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# Smoking Related Attention Alteration in Chronic Obstructive Pulmonary Disease-Smoking Comorbidity

**Feiyan Zeng**
The First Affiliated Hospital of USTC: Anhui Provincial Hospital
**Wei Hong**
University of Science and Technology of China
**Rujing Zha**
University of Science and Technology of China
**Ying Li**
University of Science and Technology of China
**Ying Liu**
The First Affiliated Hospital of USTC: Anhui Provincial Hospital
**Hao Liu**
University of Science and Technology of China
**Mengqiu Liu**
The First Affiliated Hospital of USTC: Anhui Provincial Hospital
**Mei Liu**
The First Affiliated Hospital of USTC: Anhui Provincial Hospital
**Fei Xu**
The First Affiliated Hospital of USTC: Anhui Provincial Hospital
**Daiju Hu**
The First Affiliated Hospital of USTC: Anhui Provincial Hospital
**Hongwen Song**
University of Science and Technology of China
**Yongqiang Yu**
The First Affiliated Hospital of USTC: Anhui Provincial Hospital
**Xiaochu Zhang** ( zxcustc@ustc.edu.cn )
University of Science and Technology of China https://orcid.org/0000-0002-7541-0130

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# Smoking related attention alteration in Chronic Obstructive Pulmonary Disease-Smoking Comorbidity

**Feiyan Zeng[1], Wei Hong[2], Rujing Zha[2*], Ying Li[2], Ying Liu[1], Hao Liu[3], Mengqiu Liu[1], Mei Liu[1], Fei Xu[1], Daiju Hu[1], Hongwen Song[2], Yongqiang Yu[4*], Xiaochu Zhang[2*]**

[1] The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230001, China.

[2] Key Laboratory of Brain Function and Disease, Chinese Academy of Sciences, School of Life Sciences, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230027, China.

[3] School of Earth and Space Science, University of Science and Technology of China, Hefei, Anhui, 230027, China.

[4] Department of Radiology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, 230022, China.

**CORRESPONDENCE TO**

Rujing Zha, E-mail: zharj@ustc.edu.cn (R. Zha)

Yongqiang Yu, E-mail: cjr.yuyongqiang@vip.163.com (Y. Yu).

Xiaochu Zhang, E-mail: zxcustc@ustc.edu.cn (X. Zhang), Tel: +86-551-63607295

**Co-first author**

Feiyan Zeng, Wei Hong and Rujing Zha are co-first authors

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**Abstract**

Chronic obstructive pulmonary disease is a respiratory disease that causes a wide range of cognitive impairments. Although chronic obstructive pulmonary disease-smoking comorbidity is common, the relationship between smoking and cognitive function in chronic obstructive pulmonary disease-smoking comorbidity remains unclear. In this study, we recruited 85 participants, including 42 patients with Chronic obstructive pulmonary disease(20 smokers and 22 non-smokers) and 43 healthy participants(22 smokers and 21 non-smokers). And we used the Montreal Cognitive Assessment scale and resting-state functional magnetic resonance imaging to explore effects of smoking on attention in patients with chronic obstructive pulmonary disease. Behavioral analysis revealed that smokers had a shorter course of chronic obstructive pulmonary disease and showed a worse attention performance in chronic obstructive pulmonary disease-smoking comorbidity compared to non-smokers. Resting-state functional magnetic resonance imaging analysis revealed that smokers showed lower regional homogeneity value of the fusiform gyrus in chronic obstructive pulmonary disease-smoking comorbidity than non-smokers. Importantly, the regional homogeneity of the fusiform gyrus was positively associated with attention and mediates the effect of smoking on attention in chronic obstructive pulmonary disease. In summary, our study provides behavioral and neurobiological evidence supporting the positive effect of smoking on attention in chronic obstructive pulmonary disease. This may be helpful for understanding and treating chronic obstructive pulmonary disease and even other diseases comorbid with smoking.

**Key words:** Chronic obstructive pulmonary disease, smoking, comorbidity, attention ability, functional magnetic resonance imaging

## 1. Introduction

Chronic obstructive pulmonary disease(COPD) is a chronic respiratory disease and one of the leading causes of morbidity and mortality worldwide(Spilling et al., 2019). It is characterized by persistent respiratory symptoms and limited airflow(Borson, 2008; Martinez, Richardson, Han, & Cigolle, 2014; Roncero, Campuzano, Quintano, Molina, & Miravitlles, 2016) and is an independent risk factor for cognitive impairment(Orua, 2013; Roberto, Luca, Silvia, Fernanda, & Paola, 2014). Poor cognitive function in patients with COPD may result in a greater risk of hospitalization, longer hospital stays, and worsening health status, which may lead to an increased mortality rate(Dodd, Charlton, Van, & Jones, 2013; Fix, Daughton, Kass, & Bell, 2009). Therefore, it is of great clinical significance to explore the mechanism of impaired cognitive function in COPD patients.

