Resting-State Cerebral Neurovascular Alterations Predict Mild Cognitive Impairment in Patients with Stable Chronic Obstructive Pulmonary Disease

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Research Article

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Abstract

Purpose

Mild cognitive impairment in chronic obstructive pulmonary disease (COPD) is receiving more and more attentions. Cerebral structural and functional abnormalities in COPD have been reported, the neurovascular coupling changes during resting state in COPD are rarely investigated. Our study was aimed to characterize neurovascular coupling changes in patients with COPD by using arterial spin labeling (ASL) and blood oxygenation level dependent (BOLD) techniques.

Methods

Forty-five stable COPD patients and forty gender- and age-matched healthy controls were recruited. And BOLD and ASL were acquired for calculating degree centrality (DC) and cerebral blood flow (CBF) respectively. The CBF-DC coupling and CBF/DC ratio were compared between the two groups.

Results

COPD patients showed abnormal CBF, DC and CBF/DC ratio in several regions. And lower CBF/DC ratio in left lingual gyrus negatively correlated with naming scores, lower CBF/DC ratio in medial frontal cortex/temporal gyrus positively correlated with MoCA, visuospatial/executive and delayed recall scores.

Conclusion

The abnormal neurovascular changes may be a possible neuropathological mechanism of mild cognitive impairment in stable COPD patients.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the most common chronic lung disease in the general population, and is manifested with chronic irreversible airway limitation. The prevalence rate of COPD is about 13.6% in China[7]. With the increase of age larger than 40, the mortality rate of chronic respiratory diseases showed the most obvious increasing trend. Notably, mild cognitive impairment is very common in patients with COPD[1].The prevalence of cognitive impairment is reported to be about 10%-77% in patients with COPD[12, 29]. And COPD increases the risk of cognitive impairment by about 2.5 times [6]. In recent years, the clinical relevance of cognitive impairment in COPD has been receiving more and more attentions.

Previous studies have shown that cerebral blood flow (CBF) is coupled with cerebral metabolism and oxygen consumption[24]. Furthermore, studies from B. Varkuti et al.[32] and P. Hagmann et al.[13] also

found positive correlation between cerebral structural hubs and CBF. fMRI techniques have been widely used to investigate the cerebral dysfunctions in the COPD patients, and provided evidences of abnormalities in the brain structure and function and their potential neural associations with cognitive impairment [3, 35, 37, 40]. However, as far as we know, very few studies have directly examined the relationship between functional network hubs and the cerebral blood supply in COPD patients. Therefore, it's unknown that whether resting state intrinsic functional network connectivity is closely related to CBF, and whether cerebral neurovascular changes is involving in the potential mechanisms underlying mid cognitive impairment of COPD patients.

CBF is defined as the delivery rate of arterial blood to the capillary bed in the cerebral tissue. Without complex confounding factors, resting state CBF is relatively easy to conduct, and is closely coupled with brain metabolism, including glucose utilization, oxygen consumption, and aerobic glycolysis[31]. The arterial spin labeling (ASL), with good reliability and reproducibility[25], has been validated against other perfusion method, and has been utilized to measure CBF in many studies [22, 28]. In addition, degree centrality (DC) is generally measured by extracting the time series of one voxel and correlating it with the time series of all the other voxels in the brain, and then calculating the summation of the resultant correlation coefficients. The DC could represent functional relationships between a voxel or region and the rest within the entire cerebral connectivity matrix (connectome) at the voxel level without requiring a priori selection.

Neurovascular coupling refers to the correlation between CBF and neuronal activity and metabolism in brain region, is a marker of cerebral function[19]. Yong He [36] has reported a correlation between the CBF measured with ASL and functional connectivity measured with BOLD in several network. The CBF-DC correlation represents the consistency of spatial distribution between blood supply and functional hubs. The CBF/DC ratio represents the cerebral blood supply per unit of connectivity hub, reflecting the neurovascular coupling. The two indices could be used to identify changes in the neurovascular coupling in COPD that cannot be detected by investigating the CBF and DC separately.

In our study, BOLD and ASL data of COPD patients and healthy subjects were acquired during resting state. BOLD data were used to identify functional hubs in the brain, and ASL data were exploited to measure CBF. The CBF-DC coupling and CBF/DC ratio were compared between the two groups, and the potential correlations between functional deficits and clinical characteristics were also investigated.

Materials And Methods

Participants

A total of eighty-five right-handed subjects were enrolled into this study, including forty-five patients with stable COPD and forty age- and gender-matched healthy controls. The patients with stable COPD were recruited from the Respiratory departments of the 960th Hospital from March 2018 to April 2019.

Inclusion criteria for COPD group were as following: (1) diagnosed according to pulmonary function test (PFT)[4]; (2) age >40 years; (3) lung function test findings indicating: FEV1/FVC 0.70, 30%≤FEV_1≤80% predicted); (4) Stable stage is defined as the absence of exacerbation (defined as hospital admission or prescription of antibiotics/systemic corticosteroids by a general practitioner) in the past 6 weeks (as same as the study of our prior study[34]). Exclusion criteria for all subjects were: (1) home O_2 therapy; (2) other pulmonary diseases, neurological disease, history of stroke or other cardiovascular and metabolic diseases, psychiatric disorder; (3) alcohol/substance abuse or dependence; (4) medicine, drinking or smoking within 24 hours before MRI examination; (5) body mass index (BMI) >30 kg/m^2; (6) any contraindication to fMRI examination.

