Structural and functional brain correlates of symptom presentation in post-COVID syndrome

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INTRODUCTION

Post-COVID syndrome (PCS) is a growing public health concern, with population prevalence conservatively estimated at 30%, and a high symptom burden lasting weeks to months after infection for affected individuals [1]. Symptom presentation is variable, and may include dyspnea, fatigue, hyposmia/hypogeusia and headache [2]. Although there is evidence for neural involvement in COVID-19 infection and subsequent functional impairments [3], the mechanisms giving rise to specific symptom complaints in PCS cohorts remain poorly understood. This is a critical area of investigation, so as to develop evidence-based subtyping and potentially develop targeted treatments and interventions.

The present cross-sectional observational study collected clinical and multi-parameter magnetic resonance imaging (MRI) data from patients with PCS and controls with non-COVID viral infection, as part of the Toronto-based NeuroCOVID-19 initiative [4]. This study tested whether there are distinct patterns of altered brain function and tissue microstructure associated with specific symptoms, by correlating them with resting-state functional MRI (rs-fMRI) measures of brain function and diffusion-weighted imaging (DWI) measures of white matter microstructure.

METHODS

Study participants: the study included 57 self-isolating individuals with PCS (38 female, mean age: 41.3 ± 11.9 yrs.) and 17 controls with non-COVID infection (10 female, mean age: 41.5 ± 13.1 yrs.). Diagnosis was based on rt-PCR testing, with clinical and MRI assessments conducted an average of 4-5 months post-infection.

Clinical data: this included questionnaires evaluating self-reported symptom status. The study focused on four high-prevalence symptoms: (1) dyspnea, (2) fatigue, (3) hyposmia, (4) headache.

Neuroimaging data: imaging was conducted on a 3 Tesla Siemens Prisma MRI system and included a 1-hour battery of multi-parameter brain imaging. The present study focused on rs-fMRI measures of functional connectivity, and DWI measures of mean diffusivity (MD).

Data analysis: Spearman partial correlations were calculated between imaging measures (i.e., functional connectivity and MD) and symptom presence, adjusting for age and sex; significant effects were identified at a False Discovery Rate threshold of FDR=0.05. For rs-fMRI data, functional connectivity was measured between parcels of the Brainnettome Atlas (BNA).

SUMMARY AND CONCLUSIONS

Significant patterns of altered functional connectivity were associated with ongoing PCS symptoms, including extensive fronto-parietal increases for dyspnea and hyposmia, more limited frontal increases for fatigue and extensive subcortical decreases for headache. Similarly, focal areas of reduced MD were seen in white matter, including the cerebral peduncle for dyspnea and fatigue, the corpus callosum for hyposmia, and the corona radiata and thalamic radiations for headache.

Therefore, as hypothesized, the different symptoms endorsed by the PCS cohort were associated with distinct patterns of altered brain function and tissue microstructure. These findings provide encouraging preliminary evidence for neural "phenotypes" of PCS, providing novel insights into this highly prevalent disorder. Moreover, the study finding may pave the way towards developing targeted treatments and interventions for afflicted patients.

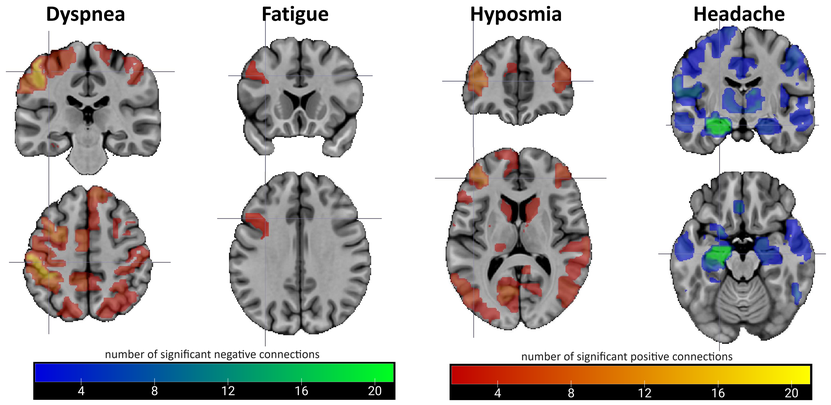
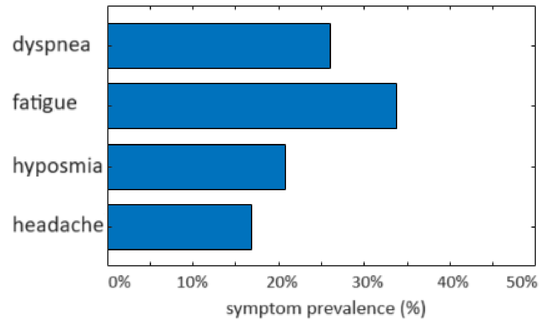


Figure 1: rs-fMRI connectivity analyses. Heatmaps show, for each brain parcel, the number of functional connections that have significant association with each PCS symptom. Symptoms were associated with increased connectivity for dyspnea (mainly parietal), fatigue (inferior frontal) and hyposmia (mainly orbitofrontal), and with decreased connectivity for headache (mainly amygdala). For all symptoms, effects tended to be left-lateralized, with headache showing the greatest number of significant connections (325) and fatigue showing the fewest (20).



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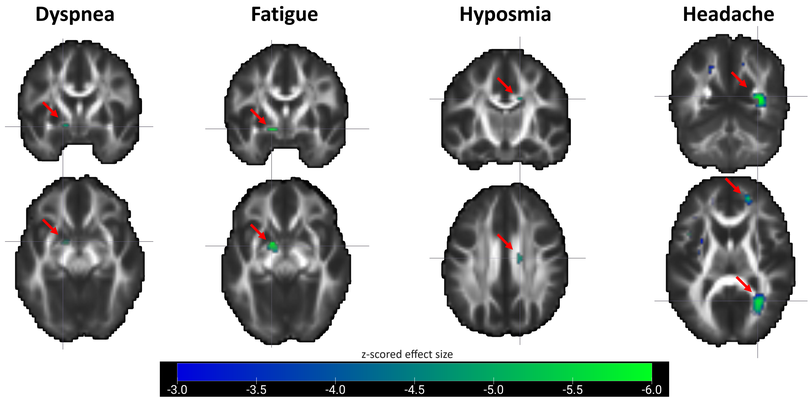

Figure 2: DWI analyses. Heatmaps show z-scored strength of association between regional MD values and each PCS symptom, for significant voxels. Symptoms were associated with decreased MD for dyspnea and fatigue (left cerebral peduncle), hyposmia (body of corpus callosum), and headache (right anterior corona radiata and posterior thalamic radiation). Headache showed the greatest extent of significant voxels (15282 mm^3), while dyspnea showed the least extensive effects (540 mm^3).