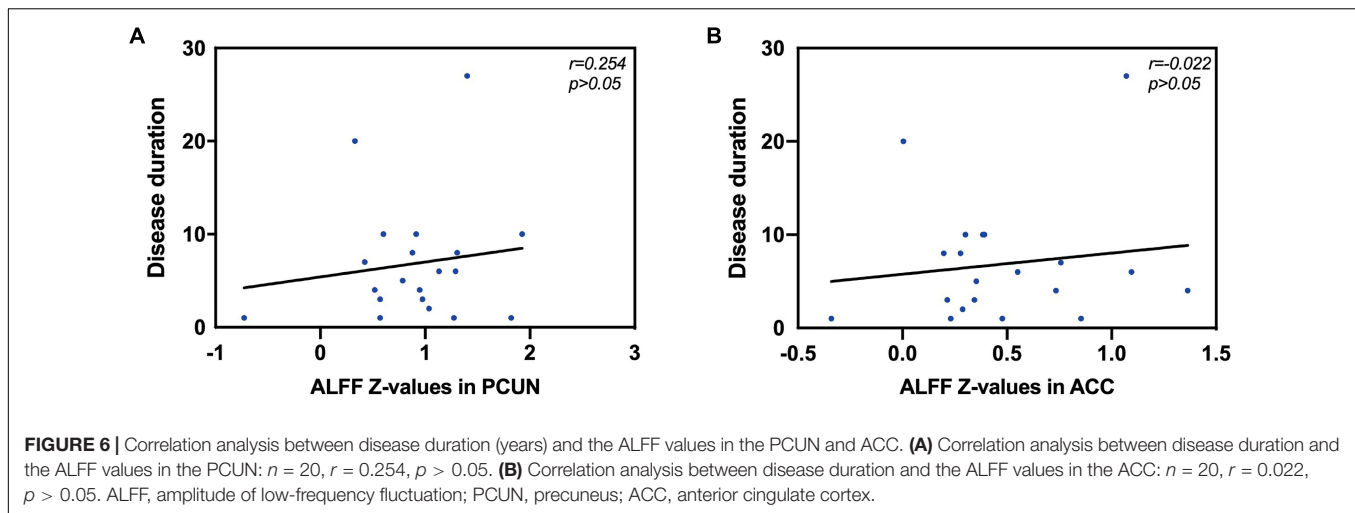
However, most of these studies are based on one-item self-reports regarding the absence or presence of brain-related symptoms and, therefore, lack a subjective and visualized assessment of psychological impairments in AR patients. The

underlying pathophysiological mechanisms of clinically relevant psychological disorders in AR patients remain elusive as well. rs-fMRI might provide a tool for visualizing the changes of the different brain regions in AR.

In this study, we report on the changes in resting-state spontaneous brain activity in AR patients. ALFF analysis was used to investigate alterations of the BOLD signal and the correlation between brain areas and clinical data. We found that AR patients mainly exhibited a significant lower ALFF in the PCUN and a significant higher ALFF in the ACC. Moreover, the ALFF values showed significant correlations with clinical indexes, and the ALFF in the PCUN reflected positive correlations with the specific IgE results of AR patients. Patients with AR may experience changes in brain function, and these changes may result in CI, memory degradation, anxiety–mood disorder, and attention deficits. The connections between the brain-related symptoms and brain function regions are shown abstractly in **Figure 8** in the form of a Sankey diagram and related to our results in the brain map. To our knowledge, this is the first report on the resting-state spontaneous brain activity in AR patients showing the activation of different brain regions and providing important information about the brain circuitry changes of AR patients.

The PCUN stands out for its distinctive role in fundamental cognitive functioning (Cavanna and Trimble, 2006). Studies have revealed that PCUN activation increased during memory retrieval (Fletcher et al., 1995; Maddock et al., 2001; Lundstrom et al., 2005; Hebscher et al., 2020), emotion processing (Fletcher et al., 1995; Maddock et al., 2001, 2003; Lundstrom et al., 2005; Cavanna and Trimble, 2006; Hebscher et al., 2020), and reward monitoring (Hayden et al., 2008). It was demonstrated that the PCUN plays an important role in memory and novelty detection (Lundstrom et al., 2003; Gur et al., 2007; Kafkas and Montaldi, 2014; Gilmore et al., 2015), especially during episodic (Fletcher et al., 1995; Maddock et al., 2001; Lundstrom et al., 2005) and autobiographical (Addis et al., 2004; Eustache et al., 2004) memory tasks within the regions of the default mode network (DMN) (Li et al., 2019). The DMN appears to play a commanding role in the large-scale functional





**TABLE 3 |** Estimation results of the multivariate linear regression coefficients on the ALFF z-values in the PCUN and ACC.

