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ORIGINAL RESEARCH

Effective Connectivity and Clinical Correlates in Chronic Obstructive Pulmonary Disease

Kyung-Il Han[1,*], Jin Ho Bae[2,*], Hang Joon Jo[2,3,*], Jae Min Park[4], Yoomi Yeo[1], Tai Sun Park[1], Dong Woo Park[5], Tae-Hyung Kim[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Seoul, Korea; [2]Department of Biomedical Engineering, Graduate School of Biomedical Science & Engineering, Hanyang University, Seoul, Korea; [3]Department of Physiology, Hanyang University College of Medicine, Seoul, Korea; [4]Department of Medicine, Hanyang University College of Medicine, Seoul, Korea; [5]Department of Radiology, College of Medicine, Hanyang University Guri Hospital, Guri, Korea

*These authors contributed equally to this work

Correspondence: Tae-Hyung Kim, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, 153, Gyeongchun-ro, Guri, Gyeonggi-do, 11923, Korea, Tel +82-31-560-2243, Fax +82-31-553-7369, Email drterry@hanyang.ac.kr

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Background: Cognitive impairment is a substantial comorbidity in chronic obstructive pulmonary disease (COPD); however, the neural mechanisms underlying this association remain poorly understood. This study aimed to assess alterations in effective connectivity (EC) in patients with COPD and investigate their relationships with clinical measures.

Methods: Resting-state functional magnetic resonance imaging (RS-fMRI) was performed in 38 patients with COPD and 30 healthy controls. EC was estimated using vector autoregressive (VAR) modelling combined with Granger causality analysis across 26 prespecified brain regions of interest derived from our previous functional connectivity study of the same cohort. Between-group differences in directed connectivity were assessed using Welch's *t*-tests. Associations between EC measures showing between-group differences and clinical measures were evaluated using age-adjusted partial Pearson correlations.

Results: At the nominal two-sided $p < 0.05$ level, 37 directed connections showed between-group differences in effective connectivity, and the mean vector autoregressive coefficients for 35 of these connections lay on opposite sides of zero between the COPD and control groups. Among the connections showing between-group differences, age-adjusted associations in patients with COPD involved pulmonary function, systemic oxygenation, cognition, affect, and health status. These associations involved distributed cortical, subcortical, and cerebellar regions, with several directed connections showing convergence across multiple clinical domains.

Conclusion: Resting-state VAR-based EC revealed distributed between-group differences in direction-sensitive BOLD temporal organization in COPD. Several of these EC measures were associated with pulmonary function, SpO_2, respiratory and COPD symptom burden, cognition, affect, and health status after age adjustment. These findings extend the functional connectivity profile of COPD by linking directed temporal relationships to its multidimensional clinical burden.

Plain Language Summary: Effective connectivity analysis revealed differences in brain network dynamics between patients with COPD and healthy controls. These differences were associated with pulmonary function, respiratory symptoms, cognition, affect, and health status, suggesting that altered brain network organization may accompany the multidimensional clinical burden of COPD.

Keywords: chronic obstructive pulmonary disease, cognitive impairment, effective connectivity

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease characterized by chronic respiratory symptoms, including dyspnea, cough, and sputum production, resulting from persistent and often progressive airflow obstruction caused by abnormalities of the airways and/or alveoli.[1] Cognitive impairment is a substantial comorbidity in COPD, affecting multiple cognitive domains such as memory, attention, and executive function.[2] The degree of cognitive

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impairment has been shown to correlate with disease severity and progression in COPD.[3] However, despite a reported prevalence of cognitive impairment of approximately 20–30% among patients with COPD, the underlying pathophysiological mechanisms remain poorly understood.[4]

Functional magnetic resonance imaging (fMRI) measures brain activity by detecting changes in blood oxygenation, which reflect underlying neural activity. Functional connectivity (FC) refers to statistical dependence between spatially distributed neurophysiological signals and is commonly estimated from temporal covariation in spontaneous blood-oxygenation-level-dependent (BOLD) fluctuations.[5] In the present study, effective connectivity (EC) was operationalized using a vector autoregressive (VAR)/Granger framework, which tests whether past values of one regional BOLD time series improve the prediction of another and thereby provides direction-sensitive information about interregional temporal dependencies.[6–8] Because these estimates are derived from temporally sampled BOLD signals, they are not interpreted as direct evidence of neuronal causation.

Previous COPD neuroimaging studies have characterized structural abnormalities, regional functional alterations, and undirected network synchrony.[9–12] However, most functional neuroimaging studies have relied on cross-sectional and correlational designs and on undirected functional metrics. While these methods are informative for understanding network organization, they are limited in their ability to characterize direction-sensitive temporal relationships.[9,10] Direction-sensitive temporal dependencies between regional BOLD signals may therefore provide a complementary view of brain organization.

Building on our previous resting-state FC findings in COPD,[12] we employed VAR-based EC within the FC-informed ROI search space to determine whether these temporal dependencies differed between patients with COPD and controls and how connections showing between-group differences were associated with clinical measures in COPD. Given the indirect nature of the BOLD signal and the potential influence of vascular or cardiopulmonary factors in COPD, the present findings are interpreted as putative EC patterns at the fMRI timescale.

Methods

Study Design and Participants

This study was a single-center investigation conducted at a university hospital in Korea. The imaging and clinical measurements were collected prospectively as primary research data within a predefined multimodal neuroimaging program and were not retrospectively extracted from routine clinical or diagnostic records. Patients with COPD were prospectively recruited from the outpatient clinic according to predefined eligibility criteria. No formal a priori sample-size calculation was performed because this was an exploratory neuroimaging study and a reliable effect size for the imaging outcomes could not be specified in advance. The target sample sizes were determined with reference to previous neuroimaging studies with comparable designs, which generally included approximately 20–30 participants per group,[13] while also considering the feasibility of MRI-based recruitment and potential exclusions due to imaging quality. Accordingly, the target sample sizes were 50 patients with COPD and 30 healthy control participants.

Fifty patients with COPD and 30 healthy control participants were initially recruited. Patients with COPD were recruited from November 2015 to December 2016. Patients aged 60 years or older with at least 1 year of clinical follow-up were eligible for inclusion. The diagnosis of COPD was established according to the Global Initiative for Chronic Obstructive Lung Disease criteria, defined as a post-bronchodilator (post-BD) forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio of < 0.7 and a post-BD FEV_1 of $< 80\%$ of the predicted value, as determined by post-BD spirometry. The control group consisted of age- and sex-matched adults without a history of respiratory disease or symptoms. Exclusion criteria included a history of dementia, major depressive disorder, other cognitive-related neurological conditions, significant cardiopulmonary disease, untreated malignancy, or autoimmune disorders. A dedicated neurological examination or standardized assessment was not performed. Cognitive status was assessed using the Korean version of the Montreal Cognitive Assessment (MoCA-K) and the Mini-Mental State Examination (MMSE) as screening measures. Peripheral oxygen saturation (SpO_2) was measured using photoplethysmographic pulse oximetry while participants were breathing room air, with no supplemental oxygen administered during the measurement. SpO_2 was measured immediately before the MRI examination, with MRI acquisition performed directly thereafter.

Nine patients with COPD were excluded after image review because of severe cerebral atrophy or brain infarction. Three additional patients with COPD were excluded from the EC analysis because extensive motion censoring resulted in markedly shortened usable resting-state fMRI time series. The final EC analysis therefore included 38 patients with COPD and 30 healthy control participants.

Written informed consent was obtained from all participants before enrollment. The study protocol was approved by the Institutional Review Board of Hanyang University Guri Hospital (IRB No. GURI 2015–05-019). The study was conducted in accordance with the Declaration of Helsinki.