Smoking has been recognized as the leading cause of chronic obstructive pulmonary disease, as the long-term stimulation of cigarette smoke eventually leads to COPD(Eltom, Stevenson, & Birrell, 2013; Forey, Thornton, & Lee, 2011). Studies have shown that approximately 80%~90% of COPD patients have a history of smoking, and half of smokers will eventually develop COPD(Lundbäck, Lindberg, & Lindström, 2003). Despite the prevalence of the comorbidity between COPD and smoking, the role

of smoking in cognition and brain damage in COPD-smoking comorbidity is largely unclear.

A line of studies has demonstrated the existence of cognitive impairments in COPD. A recent review found that COPD patients were commonly exhibit deficits in attention, memory, executive function, psychomotor function, and language(Olaithe, Bucks, Hillman, & Eastwood, 2018). Specifically, compared former smokers with and without COPD and found that smokers with COPD had impairment in attention, characterized by slow processing, inattention, and impulsivity(Croghan et al., 2019). And patients with COPD had insufficient attentional resources for successfully dealing with dual tasks, which led to greater gait variability(Nelly et al., 2018).

Another line of studies revealed abnormal brain structure and function in COPD patients. For example, the grey matter volume in the bilateral fusiform gyrus, bilateral calcarine, right superior temporal gyrus, right middle temporal gyrus, left precuneus and right inferior parietal lobule were significantly reduced in COPD patients compared with normal controls, and their forced vital capacity(FVC%) was closely related to the volume of cortical grey matter(Wang et al., 2017). Functional connectivity analysis found that the connectivity density of the right lingual gyrus(LG), bilateral supplementary motor area(SMA) and right paracentral lobules(PCL) was significantly reduced in COPD patients compared with normal controls(Li, Xin, Yu, Yu, & Peng, 2019). Further seed-based functional connection analysis revealed that COPD patients had decreased functional connections in the left anterior cerebellar lobe, left fusiform gyrus, right insula lobe, right inferior frontal lobe, left putamen and other regions.

Smoking is the most common cause of COPD(Forey et al., 2011). A line of studies has shown that smoking itself causes attention disability. Compared with non-smokers, smokers had an increased risk of cognitive impairment(Domino, 2008). Smoking also leads to chronic attention maintenance deficits(Konishi et al., 1999). Another line of studies revealed abnormal brain structure and function in smokers. Using smoking-related images can increase the activation of brain regions related to visual spatial attention, such as the bilateral parietal lobe and fusiform gyrus(Due, Huettel, Hall, & Rubin, 2002). Long-term smoking can cause damage to the prefrontal cortex, which leads to long-term attention maintenance regulation deficits(Konishi et al., 1999). Smokers had significantly smaller grey matter volume and lower grey matter density in the anterior cingulate, prefrontal cortex, orbitofrontal cortex, occipital lobe, temporal lobe and parahippocampal gyrus. The amount of tobacco smoke exposure was negatively correlated with the volume of the frontal lobe, temporal lobe, and cerebellum. Structural damage in the cortex and subcortical regions of smokers was associated with deficits in the brain networks of attention and working memory(Jürgen et al., 2006).

Although smoking leads to extensive damage to brain structures and function, its neuroprotective effect has been found in numerous molecular and cellular biological studies on nicotine in cigarette smoke(Ward, Lallemand, Witte, & Dexter, 2008). Nicotine also has a protective effect on dopaminergic neurons. In addition to potential neuroprotective behaviors, from learning and memory enhancement to addiction and neuroprotection, nicotine also has antidepressant properties and the ability to improve

cognitive activities such as attention(DAJASBAILADOR, 2004) and cognitive control(Evans, To, & Ashare, 2018).

On the one hand, studies on the long-term effect of smoking have shown smoking impaired attention ability(Due et al., 2002), we expect that smoking aggravates attention and neural impairment in COPD patients with a smoking comorbidity. On the other hand, research on the acute effect of smoking proved that smoking could improve attention(Ward et al., 2008), we expect that smoking may related to attention and neural impairment in COPD patients with a smoking comorbidity.

In the present study, first explored the effect of smoking on attention in COPD patients with a smoking comorbidity and located regions of interest(ROIs) whose regional homogeneity(ReHo) showed alterations in this population. Finally, tested the relationship between these brain regions and smoking and attention ability.

## 2. Materials and Methods

### Study Design

#### *2.1 Procedure*

Each subject underwent a pulmonary function test, resting-state functional magnetic resonance imaging(fMRI) scan, Montreal Cognitive Assessment(MoCA) Scale(Dalrymple-Alford et al., 2010), demographic survey and smoking behavior assessment only for smokers. Details see supplementary materials.