Factor	B	Standard error	t	p	VIF
Constant	-0.418	0.172	-2.424	0.028	-
VAS score	0.011	0.005	2.148	0.047	2.287
RQLQ score	0.006	0.002	2.526	0.022	3.149
Specific IgE	0.118	0.037	3.231	0.005	2.134
*The dependent variable for the above data is the ALFF z-value in the PCUN ( $F = 41.150$ , $R^2 = 0.864$ )					
Constant	-0.855	0.167	-5.123	0.000	-
VAS score	0.018	0.005	3.880	0.001	1.903
RQLQ score	0.004	0.002	2.123	0.050	2.045
Specific IgE	0.039	0.029	1.321	>0.05	1.304
*The dependent variable for the above data is the ALFF z-value in the ACC ( $F = 24.383$ , $R^2 = 0.787$ ).					

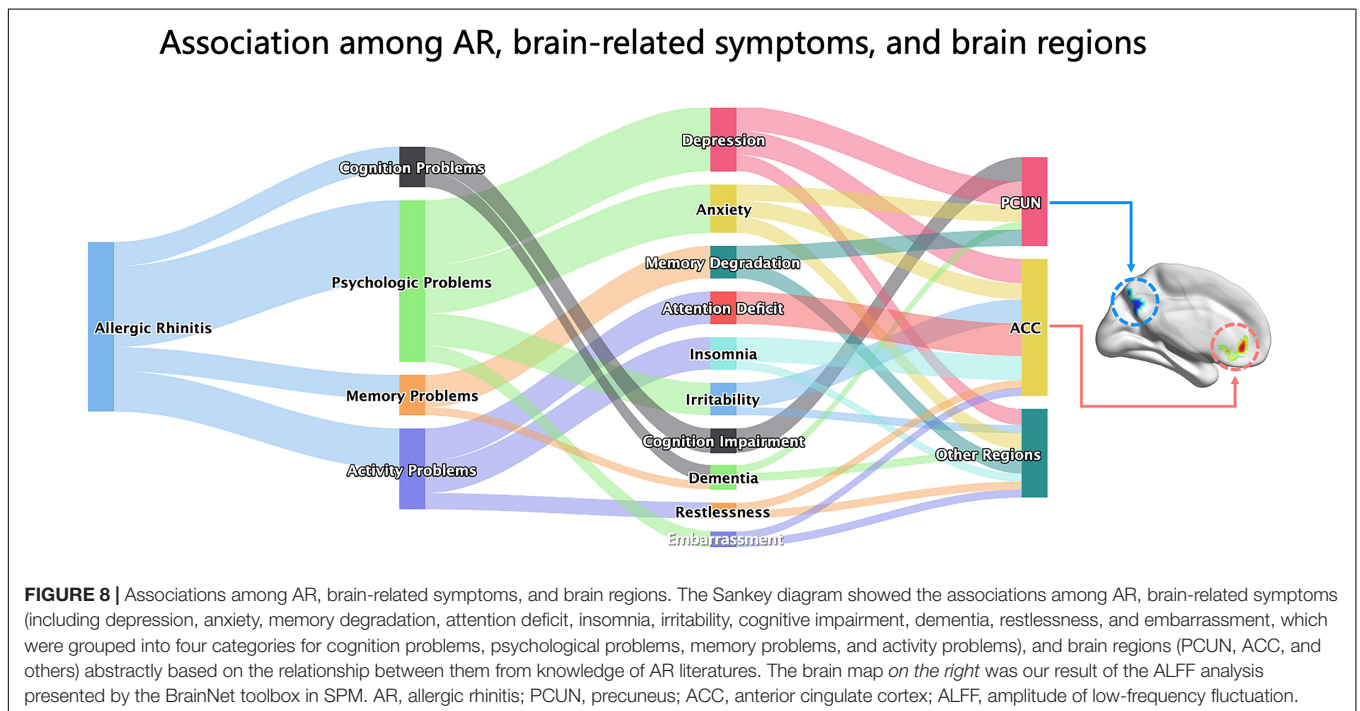
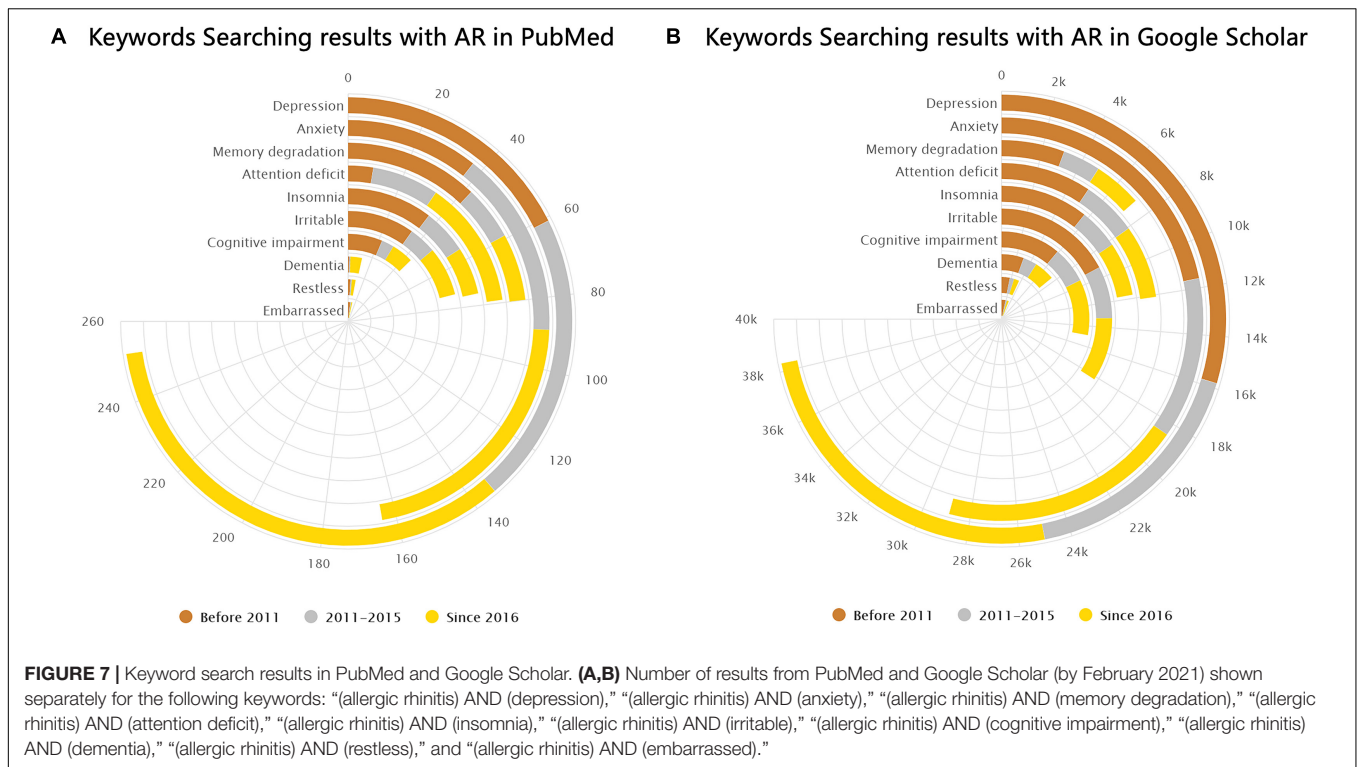
VIF, variance inflation factor; VAS, visual analog scale; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; IgE, immunoglobulin E.

organization in the resting state without tasks (Raichle, 2015), which is closely related to brain functions such as monitoring the internal and external environments, maintaining consciousness awakening, emotional processing, self-introspection, and extraction of episodic memory (Andrews-Hanna, 2012). The PCUN is also one of the brain areas associated with anxiety (Lai, 2018), sleep, and depressive problems, together with the orbitofrontal cortex (OFC) (Cheng W. et al., 2018). Consistently, the OFC is related to the olfactory system and has increased functional connectivity with the PCUN, as shown in an fMRI study (Cheng et al., 2016). Olfactory function was correlated with OFC in Alzheimer's dementia and Parkinson's disease dementia (Lee et al., 2020), which indicates that the PCUN closely relates to the olfactory system and neurodegeneration-related functions.

