A resting-state fMRI study in chronic obstruction pulmonary disease

Ai Wern Chung, James W. Dodd, Rebecca A. Charlton, Paul W. Jones, and Thomas R. Barrick

Stroke and Dementia Research Centre, St George’s University of London, London, London, United Kingdom, Division of Clinical Science, St George’s University of London, London, United Kingdom, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, United States

Introduction Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition predominantly affecting long-term smokers which includes emphysema and chronic bronchitis. It is increasingly recognised to be a multi-system disorder associated with a wide range of extra pulmonary comorbidities such as heart disease, anaemia and diabetes. Brain pathology is another potential systemic manifestation with evidence of cognitive dysfunction in hypoxaemic individuals. However, impairment is also present in the absence of hypoxaemia, in addition to widespread, white matter damage. Other possible mechanisms for cognitive dysfunction in COPD include systemic inflammation and cerebrovascular disease. Resting-state functional magnetic resonance imaging (rfMRI) measures low-frequency fluctuations in blood oxygen level-dependent signals in the brain at rest. Regions in the brain with synchronised temporal signal fluctuations are known as resting-state networks (RSN). Functional connectivity changes in RSN have been associated with cognitive dysfunction in diseases such as Alzheimer’s.

Given the presence of cognitive impairment in stable, non-hypoxaemic COPD patients, we investigate whether there are differences in the functional connectivity of RSN between COPD and control subjects.

Method

Subjects – 25 clinically diagnosed, stable, non-hypoxaemic COPD patients (mean age 67.8±8.2) and 25 age matched controls (mean age 65.3±7.9) were recruited. Patients had moderate health status impairment of 51.6±20 (SGRQ: St George’s Respiratory Questionnaire) and FEV₁ of 53±21 (% predicted forced expiratory volume in 1 second).

rfMRI acquisition – Participants were scanned on a 3T Philips Achieva TX, gradient strength 80mT m⁻³, 32-channel head coil. The protocol included 1) T₁-weighted 3D TFE – TR/TE=8200/3700ms, flip angle=8°, FOV=240mm², 160 sagittal slices, voxel dimensions=1mm³ and 2) Resting-state fMRI – T₂*-FE-EPI, TR/TE=2000/30ms, FOV=240mm², matrix=80³, 28 axial slices, voxel dimensions=3mm³. Acquisition time = 6min, yielding 180 whole brain volumes. Analysis – Resting-state fMRI data was analysed using MELODIC (FSL v4.1, www.fmrib.ox.ac.uk/fsl). Pre-processing stages included motion correction, brain extraction, application of a high-pass filter equivalent to 150 seconds (0.007 Hz), spatial smoothing using a 6mm FWHM Gaussian kernel, and registration of the functional data into MNI space (via the individual’s T₁ data). Independent component analysis (ICA) was performed on all 50 subjects’ rfMRI data temporally concatenated into a single 4D dataset and large-scale functional connectivity common to all samples were decomposed into 20 components.

To compare subject groups, dual-regression was performed to compute estimates of subject-specific spatial maps for each component. For each RSN component, differences between groups were tested using threshold-free cluster enhancement, non-parametric permutation testing (10’000 permutations). Family-wise error corrected voxels were then thresholded at p < 0.01.

Results

Figure 1 presents mean spatial maps of all 50 subjects thresholded at z > 2.3 for six RSN components identified by ICA. For each RSN, significant clusters where patients showed reduced functional connectivity compared to controls are illustrated in cold colours (p < 0.01). No significant differences were found in the visual network. Example locations of significant clusters between groups are: Default mode network – posterior cingulate gyrus, precuneous cortex and bilaterally in the lateral parietal cortices. Pre-frontal – frontal poles, anterior portion of the cingulate gyrus, and bilaterally in the inferior frontal gyrus.

Discussion

We present the first resting-state fMRI study on COPD patients. RSN have been shown to correspond with task activated functional networks and are also potential markers of disease progression such as in Alzheimer’s disease.

We have found a widespread decrease in resting-state functional connectivity in five out of six RSN for stable COPD patients compared with controls. Future work will investigate the relationship between rfMRI and cognitive dysfunction to further understand the observed group differences.

References

[9] Smith et al., PNAS, 2009; 106:13040-13045

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Figure 1 – ICA extracted RSN components from COPD patients and controls. Mean RSN spatial maps for all 50 subjects are shown using hot colours. Regions of significant group differences (p < 0.01) are shown in cold colours. DMN = Default mode network, RFP = Right fronto-parietal, LFP = Left fronto-parietal, Vis = Visual, SM+Aud = Sensorimotor and auditory, PF = Pre-frontal. MNI coordinates (mm) shown for slice locations.