### *2.2 Participants*

We recruited 85 participants, including 20 smoking COPD patients(COPD-Smoking group), 22 non-smoking COPD patients(COPD-Nonsmoking group), 22 smoking healthy subjects(NonCOPD-Smoking group) and 21 non-smoking healthy subjects(NonCOPD-Nonsmoking group), shown in TableS1 and TableS2. Inclusion and exclusion criteria see supplementary materials.

### *2.3 Resting-state fMRI analysis*

#### *2.3.1 Preprocessing*

Considering the instability of the instrument and the subjects at the beginning of the scanning, the first 10 TR of the scanning were excluded. Then slice time correction was performed at the remaining time points to reduce the heterogeneity of the data at different levels due to different acquisition times. Spatial correction was performed to correct for the effect of the head motion, any TR with head motion >2.5 mm of translation or 2.0° of rotation during the scan were excluded. The resting state functional image was registered to the structure image, and the space is normalized to the MNI standard space. For nuisance signal correction, the following nuisance parameters were included as regressors within the general linear model; 6 motion parameters and their first derivatives, white matter(WM), cerebrospinal fluid(CSF) and a linear trend term. Gaussian kernel(FWHM=6mm) was used for spatial smoothing to reduce the influence of spatial noise on scanning and improve the signal-to-noise ratio.

Linear drift removal and filtering were performed. 0.01-0.1Hz frequency band was adopted to filter out physiological noise such as breathing and heartbeat.

### *2.3.2 Functional connectivity*

After processing, we obtained the time courses of the scans of the whole brain. Then, the whole brain was divided into 90 regions according to the Anatomical Automatic Labelling(AAL) parcellation atlas(Tzourio-Mazoyer et al., 2002). Each region was calculated as an average time series and then correlated with the time series of all other regions to obtain a 90*90 correlation matrix.

### *2.3.3 ReHo*

ReHo was calculated in each region by REST software(http://www.restfmri.net/). Each voxel and its adjacent voxels were selected to calculate the ReHo in the same time series, which was then assigned to the initial voxel. The ReHo values were standardized and spatial smoothed. Statistical Parametric Mapping 8(SPM8)(Ashburner & Friston, 2005) was used to perform two-sample T-tests with whole-brain and threshold using family wise error correction(FWER) at $p < 0.05$.

### *2.3.4 Node betweenness centrality*

According to graph theory, the node betweenness centrality of each brain region was calculated based on functional connectivity. Node betweenness centrality is the fraction of all shortest paths in a network that contain a given node. In this study, the node betweenness centrality was calculated by the tools implemented in the Brain Connectivity Toolbox(version 2015-01-25)(Rubinov & Sporns, 2010).

### *2.4 Statistical analysis*

Two-way ANOVA was used to analyze the effects of smoking and COPD on cognitive function. Independent samples T tests were used to compare age, years of education, smoking index, smoking history and pulmonary function(FEV1%, FVC% and FEV1/FVC) between the COPD group and the NonCOPD group, as well as the cognitive functions, smoking index, smoking history, ReHo and node betweenness centrality of brain regions between the COPD-Smoking group and the COPD-Nonsmoking group. The Cohen's d values were calculated via G*Power 3.1 software(Faul, Erdfelder, Lang, & Buchner, 2007). The $\chi 2$ test was used to compare gender between the COPD group and the NonCOPD group. Pearson's correlation was used to analyze the relationship between smoking index/smoking history and the ReHo. Kendall's tau-b correlation analysis was used to analyze the relationship between the ReHo and MoCA cognitive scores, as well as between smoking index and MoCA cognitive scores, since the MoCA scores are rank variables. Bootstrap mediation analysis(Wen, Marsh, & Hau, 2010) was used to analyze the medicating effect of ReHo on smoking index and attention. Finally, considering the imbalance of sex ratio between smokers and non-smokers, we performed covariance analysis using gender as a covariable in the analysis of attention.

## 3. Results

### *3.1 Smokers had a shorter course of COPD in COPD-smoking comorbidity compared to non-smokers*

There were no significant differences in gender, age and years of education between the COPD group and the NonCOPD group(TableS1). There was no significant differences in smoking index( $t_{40} = 0.44, p = 0.665, d = 0.136$ ) and smoking history( $t_{40} = 0.88, p = 0.383, d = 0.272$ ) between the COPD-Smoking and NonCOPD-Smoking groups .