Each subject underwent physical examination and lung function test. The Medical Research Council Dyspnea Scale (MRC) were used to quantify the degree of dyspnea[9]. Montreal Cognitive Assessment (MoCA) was used for cognitive screening. COPD severity was also assessed by using the GOLD stage.

Our work was carried out in accordance with the Declaration of Helsinki.

Data acquisition

MRI examinations were performed at a 3T MR scanner (General Electrics) with an 8-channel head coil during resting state. 3D pseudo-continuous ASL images were acquired with the following parameters: time repetition (TR)/time echo (TE) 4632 /10.5ms, slice thickness 4mm, field of view (FOV) 240 × 240, NEX 3.00, post-labeling delay 1525ms. BOLD images were also acquired (TR/TE 2000/35ms, flip angle 90°, resolution 64 × 64, FOV 240mm× 240mm, thickness 4mm, spacing 0, slices 38, 200 volumes). High-resolution structural T1-weighted scan was performed with following parameters: TR/TE 8.2/3.2ms, flip angle 12°, resolution 256 × 256, thickness 1mm. Routine MRI examination images of all participants were acquired and checked by two experienced neuroradiologists to rule out anatomic abnormalities in the brain. For the resting state, all participants were instructed to relax and keep eyes closed without thinking of anything in particular or falling asleep during scanning.

Data processing of CBF and DC

Cerebral blood flow (CBF) images underwent following preprocessing steps, including normalization into the standard Montreal Neurological Institute (MNI) space, resampling into a 3mm voxel size, smoothing with a 6mm full-width-at-half maximum Gaussian kernel (FWHM) and removing signal of white matter and cerebrospinal fluid.

Processing steps of BOLD images included format conversion, removing first 10 time points, slice timing, realign estimation, spatially coregistration, normalization into the standard MNI space, resampling into a 3 mm voxel size, band filtering (0.01-0.08Hz) and linear detrend. Several spurious variances (white matter, cerebrospinal fluid, head motion and global mean signals) were removed via linear regression. Data were discarded if the translation exceeded 2 mm or if rotation exceeded 2◦. Using Resting-State fMRI Data Analysis Toolkit (REST version 1.8) software [27], the voxel-wise DC is computed with *r* (correlation

threshold) set at 0.25. Only positive weighted Pearson's correlation coefficients were considered in this study.

Voxel-Wise Comparisons in CBF and DC

By using REST software, the DC maps were *z*-transformed and smoothed (6×6×6 mm FWHM) to compare between the two groups. The intergroup comparisons of CBF and DC were performed in a voxel-wise manner while controlling for age and gender ($p < 0.05$, FDR correct).

Region of interest (ROI) analysis

To improve normalization, CBF maps were normalized into *z*-scores within the whole grey mask. The regions obtained from voxel-wise comparisons of CBF and DC were merged and defined as regions of interest (ROIs). The CBF and DC value of each voxel in the merged ROIs were extracted for each participant. Furthermore, correlational analyses between CBF and DC were performed for each ROI of each participant. There is a CBF-DC coefficient value for each ROI of each participant, reflecting the consistency of spatial distribution between CBF and DC at the ROI level. Then, a two-sample *t* test was used to compare the difference in CBF-DC correlation coefficients between the two groups, with age and gender as the nuisance variables.

To evaluate the amount of blood supply per unit of functional hubs, the CBF/DC ratio (both CBF and DC were original values without *z*-transformation) of each voxel were calculated and transformed into a *z*-score map to improve the normality. Based on the merged ROI, differences in CBF/DC ratio between the two groups were analyzed, with age and gender as the covariates. For each participant, the mean CBF/DC ratio of each ROI was extracted by using REST software, and then the correlation between the CBF/DC ratio and the clinical variables (lung test index, MRC, MoCA) were performed by using a Pearson's correlation analysis, with age and gender as nuisance covariates.

Results

Clinical characteristics differences

Both groups showed no significant differences in age, gender, BMI. Compared to HC, COPD showed lower lung function in FEV_1% predicted, FVC% predicted and FEV_1/FVC ($p<0.05$), and higher rating of dyspnea severity in MRC ($p<0.05$). COPD patients showed lower MoCA and sub-scale scores ($p<0.05$).

Differences in CBF and DC

The COPD group showed decreased CBF in the left dorsolateral prefrontal cortex (DLPFC), right DLPFC, left supramarginal (SMG) and bilateral anterior cingulum (ACG). However, further correlational analyses showed no significant correlations between any regions with CBF and any clinical variables in COPD group ($p>0.05$).

The COPD group showed greater DC in the left precentral gyrus (PreCG) and left SMG. The mean DC values in the left SMG showed significantly negative correlation with the visuospatial/executive score (r=-0.515, p<0.001).