Imaging Data Acquisition

Anatomical and fMRI images were obtained for all participants using a 3.0-T MRI system (Philips Ingenia, Koninklijke Philips N.V., Amsterdam, Netherlands). To minimize motion-related artefacts, all participants were provided with foam pads and earplugs, along with instructions to keep their eyes closed during the imaging session. High-resolution structural images were acquired using a T1-weighted MPRAGE sequence: repetition time (TR) = 8.4s, echo time (TE) = 4.1s, flip angle (FA) = 8°, voxel size = 1 × 1×1 mm^3. Resting-state fMRI data were subsequently collected using a gradient-echo echo-planar imaging (EPI) sequence: TR = 3.0 s, TE = 35 ms, FA = 90°, 30 slices, in-plane resolution = 1.72×1.72 mm^2, slice thickness = 5 mm. This protocol was applied identically to all participants. The 3-s TR corresponds to a sampling frequency of 0.333 Hz and a Nyquist frequency of 0.167 Hz. A total of 120 reconstructed volumes were acquired over 360 s (6 min; TR = 3.0s). The first two volumes were removed, leaving 118 resting-state fMRI time points before subject-specific motion censoring. Among participants included in the EC analysis, the retained-time-point proportions were 99.3 ± 2.1% in the COPD group (n = 38) and 99.2 ± 3.0% in the control group (n = 30). Every included patient with COPD retained at least 104 uncensored time points. In three additional patients with COPD, extensive motion censoring resulted in markedly shortened usable time series; on average, 37.3 ± 5.5 of the 118 post-discard time points remained after censoring, corresponding to a mean retained proportion of 31.6 ± 4.7%. These participants were excluded from the EC analysis. Detailed subject-level acquisition and motion-censoring information is provided in Supplementary Data (EPI QC worksheet). All imaging data underwent standardized quality assurance procedures, including systematic visual inspection by experienced imaging analysts (Dong Woo Park and Hang Joon Jo) to ensure the absence of major artefacts or acquisition errors before analysis.

Image Preprocessing

All fMRI imaging data were preprocessed using the Analysis of Functional NeuroImages (AFNI; https://afni.nimh.nih.gov) software package, following a standardized preprocessing pipeline.[14] The preprocessing steps were designed to minimize non-neuronal sources of variance while preserving the temporal dependencies relevant for EC analysis. The first two volumes were discarded, and the remaining data underwent despiking and nuisance regression incorporating physiological and motion-related confounds.[15] Slice-timing correction and rigid-body head motion correction were applied, followed by alignment to anatomical images.[16] Brain masking and voxel-wise intensity scaling were applied to standardize signal amplitudes and enhance between-subject comparability. The regression model included run-wise motion parameters (demeaned terms and temporal derivatives), physiological regressors, and tissue-based confounds derived from anatomical segmentations, such as principal components from ventricular signals and a local white matter (WM)-based regressor strategy.[17] High-motion volumes were censored, and denoised residual time series were generated. Polynomial detrending and spatial smoothing were not applied to preserve temporal structure and avoid bias in VAR-based EC estimation. Anatomical images were nonlinearly normalized to the Montreal Neurological Institute (MNI) 152 template using affine and nonlinear transformations, which were applied to the functional data to standardized space for region-of interest (ROI) time series extraction and EC analysis.[18]

EC Analysis

EC analyses were conducted in a ROI-based framework comprising 26 regions defined before the present EC analysis using the abnormal resting-state functional connectivity (RSFC) pattern reported in our previous study of the same prospectively acquired cohort.[12] This procedure defined the FC-informed analytical search space, and these ROIs were

used for all EC analyses. The present VAR analysis estimated candidate lagged directional dependencies within this prespecified ROI set. ROI masks were generated from each participant's FreeSurfer parcellation and used for time series extraction. ROI time series were derived using a principal component analysis (PCA)-based approach, combining components until 95% of variance was explained, to reduce bias from voxel-wise averaging while preserving within-ROI variance. Before VAR modelling, ROI time series were tested for cointegration (Johansen test) and stationarity (augmented Dickey-Fuller test), with first-order differencing applied when necessary.[19] For EC estimation, a VAR model with a fixed lag order of 3 was used to balance model flexibility and parameter stability, given the number of ROIs and available time points. After model fitting, directed interactions were quantified using pairwise Granger causality tests across all ordered ROI pairs, and the corresponding VAR coefficients were retained to characterize the direction and sign of temporal dependencies.[6–8] VAR coefficients describe lagged predictive relationships between regional BOLD signals at integer multiples of the 3-s sampling interval. For group-level analyses, the reported edgewise EC measure corresponded to lag-3 coefficients, and this same summary measure was used in subsequent correlation analyses. Finally, model adequacy was evaluated by computing Durbin-Watson statistics on VAR residuals to screen for remaining autocorrelation that could indicate model misfit.[20]

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables as number (percentage). Baseline demographic and clinical characteristics were compared between the COPD and control groups using Welch's *t*-test for continuous variables and Fisher's exact test for binary categorical variables. Smoking status, categorized as current, former, or never smoking, was compared using Pearson's chi-square test. Missing clinical observations were handled using variable-specific available-case analysis without imputation. In the COPD group, pack-years, Charlson comorbidity index, and MMSE were available for 37 of 38 participants, whereas the other variables were available for all 38 participants. In the control group, pulmonary function measures were available for 27 of 30 participants and pack-years for 7 participants, whereas the other demographic, anthropometric, cognitive, affective, and health-status measures were available for all 30 participants. SpO_2, CAT, COPD exacerbation history, and duration of COPD treatment were not available in the control group.

For group-level inference, differences in directed interactions between the COPD and control groups were assessed by performing Welch's *t*-tests on the VAR coefficients for each directed ROI-to-ROI connection, accounting for potential heteroscedasticity and unequal sample size. In addition to statistical significance, the sign of the VAR coefficients was examined to characterize qualitative differences in directed interactions. Given the exploratory network-level nature of the EC analysis and the evaluation of multiple directed edges, results were interpreted based on distributed connectivity patterns rather than isolated connections. A nominal two-sided $p < 0.05$ reporting level was applied consistently to both the between-group EC comparisons and the subsequent EC–clinical association analyses. The clinical relevance of EC estimates was assessed using age-adjusted partial Pearson correlation analyses between VAR coefficients and clinical parameters, restricted to edges showing significant between-group differences and conducted separately within each group to characterize group-specific EC–clinical associations. Age-related linear variance was removed from both the VAR coefficient and the corresponding clinical measure for each association. Zero-order Pearson correlations were also calculated as unadjusted comparators. Partial *r*, two-sided uncorrected *p*-values, and effective sample sizes were reported for the displayed EC–clinical associations. Pairwise explained variance among demographic and clinical variables was estimated separately within each group using univariable linear regression for continuous pairs and dummy-coded categorical predictors. All statistical analyses were performed using Python packages, and a *p*-value < 0.05 was considered statistically significant.

Patients and Public Involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research. The research questions, study design, outcome measures, and analytical methods were determined by the investigators based on existing scientific evidence and clinical considerations.

Results

The baseline demographic and clinical characteristics of the 38 patients with COPD and 30 healthy controls included in the EC analysis are summarized in Table 1. Age, sex, and height were comparable between the groups, whereas patients with COPD had significantly lower body weight and BMI and differed in smoking status compared with controls. As expected, patients with COPD had significantly impaired pulmonary function, including lower FVC, FVC % predicted, FEV_1, FEV_1% predicted, and FEV_1/FVC. Patients with COPD also had a higher Charlson comorbidity index, lower MoCA-K scores, higher BDI scores, and lower EQ-5D scores than controls. No significant between-group differences were observed in MMSE, BAI, or FSRP scores. COPD-specific clinical measures for which corresponding control data were unavailable are presented descriptively in Table 1.