First, we analyzed the impact of smoking on the course of COPD and found that the course of COPD in the COPD-Nonsmoking group was significantly higher than that in the COPD-Smoking group($t_{40} = 3.51, p = 0.001, d = 1.086$). Smoking occurred earlier than COPD in the COPD-Smoking group($t_{19} = 17.81, p < 0.001, d = 3.982$). However, there were no significant differences in FEV1%( $t_{40} = -0.74, p = 0.463, d = -0.229$ ), FVC%( $t_{40} = 0.81, p = 0.424, d = 0.250$ ) and FEV1/FVC( $t_{40} = -1.43, p = 0.163, d = -0.442$ ) between the COPD-Smoking group and COPD-Nonsmoking group, which suggested that COPD causes a consistent lung condition in these two group.

### *3.2 Smokers showed worse attention performance in COPD-smoking comorbidity compared to non-smokers*

To understand more about the effect of smoking on attention in COPD patients, two-way ANOVA of the MoCA score was performed and revealed a significant interaction effect (COPD × smoking)( $F_{(1,81)} = 5.91, p = 0.017, partial\ \eta^2 = 0.068$)on attention ability and a significant main effect of COPD($F_{(1,81)} = 37.94, p < 0.001, partial\ \eta^2 = 0.319$) and of smoking on the scores of attention ability($F_{(1,81)} = 4.90, p = 0.030, partial\ \eta^2 = 0.057$), which suggest that smokers showed less impairment of attention disability(Figure1). In particular, the score of attention ability( $t_{40} = 2.53, p = 0.016, d = 0.781$ ) was higher in the COPD-Smoking group than in the COPD-Nonsmoking group. In addition, the analysis of covariance including sex still showed significant interaction effects (COPD × smoking)($F_{(1,80)} = 5.82, p = 0.018, partial\ \eta^2 = 0.068$).

### *3.3 Smoker showed lower ReHo value in COPD-smoking comorbidity compared to non-smokers*

To explore the neural mechanisms of cognitive impairment in COPD, we performed whole-brain T test analysis. The results showed that the ReHo of the six clusters in the COPD group, which were located in the bilateral fusiform gyrus, left inferior temporal gyrus, left anterior cerebellar lobe, and pons, were lower than those in the NonCOPD group after FWER correction(Table1 and Figure2).

In particular, the ReHo of the left fusiform gyrus( $t_{40} = 2.09, p = 0.043, d = 0.646$ ), right fusiform gyrus( $t_{40} = 2.96, p = 0.005, d = 0.915$ ), left anterior cerebellum($t_{40} = 2.29, p = 0.027, d = 0.708$) and pons($t_{40} = 2.56, p = 0.014, d = 0.791$) were all higher in the COPD-Nonsmoking group than in the COPD-Smoking group(FigureS2).

### *3.4 ReHo and functional connectivity of the left fusiform gyrus correlate with attention ability*

Kendall's tau-b correlation analysis was used to analyze the relationship between the ReHo and MoCA cognitive scores, as well as between smoking index and MoCA cognitive scores, since the MoCA scores are rank variables. The analysis showed that the ReHo of the left fusiform gyrus( $r_{42} = 0.333, p = 0.005$ ), right fusiform gyrus( $r_{42} = 0.259, p = 0.030$ ) and left inferior temporal gyrus( $r_{42} = 0.316, p = 0.008$) were associated with attention ability in the COPD groups.

Two-way ANOVA of node betweenness centrality showed a main effect of smoking in the right fusiform gyrus($F_{(1,81)} = 4.40, p = 0.039, partial\ \eta^2 = 0.052$) and a main effect of COPD in the left fusiform gyrus( $F_{(1,81)} = 25.39, p < 0.001, partial\ \eta^2 = 0.239$) ) and right fusiform gyrus( $F_{(1,81)} = 14.79, p < 0.001, partial\ \eta^2 = 0.154$). However, there was no significant interaction effect (COPD×smoking)(FigureS3).

To further understand the role of these three brain regions(left fusiform gyrus, right fusiform gyrus, left inferior temporal gyrus) in cognitive dysfunction, we analyzed the

functional connectivity between them and all other brain regions. Kendall's tau-b correlation analysis found that the functional connectivity between left fusiform gyrus and left pallidum was positively correlated with attention ability($r_{42} = 0.253, p = 0.033$) and total MoCA score($r_{42} = 0.338, p = 0.002$) in the COPD groups.