CBF-DC correlational analysis

The merged maps with significantly intergroup different clusters in CBF and DC comparisons covered four brain clusters, including the left precentral gyrus/PLPFC, right DLPFC, left SMG and bilateral ACG. In both COPD and healthy control groups, the CBF was significantly correlated DC in the four merged regions. However, there was no significantly differences in the correlation coefficients of each ROI between the two groups.

Comparison of CBF-DC ratio

In voxel level, COPD group showed increased CBF/DC ratio in the bilateral medial frontal cortex (ventromedial prefrontal cortex, orbitofrontal cortex and rectus gyrus), bilateral caudate nucleus, left middle temporal gyrus (parahippocampus gyrus and fusiform gyrus), and left lingual gyrus (LNG). Furthermore, in the COPD group, the correlational analyses revealed that the CBF/DC ratio in the left LNG showed significantly negative correlations with the naming score (r=-0.709, p<0.001), and the CBF/DC ratio in the medial frontal cortex/temporal gyrus showed significantly positive correlations with MoCA score (r=0.485, p=0.001), visuospatial/executive score (r=0.646, p<0.001) and delayed recall score (r=0.468, p=0.001).

Furthermore, the mean CBF and DC values in the above regions were extracted for intergroup comparison. In the left lingual gyrus, COPD patients showed lower CBF (t=-2.174, p=0.035) and lower DC (t=-2.610, p=0.012); in the bilateral frontal cortex and left middle temporal gyrus, lower CBF (t=-3.744, p=0.001) and lower DC (t=-3.818, p<0.001) were also found in COPD group.

ROI-based analyses on CBF/DC ratio

In ROI analyses, compared to healthy controls, COPD patients exhibited decreased CBF/FCS ratio in the left PreCG/DLPFC (t=-2.711, p=0.01) and left SMG (t=-2.452, p=0.018). However, no significant correlation between the CBF/DC ratio of any ROI and any clinical characteristics was found in the COPD group. Further validation of CBF and DC changes showed that COPD patients exhibited lower CBF and higher DC in the two regions (p<0.001).

Discussion

By using resting-state 3D ASL and BOLD techniques, CBF-DC coupling changes were investigated in patients with COPD. COPD patients showed decreased CBF in the bilateral DLPFC, ACG and left SMG, and increased DC in the left PreCG and left SMG. More importantly, COPD showed increased CBF/DC ratio in the bilateral medial frontal cortex, bilateral caudate nucleus, left temporal gyrus and left LNG, and CBF/DC ratio in several brain regions significantly correlated with MoCA, visuospatial/executive and delay recall scores.

The COPD showed decreased CBF in bilateral DLPFC, ACG and left SMG. The brain constitutes only about 2% of the body weight, but easily receives up to 15-20% of the total cardiac output as CBF. CBF changes may be ascribed to the following reasons. The hypothesis of neurovascular coupling suggested that CBF is governed by neural activity changes through complex coordinated mechanisms involving neurons, glial cells, and vascular components [16, 33]. Moreover, the neural stimuli may be involved in the control of the diameter of the cerebral vessel and brain blood supply, resulting to CBF changes. Finally, chemical mediators, such as neuroinflammation factors, adenosine, nitric oxide[8, 17], hydrogen, potassium, calcium and lactate[5], may trigger hemodynamic responses resulting in vasodilation/vasoconstriction and CBF changes.

Higher DC values were found in the left PreCG and left SMG in COPD. The higher DC represents more correlations between the given voxel and the rest voxels, indicating that neurons in this voxel is more important and active. Tomasi and Volkow [30] suggested that voxels with high DC serve as the interconnection hubs, meaning effective and fast brain communication with minimal cost of energy. Widespread evidences of increased functional activation have been reported in patients with COPD. Increased resting state connection could be interpreted as a reduction in precise control over functional networks that is not beneficial, indicating a disrupt network. Our study showed a significantly negative correlation between the mean DC value of the left supramarginal gyrus and the visuospatial/executive function score, suggesting that the left SMG may be associated with visuospatial/executive dysfunction in COPD patients.

Voxel-wise analyses revealed that COPD patients showed significantly higher CBF/DC ratio in several regions. Subsequent ROI-based analyses showed lower CBF and lower DC values in these regions in COPD group than those in healthy controls. However, by using voxel-wise analyses, there is no overlap between the merged regions generated in intergroup comparisons of CBF, DC and regions with intergroup different CBF/DC ratio, we speculated that CBF/DC ratio could enlarge the differences between the COPD and healthy group. Moreover, in some merged ROIs, COPD patients showed significant lower CBF/DC ratio. We demonstrated that combination of CBF, DC and CBF/DC ratio base on voxel-wise and ROI-wise analyses may be a comprehensive and reliable method to investigate underlying mechanisms of COPD patients.

COPD patients showed increased CBF/DC ratio in the left LNG. The increased CBF/DC ratio was driven by disproportionally attenuated CBF and DC. The LNG is involved in encoding of complex images[18], object discrimination[21] and identification and recognition of words[20]. Supporting this, the LNG is functionally associated with decreased naming performance[15] and visual processing[2] and visual hallucination[11]. In the COPD group, the negative correlation between the higher CBF/DC ratio of the LNG and the naming score indicated that the attenuation degree of DC is greater than that of CBF in this region, resulting in decompensated increase of CBF per unit of functional connection in the left LNG and poor naming function.