Table 1 Demographic and Clinical Characteristics of Participants Included in the Effective Connectivity Analysis*

	COPD (n=38)	Control (n=30)	*p*-value
Age, years	69.89 ± 5.13	68.93 ± 4.72	0.425
Males, %	33 (86.84)	27 (90)	>0.999
Height, cm	163.42 ± 6.55	163.79 ± 6.77	0.819
Weight, kg	59.40 ± 9.72	65.68 ± 9.66	**0.010**
BMI, kg/m^2	22.20 ± 3.09	24.39 ± 2.55	**0.002**
Smoking status			**0.007**
Current smoker, %	12 (31.58)	7 (23.33)	
Ex-smoker, %	25 (65.79)	14 (46.67)	
Never-smoker, %	1 (2.63)	9 (30.0)	
Smoking, pack-years (n=44)	44.53 ± 28.71	32.86 ± 17.77	0.179
mMRC dyspnea scale	1.84 ± 0.86	0.00 ± 0.00	**< 0.001**
SpO_2, %	95.84 ± 4.25		
CAT	17.21 ± 8.69		
COPD exacerbations in the previous year	0.39 ± 0.82		
Duration of COPD treatment, months	68.39 ± 58.52		
Charlson comorbidity index (n=67)	1.49 ± 0.61	0.57 ± 0.77	**< 0.001**
FVC, L (n=65)	3.02 ± 0.86	3.62 ± 0.70	**0.003**
FVC, % predicted (n=65)	77.24 ± 18.30	87.81 ± 12.44	**0.007**
FEV_1, L (n=65)	1.37 ± 0.56	2.72 ± 0.58	**< 0.001**
FEV_1, % predicted (n=65)	48.50 ± 16.89	92.70 ± 13.61	**< 0.001**
FEV_1/FVC (n=65)	0.45 ± 0.12	0.75 ± 0.04	**< 0.001**
MoCA-K	22.00 ± 5.48	25.40 ± 3.81	**0.004**
MoCA-K < 23, %	17 (44.74)	6 (20.0)	**0.041**
MMSE (n=67)	25.11 ± 4.31	26.70 ± 2.20	0.056
MMSE < 24, %	7 (18.92)	3 (10.0)	0.493
BDI	18.79 ± 12.12	5.17 ± 4.55	**< 0.001**
BAI	6.11 ± 9.06	3.93 ± 7.45	0.282
EQ-5D	0.89 ± 0.10	0.94 ± 0.04	**0.008**
FSRP	10.16 ± 2.80	9.83 ± 3.16	0.660

Notes: *Values are presented using the variable-specific available sample without imputation. In the COPD group, n=38 except for pack-years, Charlson comorbidity index, and MMSE (n=37). In the control group, demographic, anthropometric, cognitive, affective, and health-status variables were available for n=30, pulmonary-function measures for n=27, and pack-years for n=7. SpO_2, CAT, COPD exacerbation history, and duration of COPD treatment were not available in the control group. Exact p-values are reported; values with $p < 0.05$ are shown in bold.

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; EC, effective connectivity; EQ-5D, EuroQol 5-Dimension; FEV_1, forced expiratory volume in 1 second; FSRP, Framingham Stroke Risk Profile; FVC, forced vital capacity; MMSE, Mini-Mental State Examination; mMRC, modified Medical Research Council; MoCA-K, Korean version of the Montreal Cognitive Assessment; SpO_2, peripheral oxygen saturation.

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Group Differences in EC Between the COPD and Control Groups

At the exploratory significance level of $p < 0.05$, 37 directed connections between the prespecified ROIs showed between-group differences. For 35 of these connections, the mean VAR coefficients in patients with COPD and control participants lay on opposite sides of zero. Group-specific VAR coefficients, Welch's *t*-statistics, and *p*-values are provided in Table 2. Figure 1A displays the group-specific mean VAR coefficients for these connections, and Figure 1B depicts the corresponding between-group differences and their anatomical distribution in a directed network. Figure 2A shows the mean VAR coefficients within the COPD group in a source-by-target matrix, while Figure 2B presents the same coefficients as a directed network across the prespecified ROIs. Supplementary Figure S1A presents an unthresholded matrix of Welch's *t*-statistics for all 650 off-diagonal directed connections among the 26 prespecified ROIs, with connections meeting the nominal two-sided uncorrected $p < 0.05$ reporting level marked separately. Complete numerical between-group results for all 650 directed connections are provided in Supplementary Data (Group_EC worksheet).

Associations Between EC and Clinical Measures in Patients with COPD

Age-adjusted partial Pearson correlations were examined for the 37 directed connections meeting the nominal group-comparison criterion. At the nominal $p < 0.05$ level in the COPD group, associations involved pulmonary function, respiratory, or COPD symptom measures (FVC, FVC%, FEV_1/FVC, mMRC, SpO_2, and CAT) and cognitive, affective, or health-status measures (MoCA-K, MMSE, BDI, BAI, and EQ-5D). Figure 3 illustrates the age-adjusted associations between EC and pulmonary function and respiratory/COPD symptom measures. Panels A–C show associations with FVC, D–E with FVC % predicted, F–G with FEV_1/FVC, H–J with mMRC, K–L with SpO_2, and M–N with CAT. Figure 4 illustrates the age-adjusted associations between EC and cognitive, affective, and health-status measures. Panel A shows the association with MoCA-K, B–C with MMSE, D–E with BDI, F–I with BAI, and J with EQ-5D. Detailed correlation coefficients and *p*-values for these associations are provided in Table 3 and Table 4. Corresponding age-adjusted EC–clinical associations in the control group are provided in Supplementary Tables S1 and S2 and Supplementary Figures S2 and S3; pulmonary-function analyses included 27 controls, whereas cognitive, affective, and health-status analyses included all 30 controls. Supplementary Figures S4 and S5 present the complete zero-order and age-adjusted correlation matrices, respectively, and Supplementary Figure S6 presents pairwise explained variance among demographic and clinical variables. Figure 5 provides an integrated anatomical and clinical summary of the 13 directed connections that showed both a between-group difference and at least one age-adjusted clinical association within the COPD group.

Discussion

The present analysis identified distributed direction-sensitive BOLD temporal relationships that differed between patients with COPD and controls and were associated with pulmonary function, respiratory/COPD symptoms, cognition, affect, and health status in COPD. These findings extend our previous resting-state FC study of the same prospectively acquired cohort[12] by characterizing directed temporal relationships among the prespecified FC-informed ROIs.

The principal clinical finding was the convergence of pulmonary, symptomatic, cognitive, affective, and health-status measures at a limited set of directed connections. Posterior-cingulate source connections were prominent: the directed connection from the left PCC to the right iCC was associated with SpO_2, CAT, and BAI; that from the left PCC to the right SPG with FVC%, BAI, and EQ-5D; and that from the left PCC to the left BSTS with FVC, FVC%, and mMRC. These relationships associate posterior-cingulate temporal dynamics with both respiratory disease burden and cognitive–affective experience in COPD. Posterior-cingulate abnormalities have previously been related to pulmonary function and cognition in COPD.[12,21] Within the FC-informed ROI system examined here, the EC results further show that PCC-source temporal dependencies vary with respiratory symptoms, anxiety, and health status.

Systemic oxygenation was associated with the directed connections from the right PCu to the left MTC and from the left PCC to the right iCC. In hypoxemic COPD, oxygen supplementation improves cerebral oxygen delivery and neurovascular function,[22] linking systemic oxygen availability to physiological processes that shape regional BOLD dynamics. The SpO_2 associations therefore place these parietal–temporal and posterior–cingulate relationships within an

Table 2 Between-Group Comparison of VAR-Based Effective Connectivity Coefficients in Patients with COPD and Control Participants