### *3.5 Mediating analysis: ReHo of the left fusiform gyrus mediated the influence of smoking on attention ability*

To understand more about the mechanism of the impact of smoking on cognitive function in COPD patients, we analyzed the relationships between smoking index and cognitive function and the ReHo. First, Kendall's tau-b correlation analysis found that the smoking index was positively related to attention ability in COPD patients($r_{42} = 0.336, p = 0.030$), including the COPD-Smoking group and COPD-Nonsmoking group. Pearson's correlation was used to analyze the relationship between smoking index/smoking history and the ReHo, since these are all continuous variables, and found that the smoking index was negatively related to the ReHo of the left fusiform gyrus in COPD patients($r_{39} = -0.345, p = 0.025$). Mediation analysis revealed that the ReHo of the left fusiform gyrus completely mediated the effect of the smoking index on attention ability in COPD patients ( LLCI~ULCI: $-0.0002$ ~$0.0011$, BootLLCI~BootULCI： $0.0001$~$0.0008$) but not in NonCOPD group(Figure3).

## 4. Discussion

COPD is often comorbid with smoking; however, the way in which smoking modulates behavior and its neural basis in COPD-smoking comorbidity remains unclear. At the behavioral level, we found that smokers showed less attention impairment in COPD-smoking comorbidity. At the neural level, we found that the ReHo of the left fusiform gyrus completely mediated the effect of smoking on attention ability. Totally, the funding of this study suggested that smokers showed less impairment of attention ability in COPD-smoking comorbidity, which related to the function of left fusiform gyrus.

Not only is nicotine an important component in cigarettes that causes smoking addiction but it also has a protective effect on dopaminergic neurons. Neuronal nicotinic acetylcholine receptors in the brain are more often associated with neuromodulation than mediation of synaptic transmission. The complex $Ca^{2+}$ response generated by the activation of the nicotinic acetylcholine receptor can transmit information beyond the initial domain and promote the activation of many intracellular signaling pathways. These mechanisms form the basis for the diversity of nicotinic neuron activity in the brain, from the enhancement of learning and memory to addiction and neuroprotection(DAJASBAILADOR, 2004). Thus, the protective mechanism of nicotine may be responsible for the less cognitive impairment in COPD-smoking comorbidity. Moreover, smoking occurred earlier than COPD in the COPD-Smoking

group. Presumably, smoking may preempt a protective mechanism that buffers cognitive impairment in COPD-smoking comorbidity.

We found that the ReHo of the left fusiform gyrus mediates the influence of smoking on attention ability, which suggests that it may be the central brain region of the acute effect of smoking. The fusiform gyrus is an integral part of the ventral occipito-temporal conjoint brain region. Previous studies have shown that this region is widely involved in cognitive processes such as face recognition, object position and vocabulary and is associated with visual spatial attention(Han et al., 2012). Thus, the fusiform gyrus is likely a central factor in the effect of smoking on attention ability in COPD-smoking comorbidity. In addition, whole-brain analysis also found differences in left inferior gyrus, left anterior cerebellum and pons between COPD and non-COPD groups. Previous studies have shown that inferior gyrus(IFG) maybe related with the phonological information storage, behavior chosen or attention modulation(Yang, Xiao, Liu, Weng, & Zhang, 2006). And the neural network involved in the age-related decrements in memory and attention included IFG and the cerebellum(Iidaka et al., 1999), which means these brain regions may be the key factor in cognitive impairment for COPD patients.

We were also concerned about other cognitive functions in the MoCA, including visuospatial execution ability, naming ability, language ability, abstraction ability and delayed recall ability. We found that these functions were all impaired in COPD patients(Table S3). This finding is consistent with previous studies(Antonelli-Incalzi et al., 2008; Villeneuve, Pépin, Rahayel, Bertrand, & Gagnon, 2012; Zhang H, Wang X,

& Lin J, 2012). Specifically, only visuospatial execution ability and abstraction ability were significantly worse in COPD-Nonsmoking than in COPD-Smoking(FigureS1 and TableS6), but no mediation effect was found. In addition, researchers have found that smoking also harms cognitive functions independently, such as memory(Liu et al., 2013) and execution ability(Crean, Crane, & Mason, 2011). In this study, we also found that delayed recall ability was worse in the NonCOPD-Smoking group than in the NonCOPD-Nonsmoking group(FigureS1). Overall, the independent effects of smoking and COPD on other cognitive functions are consistent with previous studies. The role of smoking in the impairment of these cognitive functions in COPD patients may be similar to that in the impairment of attention ability, but the neural mechanisms remain unclear and deserve further study.

Although we aimed to ensure a high-quality study, there were still some limitations. First, there is imbalance of sex ratio between smokers and non-smokers, which is due to very low prevalence(2.7%) of female Chinese smokers and the possible influence of the menstrual cycle phase on smoking cue reactivity and cigarette craving(Franklin et al., 2015). Tring to eliminate the influence of sex on the results of this study, we performed covariance analysis on the main results using sex as a covariable, and the results was consistent(see Results). Second, the subjects in this study were older and generally less educated, which may have led to an over evaluation of the degree of cognitive decline. Third, the sample size of this study was too small to stratify disease according to severity. It is hoped that in future work, more female smokers, more

accurate indicators and larger sample sizes can be included, and stratified studies can be conducted according to the severity of the disease or other factors.