In addition, COPD patients also showed higher CBF/DC ratio in the bilateral medial frontal cortex, bilateral caudate nucleus, and left middle temporal cortex. Several COPD studies on grey matter have provided evidences of reduced thickness and volume in these regions[3, 39]. And the frontal cortex is involved in processing of emotion information with visual input during the observation and execution tasks[10, 23]. Increased CBF/DC ratio of these regions may play a compensatory role for the reduced grey matter volume. In the present study, the increased CBF/DC ratio in bilateral medial frontal cortex and left middle temporal cortex is driven by decreased CBF and DC. And the CBF decline may be the cause of the decreased grey matter volume. Consist with our study, hypoperfusion in the frontal cortex and cognitive abnormalities has been found in COPD patients[14]. The positive correlation between higher CBF/DC ratio in this region and MoCA, visuospatial/executive and delayed recall functions may suggest that the abnormal neurovascular changes in this region are related with dysfunctional visuospatial/executive and delayed recall in COPD patients.

In the ROI analyses, COPD patients exhibited decreased CBF/DC ratio in the left PreCG/DLPFC and left SMG, which are involved in somatic motor function and spatial working memory[26]. Decreased grey matter density and neural activation in the left PreCG have been found in COPD patients [38–40]. The DLPFC is a key part of dorsal visual processing stream regions which are involved in visual reproduction impairment in COPD. Using surface-based morphometry, Chen et al. [3] provided evidence that the thinner DLPFC was predictive factor of poorer visual reproduction performance, they also found reduced cortical thickness and surface in the PreCG and SMG in COPD. In our study, these regions showed lower CBF and higher DC, suggesting that the decreased CBF/DC ratios in these regions were driven by the CBF decrease and DC increase, which might be attributed to reduced cortical thickness and surface, rendering to cognitive impairment in COPD.

In this study, significant correlations between CBF and DC were found in the four merged ROIs in both COPD and healthy groups. However, further comparison analyses showed no significant differences in the correlation coefficients between two groups which meant normal neurovascular coupling in all subjects and no significant differences in the four ROIs between the two groups. To minimize effects of interference factors, we excluded participants with other diseases or disorders which may affect the cerebral function and structure, such as cardiovascular, metabolic diseases, neurosis and psychosis. We speculated that this finding may be associated with current status of COPD patients in this study. More COPD patients with different stages may be needed to investigate in the further studies.

Unexpectedly, no associations between abnormal brain functions and pulmonary-specific disease markers were found, we speculate that the extrapulmonary manifestations of COPD may not be strongly related to pulmonary-specific disease markers. In addition, various studies provided evidences that cigarette smoking may involve in the cerebral functional or structural abnormalities in patients with COPD. However, no correlation between the duration or the amount of smoking and the cerebral abnormalities were found in all smokers.

Several limitations should be taken into account when interpret our findings. Firstly, relatively small sample size may influence our interpretations, more COPD patients are needed in the further investigations. Secondly, CBF and DC are indirect indices, preventing us from direct and more reliable measurements of cerebral perfusion and neural activity. Finally, COPD patients after oxygen therapy are not enrolled into this study, a follow-up study with longitudinal comparison is needed for validity of the present findings.

Conclusion

Our study revealed that the abnormal CBF/DC ratio in cognitive regions contributes to visuospatial/executive, delay recall and naming deficits, and provided an integrative view of disrupted brain network and valuable information of mechanism underlying mild cognitive impairment of COPD patients.

Declarations

Funding

Not applicable

Conflict of interest

Not applicable

Ethics approval

The protocol was approved by the ethics committee of The Changzheng hospital (2018SL028)

Consent to participate

written informed consent of all participants were given after a full written and verbal explanation of this study.

Consent for publication

All listed authors have seen and approved the submission and publication.

Availability of data and material

Not applicable

Code availability

Not applicable

Authors' contributions

Zhaohui Peng: Conceptualization, Methodology, Data curation, Software, Formal analysis, Writing-Original draft preparation, Writing - Review & Editing.

Hongtao Zhang: Data curation, Resources, Writing - Review & Editing.

Gang Wang: Data curation, Resources, Formal analysis.

Qian Shaowen: Methodology, Software, Formal analysis, Writing - Review & Editing.

Wang Wei: Conceptualization, Methodology, Supervision, Writing - Review & Editing.

