



INTRODUCTION

Among the lingering effects of COVID-19, one of the most pernicious is the phenomenon of "brain fog." Cognitive problems are recognized facets of Post-COVID-19 Condition (PCC) involving difficulties with concentration and attention, and maintaining alertness during waking hours. All of these symptoms are potentially linked to the operation of the prefrontal cortex, under the umbrella term of executive functions.

Beyond this, the lateral PFC is also involved in the modulation of emotional responses, particularly reactive negative emotions such as anxiety and irritability. Additionally, the dlPFC is typically hypoactive in major depression. To the extent that COVID-19 adversely affects the prefrontal cortex, the above cognitive and emotional regulatory processes may also be affected, increasing the chances of psychiatric symptoms emerging.

The current investigation used a lab study and interlinked population survey to explore the associations among brain oxygen saturation, cognitive problems and psychiatric symptoms. It was hypothesized that symptomatic COVID-19 would be linked to increased inhibitory and attentional problems, and later development of psychiatric symptoms. It was further anticipated that COVID-19 would be linked to reduced oxygen saturation within the lateral PFC.

METHODS

To test the above hypothesis, we examined data from the Canadian COVID-19 Experiences project (CCEP). This investigation included a laboratory study (Study 1), and an interlinked national population survey (Study 2).

Participants in Study 1 were 120 fully vaccinated adults. In the laboratory, participants completed a Flanker interference task (a measure of the inhibition facet of executive function) as well as a delay discounting task (DD; a measure of decision making) via desktop computer. Task-related oxygenated hemoglobin (Δ HbO) was measured in real time using functional near-infrared spectroscopy (fNIRS), and psychiatric symptoms were self-reported. **Participants in Study 2** were 2002 adults drawn from a nationally representative survey panel (~50% fully vaccinated). In this prospective study, SARS-CoV-2 infection status was assessed at baseline and symptoms of cognitive problems (executive function) and psychiatric symptoms (anxiety, depression and irritability) were assessed at 6-month follow-up. Latent variable modelling was used to examine associations between these three variables over time, using demographic factors as covariates.

Psychiatric Symptoms (both studies). Psychiatric symptoms were assessed using the Center for Epidemiological Studies Depression 10-item scale (CESD-10; Andresen et al., 1994), the Generalized Anxiety Disorder Scale 7-item measure (GAD-7; Spitzer et al., 2006), and a custom developed, 3-item agitation symptom measure assessed using the following items: "I felt agitated", "I lashed out at other people in a way that was not like me", and "I was much more irritable than usual". Responses were provided to each stem on a 4-point scale, where 1 = "Rarely or none of the time (Less than 1 day)", 2 = "Some or a little of the time (1-2 days)", 3 = "Occasionally or a moderate amount of time (3-4 days)", and 4 = "All of the time (5-7 days)". Internal consistency reliabilities for the CESD-10, GAD-7 and agitation items were all acceptable ($\alpha = .802, .864, 0.704$). These measures were significantly intercorrelated (p 's < 0.001; r 's > 0.500), and visual inspection of a scree plot clearly indicated the underlying presence of a single factor representing 73.32% of the variance, with factor loadings of .860 for CESD-10, 0.878 for GAD-7, and 0.830 for agitation items. As such, for the sake of parsimony, scores on each of these psychiatric symptoms measures were subjected to z-score transformations and then averaged together to yield a psychiatric symptoms score index, with higher scores indicating higher levels of psychiatric symptoms.

Cognitive function. In Study 1, cognitive function was assessed using two computer based tasks: a Flanker task, and a Delay Discounting task (DD; Koffarnus and Bickel, 2014). In Study 2, cognitive function was assessed using a self-reported measure of cognitive dysfunction (Barkley Deficits in Executive Functioning Scale; Barkley, 2011).

RESULTS

In Study 1, a positive history of COVID-19 was associated with significantly worse performance on the Flanker task (coefficient: -22.862 , $SE=10.096$, $t=2.265$, $p=.026$). fNIRS findings indicated reduced task-related HbO concentrations in the superior frontal gyrus, an effect that was significantly stronger for older women than other demographic subgroups ($F_{1,143.1}=6.352$, $p=.013$).