## 5. Conclusions

This study revealed the effect of smoking on attention ability in COPD-smoking comorbidity**.** Smokers showed less attention impairment in COPD-smoking comorbidity, which mediated by the ReHo of the fusiform gyrus. The results support the acute effect of smoking on behaviors in COPD-smoking comorbidity. While previous studies have tended to exclude smoking from their focus on COPD, the findings in this paper are the first to reveal the positive aspect of smoking in COPD, suggesting an important role of smoking in COPD-smoking comorbidity and potentially in other diseases.

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## Declarations


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### Competing interests

All authors claim that there are no conflicts of interest.

### Ethics approval

This study was approved by the Institutional Review Boards of University of Science and Technology of China and Anhui Provincial Hospital. And the IRB approval number is 2020-N(H)-186.

### Consent to Participate

Informed consent was obtained from all participants in the study.

### Consent to Publish

We consent to publication of this paper.

### Availability of data and materials

Additional material and all other data for this study can be available from the corresponding authors with reasonable request.

## Code Availability

Code will be provided to qualified researchers upon reasonable request.

## Author contributions

Feiyan Zeng, Wei Hong, Rujing Zha, Yongqiang Yu and Xiaochu Zhang contributed to the study design. All authors contributed to the acquisition, analysis, or interpretation of the data. Feiyan Zeng, Wei Hong, Rujing Zha and Xiaochu Zhang contributed to the critical revision of the manuscript for important intellectual content. Feiyan Zeng, Wei Hong, Rujing Zha, Ying Liu, Hao Liu contributed to the statistical analysis.

## Additional information

Additional supporting information may be found in the Supporting Information section at the end of this article.

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## Figure legends

***Figure 1***. *The attention ability of the four groups (COPD-Smoking/COPD-Nonsmoking/NonCOPD-Smoking/NonCOPD-NonSmoking) was compared (error bars: SE). The p values were adjusted by Bonferroni's correction for multiple comparisons. (*: p<0.05; **: p<0.01; ***: p<0.001).*

***Figure 2***. *The differences in the ReHo between the COPD and NonCOPD groups are shown in axial, sagittal and coronal sections. Six clusters were found on whole brain T test analysis, and the red areas indicate higher ReHo values. a) Left fusiform gyrus; b) Right fusiform gyrus; c) Left anterior cerebellum; d) Pons; e) Left inferior temporal gyrus (cluster-1); f) Left inferior temporal gyrus (cluster-2).*

***Figure 3***. *The ReHo of the left fusiform gyrus completely mediates the influence of smoking on attention ability. The regression coefficient is shown in the figure. (*: $p<0.05$; **: $p<0.01$).*