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Figures

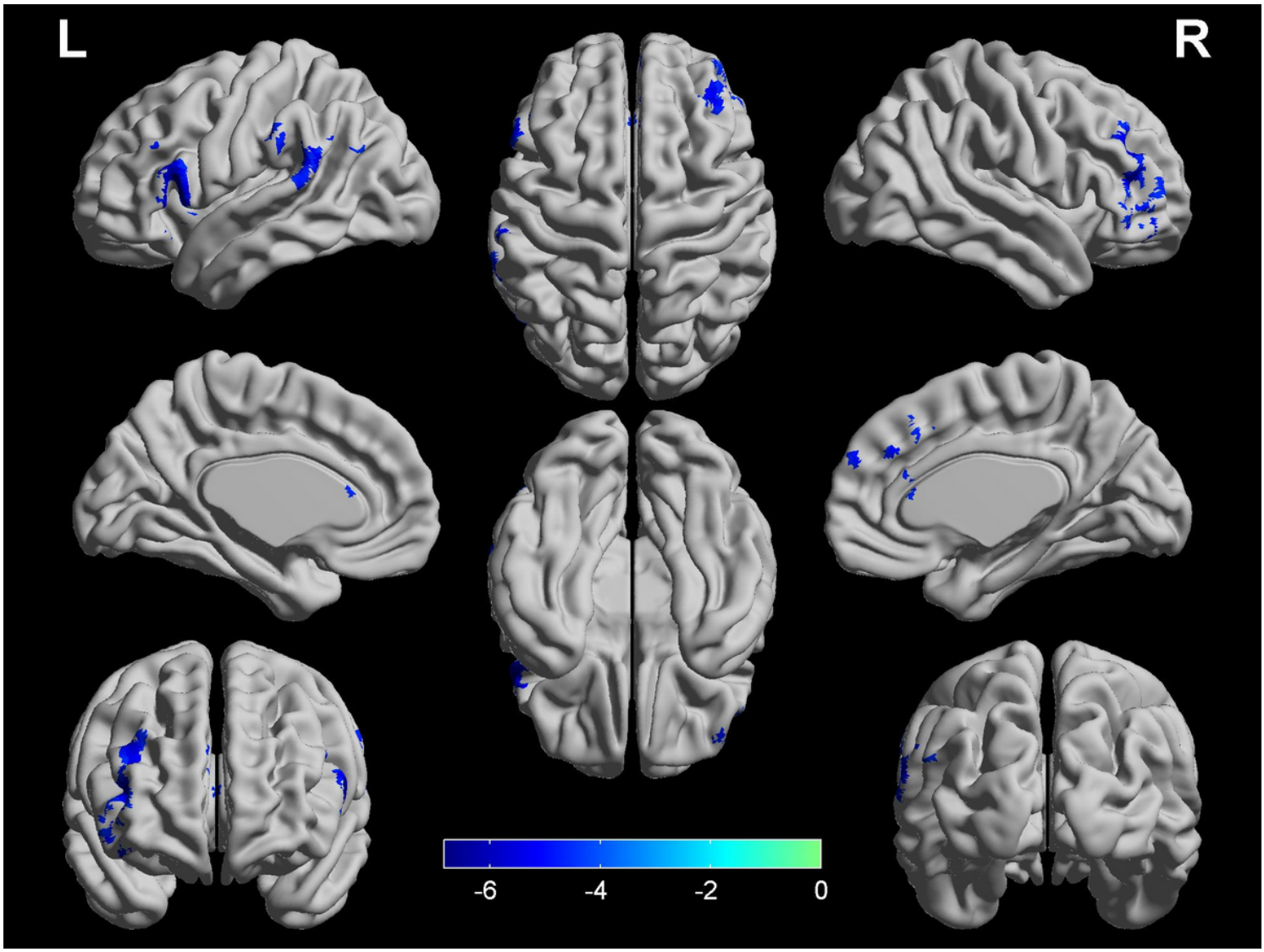

Figure 1

Significant differences in CBF between COPD patients and HC. Four regions (left DLPFC, right DLPFC, left SMG and bilateral ACG) showed lower CBF in COPD patients ($p<0.05$, FDR corrected) while controlling for the age and sex. CBF, cerebral blood flow; COPD, chronic obstructive pulmonary disease; HC, healthy controls; DLPFC, dorsolateral prefrontal cortex; L, left; R, right.