COPD > Control						Control > COPD					
Edges (E01–E17)		VAR Coefficient (mean ± SD)		*t*-statistic	*p*-value	Edges (E18–E37)		VAR Coefficient (mean ± SD)		*t*-statistic	*p*-value
Source ROI	Target ROI	COPD	Control			Source ROI	Target ROI	COPD	Control		
Right PreCG	Right iCC	0.26 ± 0.44	−0.12 ± 0.57	+3.01	0.004	Right MTC	Right SPG	0.03 ± 0.50	0.29 ± 0.49	−2.13	0.037
Left PCC	Left LOC	0.24 ± 0.71	−0.18 ± 0.58	+2.69	0.009	Left PCC	Left BSTS	−0.06 ± 0.58	0.20 ± 0.42	−2.09	0.041
Right PreCG	Right CN	0.21 ± 0.51	−0.17 ± 0.50	+3.09	0.003	Right CB	Left FG	−0.07 ± 0.50	0.16 ± 0.40	−2.09	0.041
Right Th	Left MTC	0.19 ± 0.66	−0.27 ± 0.67	+2.85	0.006	Right PCu	Left MTC	−0.08 ± 0.59	0.25 ± 0.68	−2.09	0.041
Right SPG	Left Th	0.15 ± 0.52	−0.14 ± 0.61	+2.08	0.042	Left FG	Right LOC	−0.11 ± 0.61	0.23 ± 0.62	−2.25	0.028
Left PCC	Right iCC	0.15 ± 0.65	−0.25 ± 0.53	+2.78	0.007	Left Th	Right PCC	−0.13 ± 0.59	0.15 ± 0.48	−2.16	0.034
Right LOC	Left MTC	0.13 ± 0.73	−0.32 ± 0.57	+2.84	0.006	Right Th	Left PCC	−0.13 ± 0.61	0.19 ± 0.55	−2.26	0.027
Left CB	Right Th	0.13 ± 0.50	−0.14 ± 0.33	+2.59	0.012	Left PCC	Left FG	−0.13 ± 0.63	0.22 ± 0.58	−2.34	0.022
Left PreCG	Left PCC	0.12 ± 0.60	−0.29 ± 0.57	+2.89	0.005	Right CN	Right PCu	−0.13 ± 0.43	0.18 ± 0.28	−3.59	0.001
Right FG	Left MTC	0.12 ± 0.56	−0.26 ± 0.68	+2.47	0.016	Right SFG	Left CN	−0.13 ± 0.60	0.15 ± 0.52	−2.10	0.040
Left CB	Left MTC	0.12 ± 0.55	−0.13 ± 0.40	+2.16	0.034	Right SFG	Right PreCG	−0.16 ± 0.62	0.24 ± 0.47	−3.02	0.004
Left CN	Left PCC	0.12 ± 0.54	−0.17 ± 0.47	+2.36	0.021	Left iCC	Right iCC	−0.17 ± 0.56	0.16 ± 0.58	−2.29	0.025
Right PreCG	Left iCC	0.11 ± 0.52	−0.14 ± 0.40	+2.21	0.031	Right LOC	Left SPG	−0.17 ± 0.63	0.16 ± 0.54	−2.30	0.024
Right SPG	Right BSTS	0.11 ± 0.51	−0.23 ± 0.44	+2.90	0.005	Right LOC	Right SFG	−0.17 ± 0.54	0.14 ± 0.56	−2.31	0.024
Right iCC	Right PCu	0.11 ± 0.74	−0.37 ± 0.54	+3.08	0.003	Right CB	Right LOC	−0.22 ± 0.60	0.07 ± 0.45	−2.31	0.024
Right SFG	Left PCu	0.06 ± 0.45	−0.30 ± 0.48	+3.14	0.003	Left PCC	Right SPG	−0.23 ± 0.66	0.13 ± 0.65	−2.25	0.028
Left BSTS	Right MTC	0.05 ± 0.72	−0.39 ± 0.50	+3.00	0.004	Right Th	Right BSTS	−0.24 ± 0.43	0.03 ± 0.52	−2.27	0.027
						Left iCC	Left FG	−0.26 ± 0.66	0.24 ± 0.66	−3.13	0.003
						Right CB	Left LOC	−0.27 ± 0.58	0.05 ± 0.38	−2.70	0.009
						Left SPG	Left FG	−0.33 ± 0.59	−0.04 ± 0.52	−2.10	0.040

Notes: Welch's *t*-tests were applied separately to each directed connection between the 26 prespecified ROIs. The source and target regions, group-specific mean ± sample standard deviation, Welch's *t* statistic, and exact two-sided uncorrected *p*-value are reported for the 37 connections meeting the nominal $p < 0.05$ reporting level. Positive *t* statistics indicate a larger mean VAR coefficient in patients with COPD; negative values indicate a larger mean in control participants. Edge identifiers E01–E37 correspond to Figures 1–2. Results for all 650 off-diagonal directed connections are provided in Supplementary Figure S1 and Supplementary Data (Group_EC worksheet).

Abbreviations: COPD, chronic obstructive pulmonary disease; VAR, vector autoregressive; ROI, region of interest; PreCG, precentral gyrus; iCC, isthmus of cingulate cortex; PCC, posterior cingulate cortex; LOC, lateral occipital cortex; CN, caudate nucleus; Th, thalamus; MTC, middle temporal cortex; SPG, superior parietal gyrus; BSTS, banks of the superior temporal sulcus; PCu, precuneus; SFG, superior frontal gyrus; FG, fusiform gyrus; CB, cerebellum.

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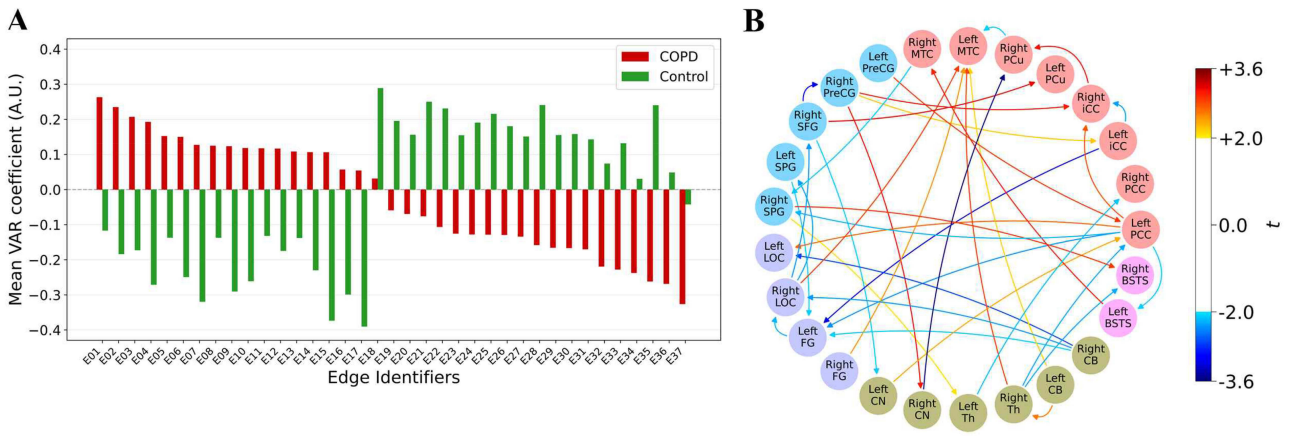

Figure 1 Results of the between-group comparison of VAR-based effective connectivity coefficients in patients with COPD and control participants. (**A**) Group-specific mean VAR coefficients are shown for the 37 directed connections meeting the nominal two-sided uncorrected $p < 0.05$ reporting level in Welch's t tests. Patients with COPD are shown in red and control participants in green. Connections are ordered by the mean coefficient in the COPD group; E01–E37 correspond to Table 2. (**B**) Circular representation of the same connections. Edge color denotes the Welch's t-statistic: positive values indicate a larger mean coefficient in patients with COPD and negative values a larger mean in control participants. Arrowheads indicate the direction from source to target. ROI colors denote anatomical location groups used for visual organization.

Abbreviations: VAR, vector autoregressive; COPD, chronic obstructive pulmonary disease; ROI, region of interest; PreCG, precentral gyrus; iCC, isthmus of cingulate cortex; PCC, posterior cingulate cortex; LOC, lateral occipital cortex; CN, caudate nucleus; Th, thalamus; MTC, middle temporal cortex; SPG, superior parietal gyrus; BSTS, banks of the superior temporal sulcus; PCu, precuneus; SFG, superior frontal gyrus; FG, fusiform gyrus; CB, cerebellum.