# Figures

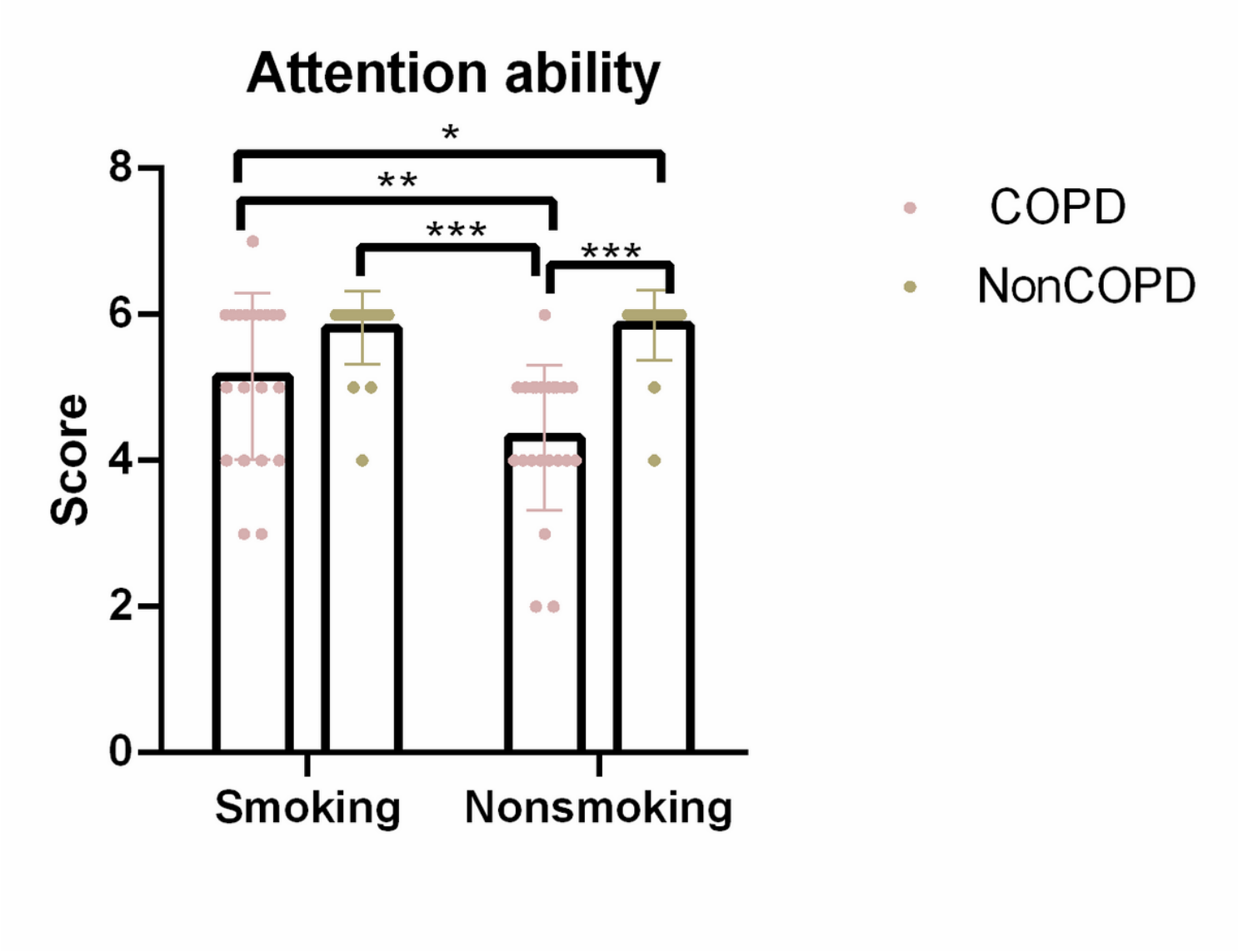


**Figure 1**

The attention ability of the four groups (COPD-Smoking/COPD-Nonsmoking/NonCOPD-Smoking/NonCOPD-NonSmoking) was compared (error bars: SE). The p values were adjusted by Bonferroni's correction for multiple comparisons. (*: $p<0.05$; **: $p<0.01$; ***: $p<0.001$).