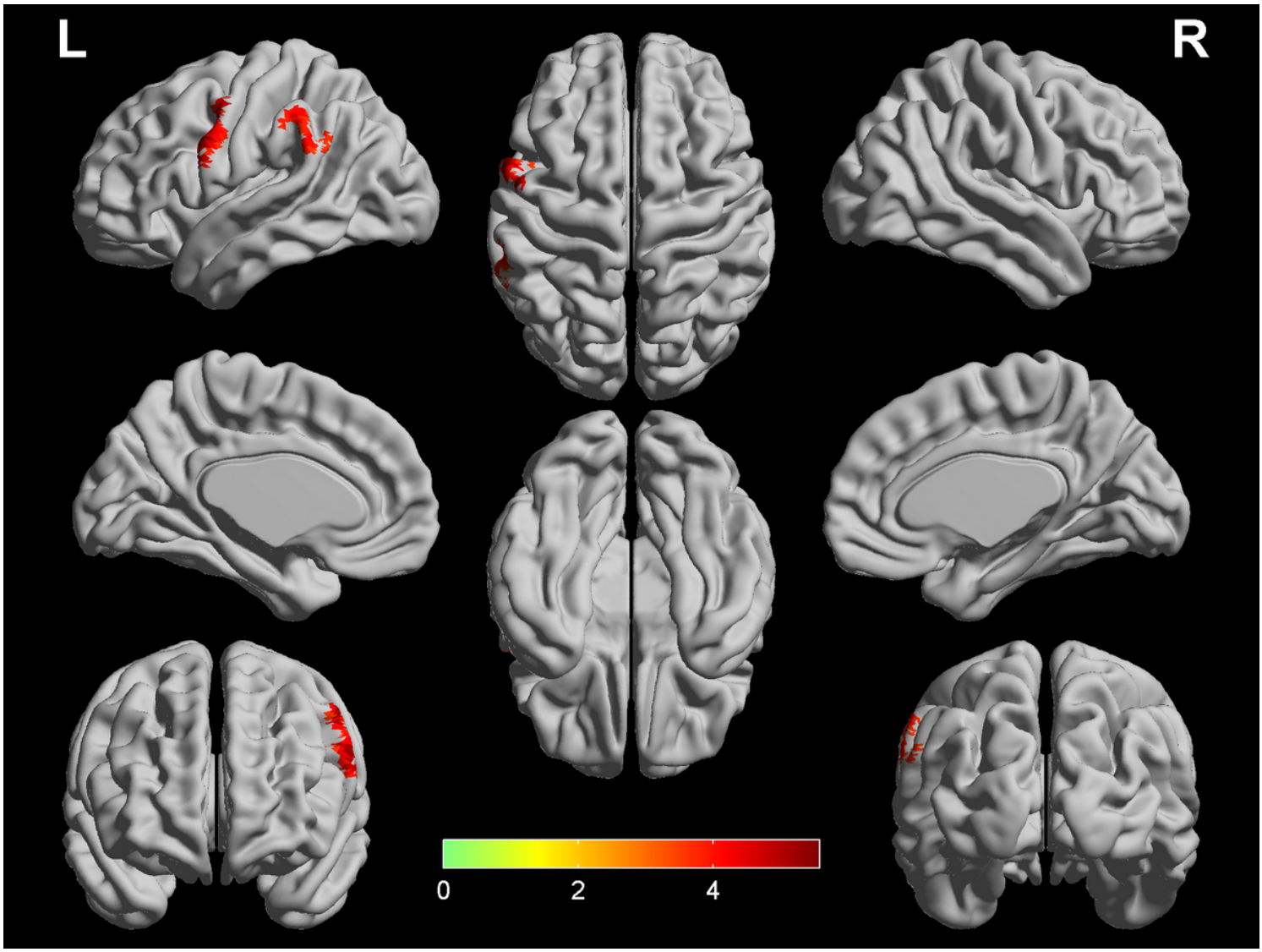

Figure 2

Significant differences in DC between COPD patients and HC. Two regions (left PreCG and left SMG) showed higher DC in COPD patients ($p<0.05$, FDR corrected) while controlling for the age and sex.