The ACC has a near-ubiquitous presence in the neuroscience of cognition within the region of the limbic system (Shenhav et al., 2013; Rolls, 2019). It has been implicated in a diversity of functions, from reward processing and performance monitoring to the execution of control and action selection (Shenhav et al., 2013). The ACC also receives information from the OFC about reward and non-reward outcomes. It is involved in emotion for it connects rewards to actions (Rolls, 2019). The ACC is a critical hub for mood disorders (Barthas et al., 2015) and is involved

in the appraisal and expression of negative emotion, especially depression, anxiety, and fear (Etkin et al., 2011; Godlewska et al., 2018; Rolls et al., 2019). Irritability is a common clinical problem in AR patients. The ACC was found to present hyperactivity in irritable youth (Leibenluft, 2017). Attention deficit was also found to have a relationship with ACC, as mentioned above in ADHD (Bauer et al., 2018; Naaijen et al., 2018; Vogt, 2019), which was consistent with our clinical findings of concentration disorders in AR patients. Fatigue (Capuron et al., 2005) and embarrassment (Sturm et al., 2013; Morita et al., 2014) were reported to have a connection with ACC as well. Besides, a pharmacological MRI design was undertaken in AR patients allergic to house dust mite, and the results showed that several brain regions, including the ACC, were activated after nasal histamine provocation (Callebaut et al., 2020). However, rs-fMRI is more reflective of a patient's usual functional brain activity than is task-state functional MRI.

Our neuroimaging results also corresponded with our clinical findings. In this study, we showed significant correlations between the ALFF values of AR patients and clinical indexes. We found that the VAS scores, RQLQ scores, and the RQLQ subscales of "non-nasal/eye symptoms and emotional function" had positive correlations with the



ALFF in the PCUN. As shown in **Table 2**, non-nasal/eye symptoms include indexes of “fatigue, thirsty, productivity degradation, tired, attention deficit, headache, and exhausted” and emotional function includes indexes of “depression, impatient or restless, irritable, and embarrassed.” In the ACC, we found that the VAS scores and the RQLQ subscale of

practical problems including indexes of “have to carry tissues, need to rub nose/eyes, and need to blow nose” had positive correlations. Moreover, we found that the specific IgE index had positive correlations with the ALFF values, which indicated the potential relationship between allergic immunological abnormalities and the brain-related symptoms of AR patients.



In addition, we also found statistically significant effects of the VAS scores, RQLQ scores, and specific IgE on the ALFF values in the PCUN and ACC through multivariate linear regression analysis, as shown in **Table 3**. These associations suggest that more severe clinical symptoms would indicate stronger functional brain activity.

Given the evidence for the relationship between allergic rhinitis and brain-related symptoms, the possible pathogenesis might include, but is not limited to, the following perspectives: (1) physiological effects—the physiological role of nasal obstruction and its impairing impact on sleep may, together, subsequently affect psychiatric symptoms negatively (Léger et al., 2006; Fang et al., 2010); (2) cytokines—pro-inflammatory cytokines could access the central nervous system and interact with a cytokine network in the brain, which may virtually influence every aspect of brain-related behavior through different pathways (Capuron and Miller, 2011); (3) neuroinflammation—the involvement of the microglia and astrocytes in the initiation of both pro- and anti-inflammatory events indirectly points toward the degeneration of neurons (De Virgilio et al., 2016; Gelders et al., 2018; Passamonti et al., 2019); and (4) genetics—there exists a possible shared genetic risk between allergic disorders and depression (Wamboldt et al., 2000).

Our study also has limitations and caveats. The number of our case samples was small, which limited our comprehensive understanding of the relationship between the activated brain regions and the severity of AR. Moreover, we did not conduct a cognitive or psychological analysis using professional scales or a questionnaire for each patient. We will continue to collect clinical samples for further research. To the best of our knowledge, our current study is one of the first resting-state functional neuroimaging studies in the field of allergic rhinitis and is one of the first studies to connect clinical indexes with fMRI values. According to our results, early intervention and therapy for brain-related symptoms in AR will be recommended. AR patients, otherwise, may have a risk of AD or other neurodegeneration diseases.

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## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human Research Ethics Committee of Renmin Hospital of Wuhan University (Wuhan, China). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

ZG and YX designed the whole study. RX, WZ, and LT selected the patients, analyzed the data, and prepared the questionnaires. XC and ZG performed the scanning for participants. PL undertook the statistical analysis. WF and HL participated in the interpretation of data. ZG and HL wrote the manuscript. PL and YX revised the manuscript. All authors read and approved the final manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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