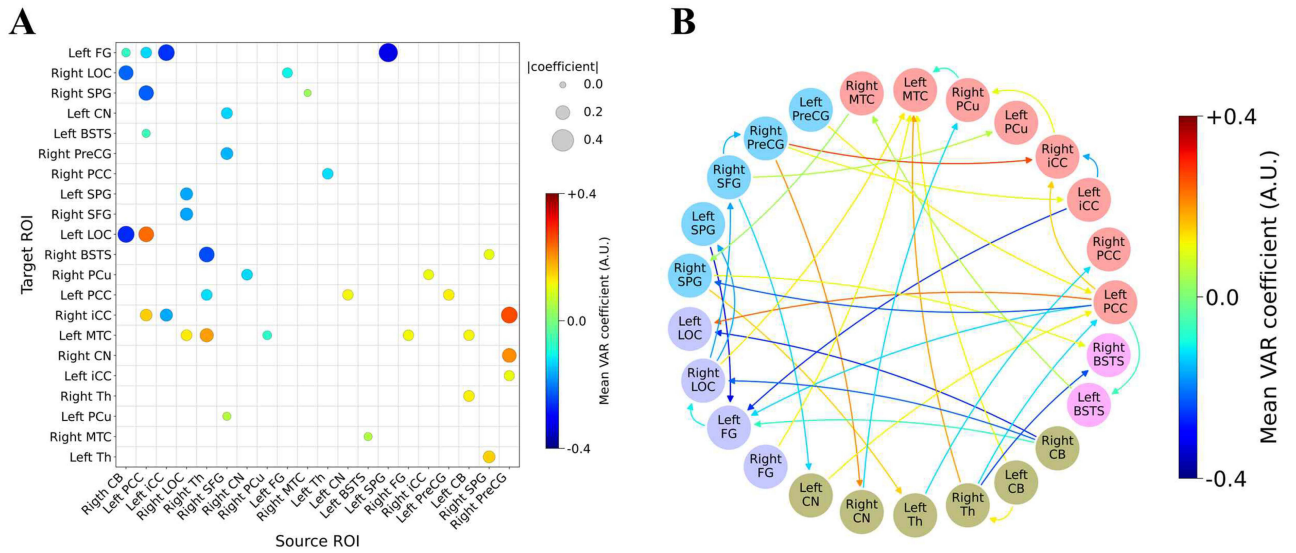

Figure 2 VAR-based effective connectivity coefficients in patients with COPD for connections identified by the between-group comparison. (**A**) Bubble matrix of the mean VAR coefficients in the COPD group for the 37 directed connections meeting the nominal two-sided uncorrected $p < 0.05$ reporting level. Bubble color denotes the coefficient value and bubble area its absolute magnitude. Rows represent target regions and columns represent source regions. (**B**) Circular representation of the same coefficients. Edge color denotes the mean coefficient in the COPD group, and arrowheads indicate the direction from source to target. ROI colors denote anatomical location groups used for visual organization.

Abbreviations: VAR, vector autoregressive; COPD, chronic obstructive pulmonary disease; ROI, region of interest; PreCG, precentral gyrus; iCC, isthmus of cingulate cortex; PCC, posterior cingulate cortex; LOC, lateral occipital cortex; CN, caudate nucleus; Th, thalamus; MTC, middle temporal cortex; SPG, superior parietal gyrus; BSTS, banks of the superior temporal sulcus; PCu, precuneus; SFG, superior frontal gyrus; FG, fusiform gyrus; CB, cerebellum.

oxygenation-sensitive cerebrovascular context and suggest that altered oxygen delivery and neurovascular regulation contribute to this component of EC variation.

Respiratory symptom burden and affective measures converged at several connections. The directed connection from the left CB to the left MTC was associated with FEV_1/FVC, mMRC, and CAT; that from the right MTC to the right SPG with mMRC and BDI; and that from the left PCC to the right iCC with CAT and BAI. Dyspnea in COPD reflects the

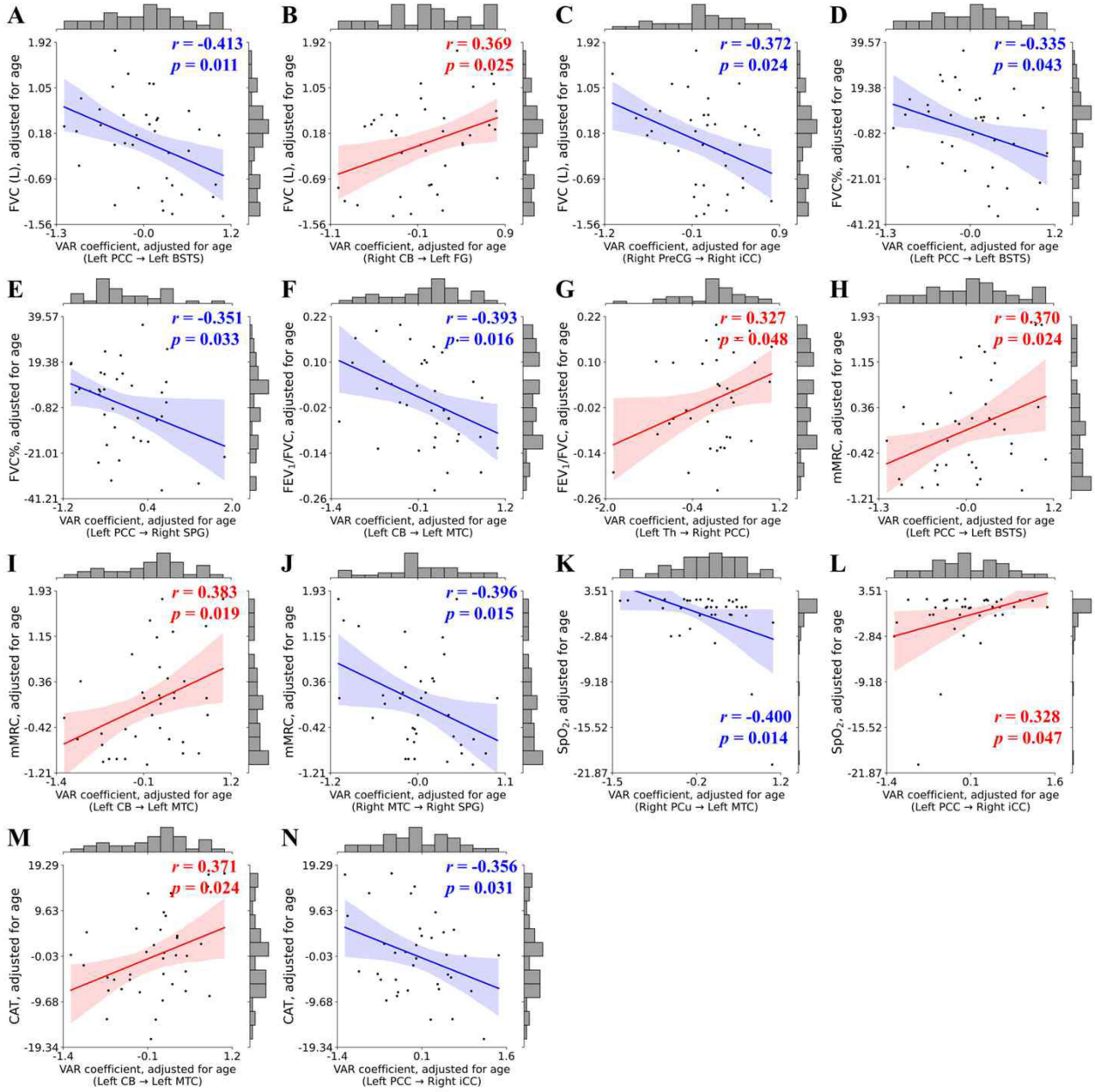

Figure 3 Age-adjusted associations of VAR-based effective connectivity coefficients with pulmonary function and respiratory/COPD symptom measures in patients with COPD. Panels **A–C** show associations with FVC for the directed connections from the left PCC to the left BSTS, from the right CB to the left FG, and from the right PreCG to the right iCC, respectively; **D–E** with FVC % predicted for the connections from the left PCC to the left BSTS and from the left PCC to the right SPG; **F–G** with FEV_1/FVC for the connections from the left CB to the left MTC and from the left Th to the right PCC; **H–J** with mMRC for the connections from the left PCC to the left BSTS, from the left CB to the left MTC, and from the right MTC to the right SPG; **K–L** with SpO_2 for the connections from the right PCu to the left MTC and from the left PCC to the right iCC; and M–N with CAT for the connections from the left CB to the left MTC and from the left PCC to the right iCC. Scatterplots show associations meeting the nominal two-sided uncorrected $p < 0.05$ reporting level among the 37 connections identified by the between-group comparison. Age-adjusted values are residuals obtained after separately regressing age from the VAR coefficient and clinical measure. Each panel reports the first-order partial Pearson correlation coefficient (*r*), exact *p*-value, and effective sample size. Lines show the fitted linear association, with shaded 95% confidence intervals.