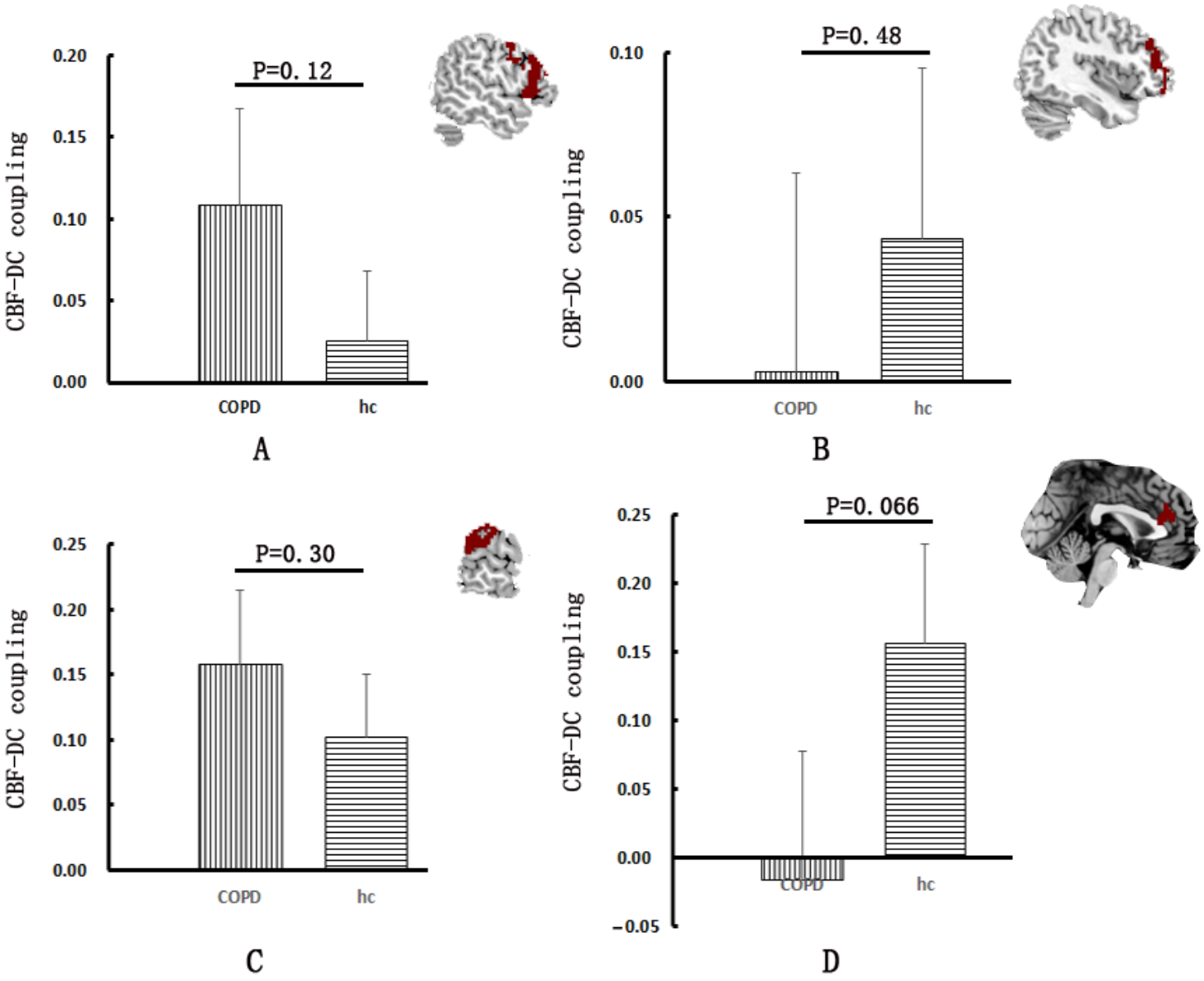

Figure 3

Intergroup statistical histograms of the CBF-DC correlations within the merged ROIs. No significant difference of CBF-DC correlations was found in the left PreCG/DLPFC(A), right DLPFC(B), left SMG (C) and bilateral ACG between the COPD and HC groups (p>0.05).

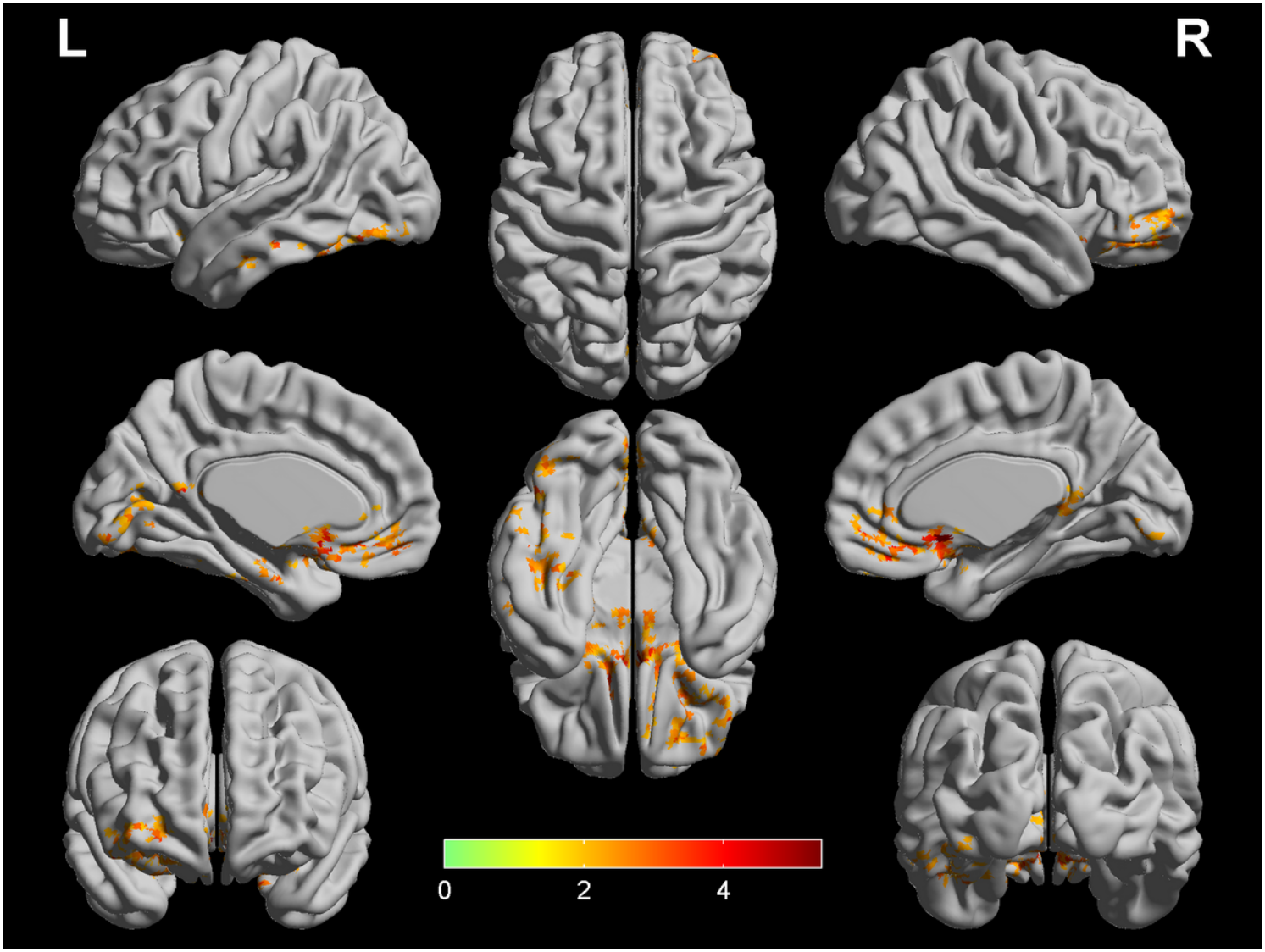

Figure 4

Comparison of CBF/DC ratio between COPD patients and HC. Two regions (bilateral media frontal cortex/temporal gyrus and left supramarginal gyrus) showed higher CBF/DC ratio in COPD patients ($p<0.05$, FDR corrected) while controlling for the age and sex.