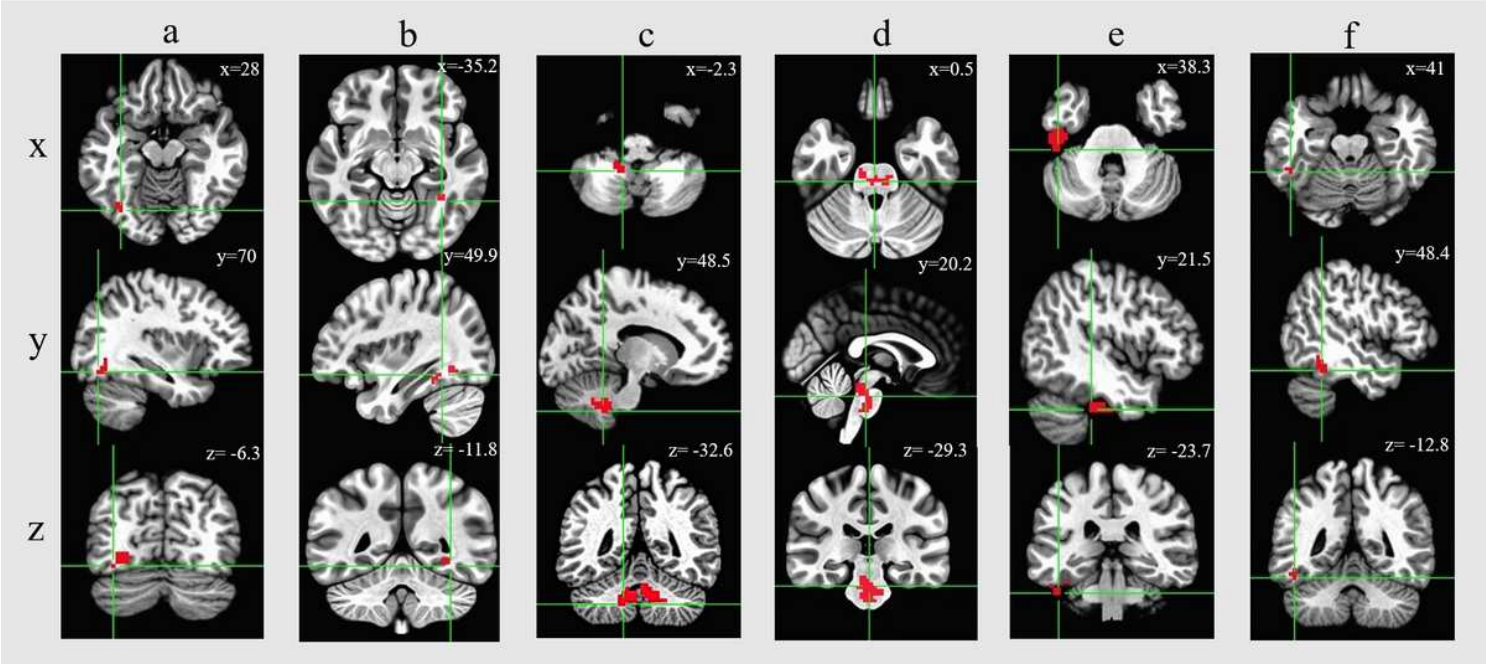


**Figure 2**

The differences in the ReHo between the COPD and NonCOPD groups are shown in axial, sagittal and coronal sections. Six clusters were found on whole brain T test analysis, and the red areas indicate higher ReHo values. a) Left fusiform gyrus; b) Right fusiform gyrus; c) Left anterior cerebellum; d) Pons; e) Left inferior temporal gyrus (cluster-1); f) Left inferior temporal gyrus (cluster-2).

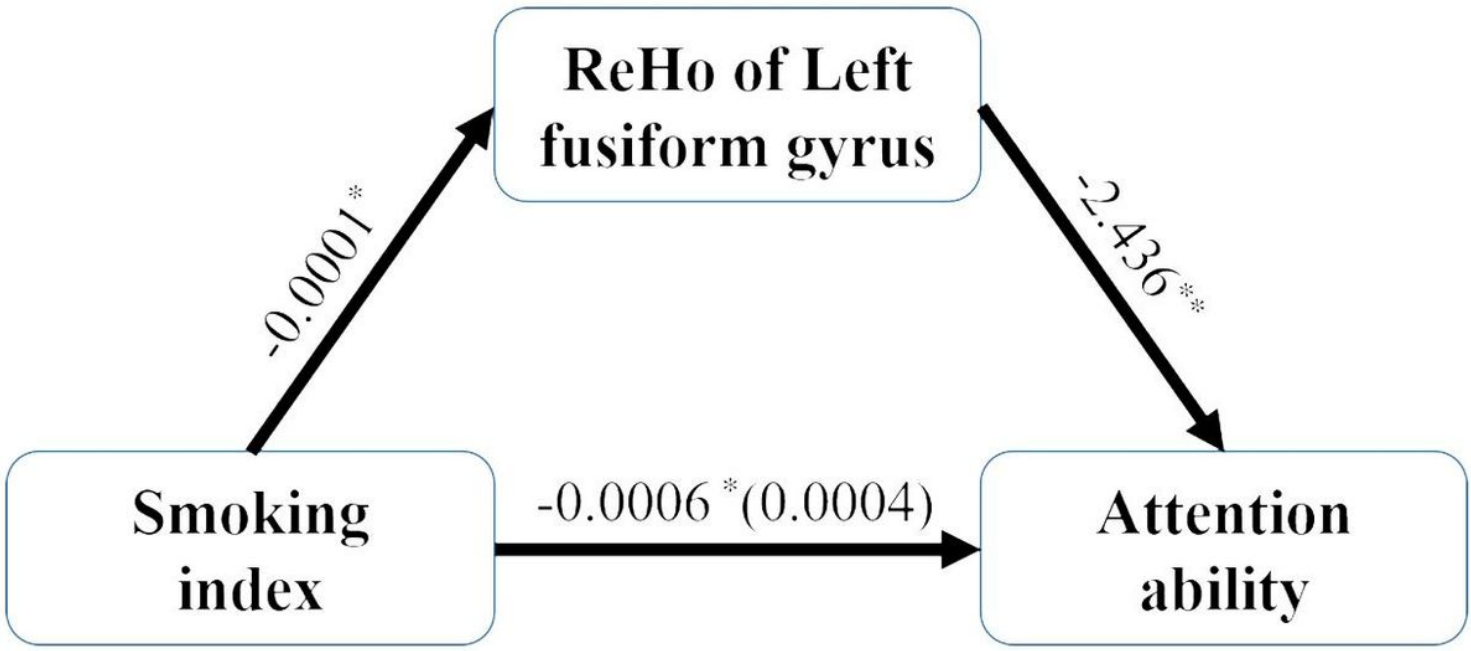

**Figure 3**

The ReHo of the left fusiform gyrus completely mediates the influence of smoking on attention ability. The regression coefficient is shown in the figure. (*: p<0.05; **: p<0.01).

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