Abbreviations: VAR, vector autoregressive; COPD, chronic obstructive pulmonary disease; ROI, region of interest; EC, effective connectivity; FVC (L), forced vital capacity; PCC, posterior cingulate cortex; BSTS, banks of the superior temporal sulcus; CB, cerebellum; FG, fusiform gyrus; PreCG, precentral gyrus; iCC, isthmus of cingulate cortex; FVC%, percent predicted forced vital capacity; SPG, superior parietal gyrus; FEV_1/FVC, FEV_1-to-FVC ratio; MTC, middle temporal cortex; Th, thalamus; mMRC, modified Medical Research Council; SpO_2, peripheral oxygen saturation; PCu, precuneus; CAT, COPD Assessment Test.

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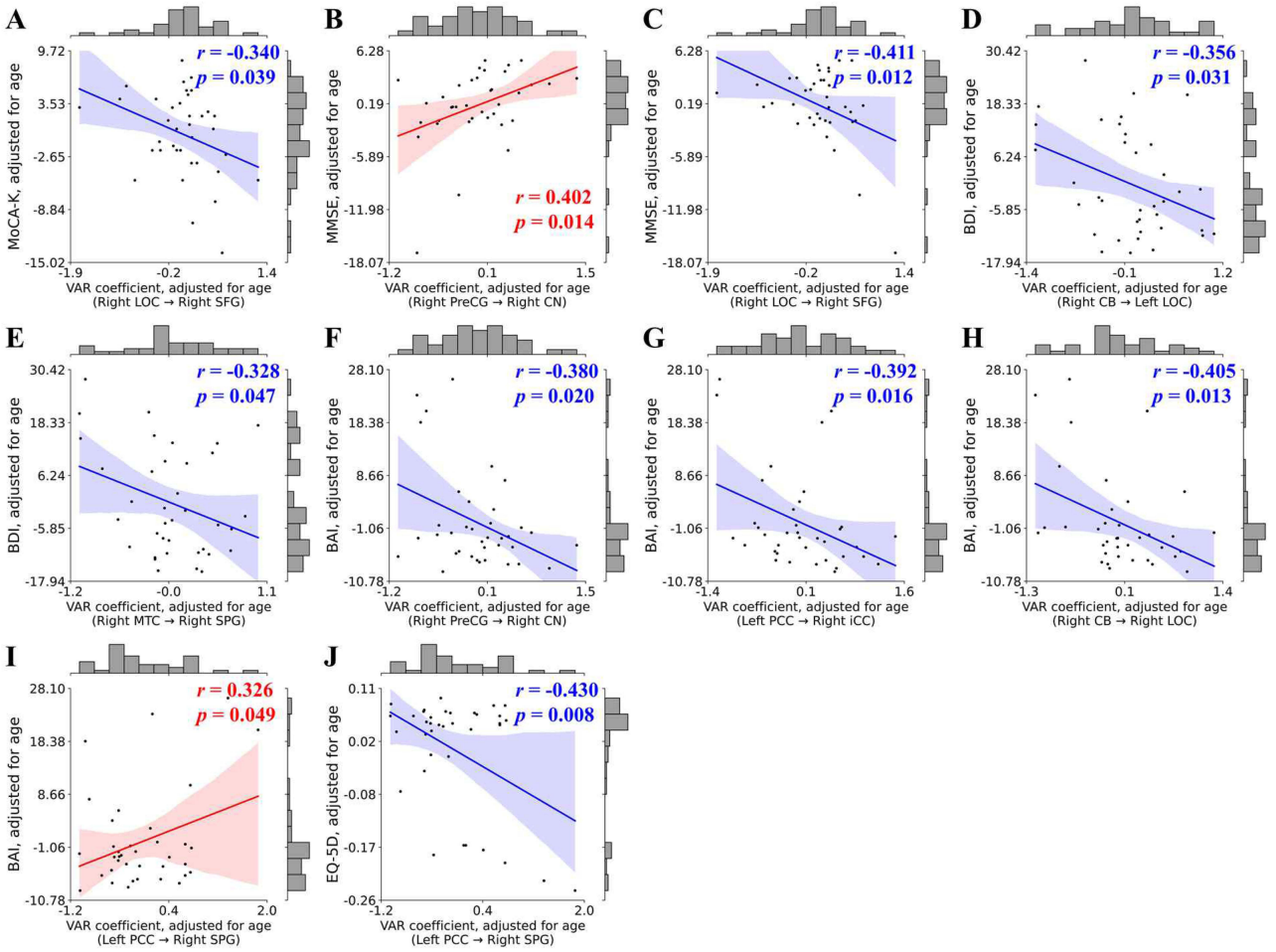

Figure 4 Age-adjusted associations of VAR-based effective connectivity coefficients with cognitive, affective, and health-status measures in patients with COPD. Panel **A** shows the association with MoCA-K for the directed connection from the right LOC to the right SFG; **B–C** with MMSE for the connections from the right PreCG to the right CN and from the right LOC to the right SFG, respectively; **D–E** with BDI for the connections from the right CB to the left LOC and from the right MTC to the right SPG; **F–I** with BAI for the connections from the right PreCG to the right CN, from the left PCC to the right iCC, from the right CB to the right LOC, and from the left PCC to the right SPG; and **J** with EQ-5D for the connection from the left PCC to the right SPG. Scatterplots show associations meeting the nominal two-sided uncorrected p < 0.05 reporting level among the 37 connections identified by the between-group comparison. Age-adjusted values are residuals obtained after separately regressing age from the VAR coefficient and clinical measure. Each panel reports the first-order partial Pearson correlation coefficient (*r*), exact *p*-value, and effective sample size. Lines show the fitted linear association, with shaded 95% confidence intervals. The effective sample size was 38 except for MMSE analyses (n=37).

Abbreviations: VAR, vector autoregressive; COPD, chronic obstructive pulmonary disease; ROI, region of interest; MoCA-K, Korean version of the Montreal Cognitive Assessment; LOC, lateral occipital cortex; SFG, superior frontal gyrus; MMSE, Mini-Mental State Examination; PreCG, precentral gyrus; CN, caudate nucleus; BDI, Beck Depression Inventory; CB, cerebellum; MTC, middle temporal cortex; SPG, superior parietal gyrus; BAI, Beck Anxiety Inventory; PCC, posterior cingulate cortex; iCC, isthmus of cingulate cortex; EQ-5D, EuroQol 5-Dimension.

integration of respiratory sensation with attention, expectation, and affect.[23] Functional imaging studies have shown engagement of prefrontal and emotion-related regions by dyspnea-related cues and distinct brain-activity patterns across breathlessness symptom profiles.[24] The present associations indicate that this respiratory–affective integration is also expressed in resting temporal relationships among cingulate, temporal, parietal, and cerebellar ROIs.