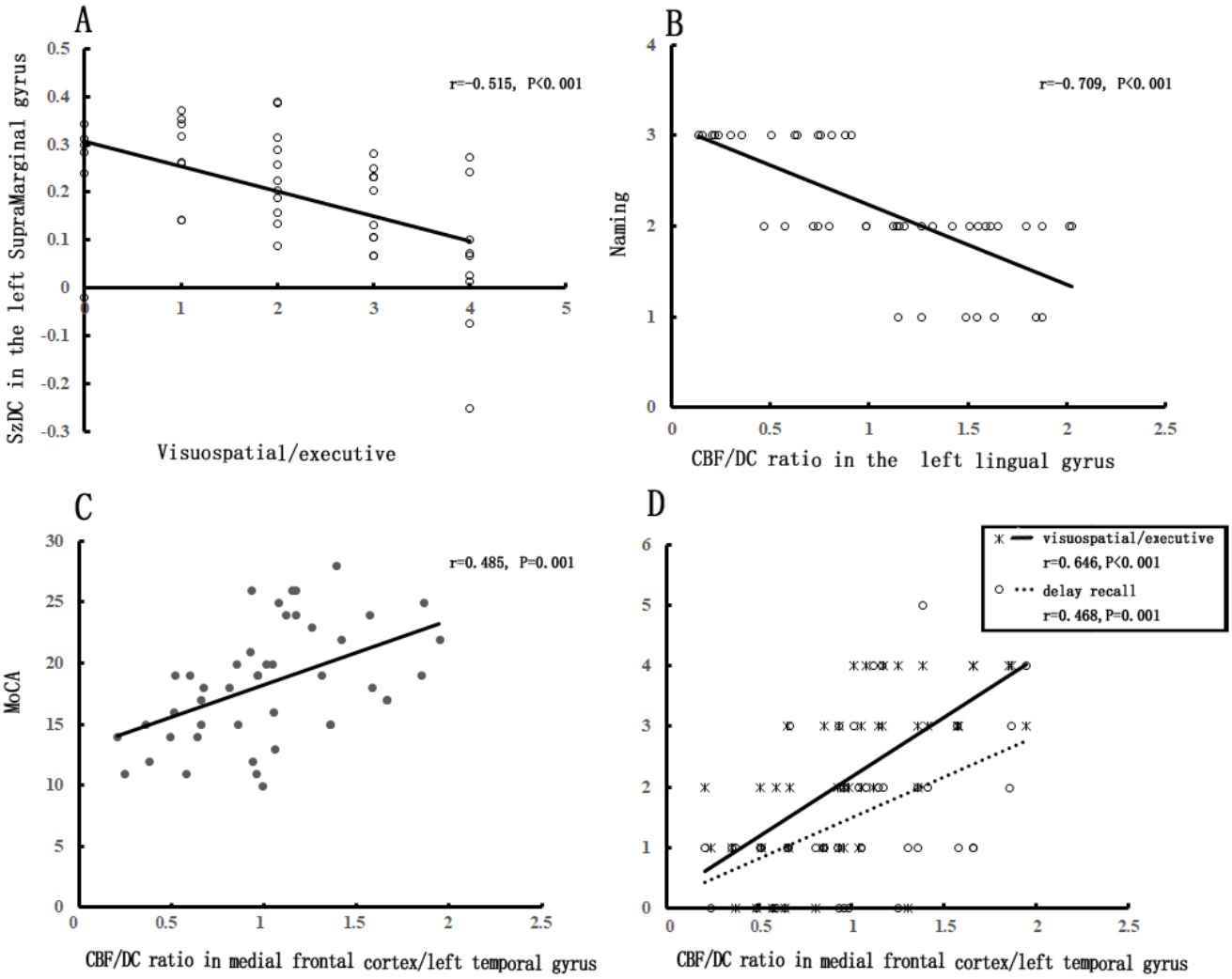

Figure 5

Correlational results of functional index (DC and CBF/DC ratio) and clinical characteristics in COPD group. A: DC in left SMG showed significantly negative correlation with visuospatial/executive score (r=-0.515, p<0.001); B: CBF/DC ratio in left LNG showed significantly negative correlation with naming score (r=-0.709, p<0.001); CBF/DC ratio in medial frontal cortex/left temporal cortex showed significantly positive correlation with MoCA (r=0.485, p=0.001)(C), visuospatial/executive score (r=0.646, p<0.001) and delay recall score (r=0.464, p=0.001) (D).

Supplementary Files

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

- BIBChecklist.pdf