Cognitive measures showed a related cortical–subcortical pattern: the directed connection from the right LOC to the right SFG was associated with both MoCA-K and MMSE, and that from the right PreCG to the right CN with MMSE and BAI. The first relationship links general cognitive status to occipital–frontal temporal organization, whereas the second places cognitive and anxiety-related variation within a cortico-striatal connection. Pulmonary function was also associated with the directed connection from the right PreCG to the right iCC (FVC) and that from the left Th to the right PCC (FEV_1/FVC), linking perirolandic–cingulate and thalamic–cingulate temporal relationships to respiratory physiology. Frontal, cingulate, thalamic, and basal-ganglia circuitry contributes to non-motor inhibitory control.[25] The

Table 3 Age-Adjusted Associations of VAR-Based Effective Connectivity Coefficients with Pulmonary Function and Respiratory/COPD Symptom Measures in Patients with COPD

Clinical Measure	Edges		Partial Pearson Correlation Coefficient (*r*)	*p*-value
	Source ROI	Target ROI		
FVC (L)	Left PCC	Left BSTS	−0.413	0.011
	Right CB	Left FG	+0.369	0.025
	Right PreCG	Right iCC	−0.372	0.024
FVC%	Left PCC	Left BSTS	−0.335	0.043
	Left PCC	Right SPG	−0.351	0.033
FEV_1/FVC	Left CB	Left MTC	−0.393	0.016
	Left Th	Right PCC	+0.327	0.048
mMRC	Left PCC	Left BSTS	+0.370	0.024
	Left CB	Left MTC	+0.383	0.019
	Right MTC	Right SPG	−0.396	0.015
SpO_2	Right PCu	Left MTC	−0.400	0.014
	Left PCC	Right iCC	+0.328	0.047
CAT	Left CB	Left MTC	+0.371	0.024
	Left PCC	Right iCC	−0.356	0.031

Notes: First-order partial Pearson correlations controlling for age were calculated for the 37 connections identified by the between-group comparison. The table reports the source and target regions, clinical measure, partial correlation coefficient (*r*), exact two-sided uncorrected *p*-value, and effective sample size for associations meeting the nominal $p < 0.05$ reporting level. Complete zero-order and age-adjusted correlation matrices are provided in Supplementary Figures S4 and S5.

Abbreviations: VAR, vector autoregressive; COPD, chronic obstructive pulmonary disease; ROI, region of interest; EC, effective connectivity; FVC (L), forced vital capacity; PCC, posterior cingulate cortex; BSTS, banks of the superior temporal sulcus; CB, cerebellum; FG, fusiform gyrus; PreCG, precentral gyrus; iCC, isthmus of cingulate cortex; FVC%, percent predicted forced vital capacity; SPG, superior parietal gyrus; FEV_1/FVC, FEV_1 to FVC ratio; MTC, middle temporal cortex; Th, thalamus; mMRC, modified Medical Research Council; SpO_2, peripheral oxygen saturation; PCu, precuneus; CAT, COPD Assessment Test.

Table 4 Age-Adjusted Associations of VAR-Based Effective Connectivity Coefficients with Cognitive, Affective, and Health-Status Measures in Patients with COPD

Clinical Measure	Edges		Partial Pearson Correlation Coefficient (*r*)	*p*-value
	Source ROI	Target ROI		
MoCA-K	Right LOC	Right SFG	−0.340	0.039
MMSE	Right PreCG	Right CN	+0.402	0.014
	Right LOC	Right SFG	−0.411	0.012
BDI	Right CB	Left LOC	−0.356	0.031
	Right MTC	Right SPG	−0.328	0.047
BAI	Right PreCG	Right CN	−0.380	0.020
	Left PCC	Right iCC	−0.392	0.016
	Right CB	Right LOC	−0.405	0.013
	Left PCC	Right SPG	+0.326	0.049
EQ-5D	Left PCC	Right SPG	−0.430	0.008

Notes: First-order partial Pearson correlations controlling age were calculated for the 37 connections identified by the between-group comparison. The source and target regions, clinical measure, partial correlation coefficient (*r*), exact two-sided uncorrected *p*-value, and effective sample size are reported for associations meeting the nominal $p < 0.05$ reporting level. The effective sample size was 38 except for analyses involving MMSE (n=37). Complete zero-order and age-adjusted correlation matrices are provided in Supplementary Figures S4 and S5.

Abbreviations: VAR, vector autoregressive; COPD, chronic obstructive pulmonary disease; ROI, region of interest; MoCA-K, Korean version of the Montreal Cognitive Assessment; LOC, lateral occipital cortex; SFG, superior frontal gyrus; MMSE, Mini-Mental State Examination; PreCG, precentral gyrus; CN, caudate nucleus; BDI, Beck Depression Inventory; CB, cerebellum; MTC, middle temporal cortex; SPG, superior parietal gyrus; BAI, Beck Anxiety Inventory; PCC, posterior cingulate cortex; iCC, isthmus of cingulate cortex; EQ-5D, EuroQol 5-Dimension.

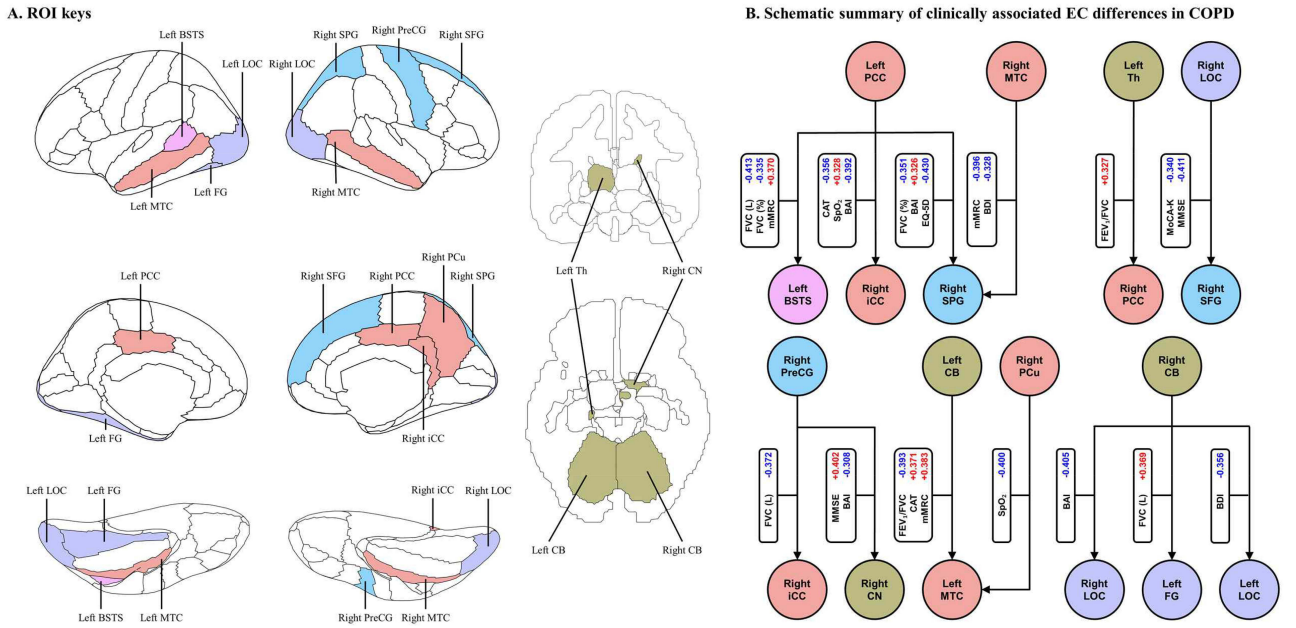

Figure 5 Anatomical and clinical summary of directed effective connectivity findings in patients with COPD. (**A**) Anatomical key for the cortical, subcortical, and cerebellar regions included in the schematic. Cortical regions are displayed in lateral, medial, and ventral views; subcortical and cerebellar regions are displayed separately. ROI colors denote anatomical location groups used for visual organization. (**B**) The 13 directed connections that showed a between-group difference at the nominal two-sided uncorrected $p < 0.05$ reporting level and at least one age-adjusted clinical association within the COPD group at the same reporting level. Arrowheads indicate the direction from source to target. Clinical measures are shown alongside their corresponding connections; red and blue values denote positive and negative partial Pearson correlation coefficients (r), respectively.

Abbreviations: VAR, vector autoregressive; EC, effective connectivity; COPD, chronic obstructive pulmonary disease; ROI, region of interest; PCC, posterior cingulate cortex; BSTS, banks of the superior temporal sulcus; iCC, isthmus of cingulate cortex; SPG, superior parietal gyrus; MTC, middle temporal cortex; LOC, lateral occipital cortex; PreCG, precentral gyrus; SFG, superior frontal gyrus; PCu, precuneus; FG, fusiform gyrus; Th, thalamus; CN, caudate nucleus; CB, cerebellum; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; mMRC, modified Medical Research Council; SpO_2, peripheral oxygen saturation; CAT, COPD Assessment Test; MoCA-K, Korean version of the Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; EQ-5D, EuroQol 5-Dimension.

convergence across these cortical–subcortical connections suggests that broader cognitive-control processes may contribute to cognitive–affective variation in COPD.

Cerebellar source connections formed another consistent component of the clinical-association pattern. The directed connection from the left CB to the left MTC varied with FEV_1/FVC, mMRC, and CAT; that from the right CB to the left FG with FVC; that from the right CB to the left LOC with BDI; and that from the right CB to the right LOC with BAI. The cerebellum participates in motor, cognitive, and affective regulation,[26] and cerebellar involvement was also observed in our earlier FC analysis of this cohort.[12] The alignment of cerebellar-source EC with respiratory and affective measures suggests a role in coordinating internal respiratory state, symptom appraisal, and affective response in COPD. Across all recurrent connections, EC varied with complementary dimensions of disease burden, including spirometry, oxygen saturation, dyspnea, COPD symptoms, cognition, affect, and health status. This multidimensional convergence provides a clinically meaningful description of central-nervous-system involvement in patients with COPD and may help characterize variation in symptoms and cognitive burden among patients with similar degrees of airflow limitation.

One notable finding was the connectivity between the right PreCG and the right CN. The PreCG corresponds to the primary motor cortex and plays a central role in voluntary motor control, whereas the CN, a component of the basal ganglia, is involved in motor planning, cognitive processes, and emotional regulation. In the COPD group, the directed connection from the right PreCG to the right CN was positively associated with MMSE and negatively associated with BAI. In the control group, the same connection was positively associated with FEV_1 and FEV_1/FVC. These group-specific associations suggest differential clinical coupling of the PreCG–CN connection across respiratory, cognitive, and affective domains. Furthermore, the PreCG showed negative correlations with FVC in patients with COPD but positive correlations with pulmonary indices in controls. Thus, the PreCG–CN connection was associated with cognitive and affective measures in patients with COPD, whereas its associations in controls involved pulmonary function. The present

results included a directed connection from the right precentral gyrus to the right caudate nucleus. Liang et al's ALE meta-analysis identified convergent grey-matter abnormalities in the left precentral, right postcentral, and left cingulate/paracentral regions,[3] and Li et al's whole-brain degree-centrality and seed-based FC study reported reduced functional hub measures in bilateral supplementary motor areas and the right paracentral lobule.[10] Yu et al also reported altered motor-cortex connectivity and Granger-based information flow at rest and during inspiratory loading.[9] Collectively, these studies place precentral and related motor-cortical regions within the COPD neuroimaging literature. The present VAR result adds direction-sensitive information by identifying a candidate lagged relationship from the right PreCG to the right CN. Variation in exact connections across studies is consistent with differences in structural versus functional measures, ROI definition, resting versus loaded-breathing conditions, acquisition and preprocessing, and cohort characteristics. Our previous FC study provided the closest regional comparator and links the present analysis to the predefined ROI set.[12]

Notably, several connections showed either shared or group-specific clinical associations. In the COPD group, the directed connection from the right CB to the left LOC was negatively associated with BDI. Previous studies have reported functional abnormalities in visual cortex regions in patients with major depressive disorder. In that context, the present findings may be compatible with the possible involvement of visual cortical networks in mood-related symptoms, although no specific mechanism can be inferred from the current data.[27] Moreover, Li et al reported that altered FC involving occipital regions may contribute to the early identification of depressive symptoms in individuals with subthreshold depression.[28]

Another key finding was the connectivity between the right Th and the left MTC. This connection showed a positive correlation with SpO_2 in the COPD group and a negative correlation with the BDI in the control group. Beyond the directed connection from the right PreCG to the right CN, findings showing between-group differences and clinical associations involved cingulate (PCC and iCC), parietal (SPG and PCu), occipital and ventral temporal (LOC and FG), lateral temporal (MTC and BSTS), thalamic, and cerebellar ROIs. Hu et al reported posterior-cingulate connectivity abnormalities related to cognitive and pulmonary measures;[21] Tang et al identified distributed static and dynamic connectivity alterations[11] and Lv et al described local static and dynamic activity changes in basal-ganglia and hippocampal/parahippocampal regions associated with oxygenation, pulmonary function, or cognition.[29] Our preceding FC study of the same cohort also implicated cingulate, temporal, thalamic, precuneus, occipital, and cerebellar regions.[12] Across these studies, COPD-related brain alterations converge on distributed cortical, subcortical, and cerebellar regions. Differences in the exact regional relationships reflect the distinct properties measured by morphology, conventional FC, dynamic connectivity, local-activity indices, and VAR-based EC, together with differences in ROI definition, acquisition, preprocessing, and cohort characteristics. Reduced oxygenation is a common pathophysiological feature of COPD, and chronic hypoxemia may disrupt thalamocortical signaling and impair cognitive network modulation. Therefore, the observed association between thalamocortical connectivity and oxygen saturation may reflect the influence of systemic oxygenation on brain network organization. Further studies are required to clarify the functional significance of this connection and its relationship with disease severity.

The clinical significance of the present findings lies in the convergence of EC associations across pulmonary physiology, respiratory symptoms, cognition, affect, and health status. The recurrence of a limited set of directed connections across several clinical domains links EC variation to the multidimensional burden of COPD. In patients with similar degrees of airflow limitation, these central patterns provide biological context for variation in dyspnea, anxiety, cognitive status, and perceived health. They may therefore help direct attention to respiratory, cognitive, and affective domains that are incompletely represented by spirometry alone. Breathlessness-related brain activity has been associated with improvement during pulmonary rehabilitation,[30] supporting the clinical relevance of cerebral respiratory-symptom processing to COPD management. Together, the present findings position resting temporal relationships as a systems-level correlate of clinically meaningful respiratory, cognitive, and affective variation.

Limitations

Some limitations of this study should be acknowledged. First, the cross-sectional design limits the ability to infer causal relationships between COPD progression and changes in brain EC. Longitudinal studies are required to clarify how EC alterations evolve with disease progression and whether they predict future cognitive decline in patients with COPD.

Second, the modest cohort size limits the generalizability of the findings and the evaluation of their clinical relevance at the individual-patient level. Recruitment of older adults with COPD and appropriately age-matched control participants who satisfy the clinical, imaging-eligibility, and quality-control criteria remains challenging. Medication exposure and some clinical characteristics were incompletely or heterogeneously documented, while the modest sample size limited stable multivariable adjustment for smoking history, COPD severity, and other potential confounding factors. Residual confounding by these factors therefore cannot be excluded. Larger multicenter or consortium-based longitudinal studies would enable more rigorous evaluation of the reproducibility and clinical utility of the observed EC patterns.

Third, although EC analysis provides information on the directionality of interactions between brain regions, it does not fully capture the complex neurophysiological mechanisms underlying these interactions. Resting-state fMRI-based VAR analysis captures direction-sensitive temporal dependencies in hemodynamically filtered BOLD signals, which limits detailed biological interpretation. In addition, because BOLD fMRI is an indirect hemodynamic measure, group differences in COPD may also be influenced by vascular dysfunction, cardiopulmonary physiology, or medication-related effects, which should be considered when interpreting directed temporal dependencies. Therefore, the interpretation of directed connectivity should be approached with caution. A multimodal approach incorporating complementary neuroimaging and physiological measures would help clarify the neurobiological mechanisms underlying the observed EC alterations.

Finally, cognitive function in this study was assessed using global screening tools such as MoCA-K and MMSE, which may not capture subtle domain-specific cognitive impairments. Future studies incorporating detailed neuropsychological assessments may provide deeper insights into the relationship between brain network alterations and specific cognitive domains in COPD.

Conclusion

In conclusion, resting-state VAR-based EC revealed distributed between-group differences in direction-sensitive BOLD temporal organization in COPD. Among the EC measures that differed between groups, several were associated with pulmonary function, SpO_2, respiratory and COPD symptom burden, cognition, affect, and health status after age adjustment. These findings extend the FC profile of the same cohort and show that directed temporal relationships among the implicated cortical, subcortical, and cerebellar ROIs covary with the multidimensional burden of COPD.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgment

An unauthorized version of the Korean MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no relevant conflicts of interest.

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