In Study 2, we used latent variable modelling to test a mediation model linking COVID-19 history at baseline with psychiatric symptoms at follow up, as mediated through self-reported symptoms of cognitive dysfunction, as assessed by BDEFS scores. The path models fit well in both prospective (RMSEA = 0.023; SRMR = 0.024; CFI = 0.984; TLI = 0.972) and cross-sectional (RMSEA = 0.025; SRMR = 0.020; CFI = 0.981; TLI = 0.967) analyses. The measurement models indicated reasonable measurement properties, with all estimated factor loadings being positive and statistically significant, and of at least moderate magnitude (Fig. 2). Following adjustment for confounders (age, sex, geographic region), there was a significant association between symptomatic COVID-19 and BDEFS scores. Specifically, using all variables as continuous, there was a significant indirect effect of symptomatic COVID-19 on psychiatric symptoms, mediated through BDEFS scores (prospective indirect effect = 0.434, $SE = 0.210$, $p = .039$; cross-sectional indirect effect = 0.214, $SE = 0.067$, $p = .001$).

Finally, new incident COVID-19 among previously uninfected participants between Waves 1 and 2 predicted marginally greater psychiatric symptoms for unvaccinated individuals (est=0.589, $SE=0.321$, $p=.066$) as compared with vaccinated individuals.

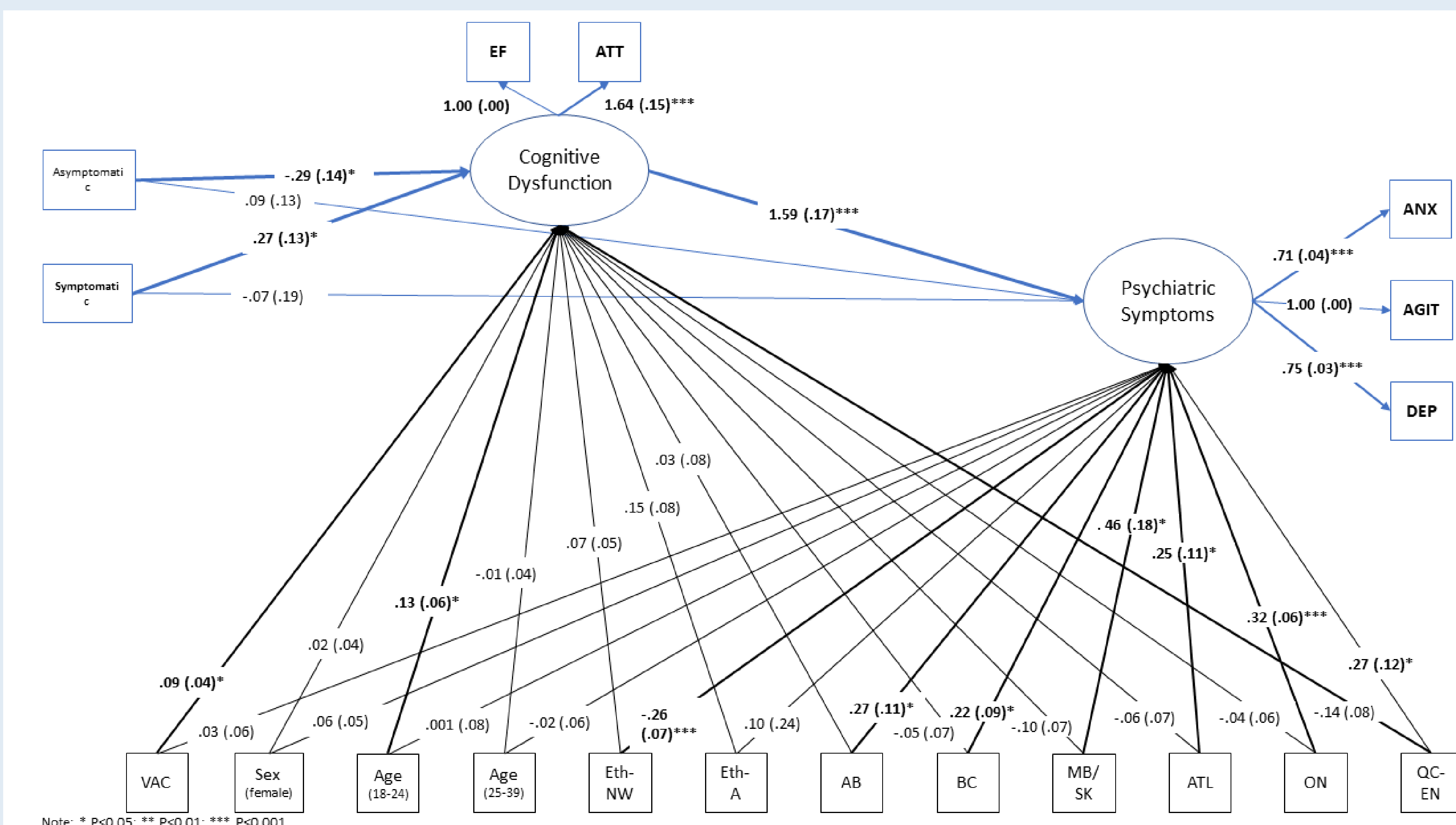
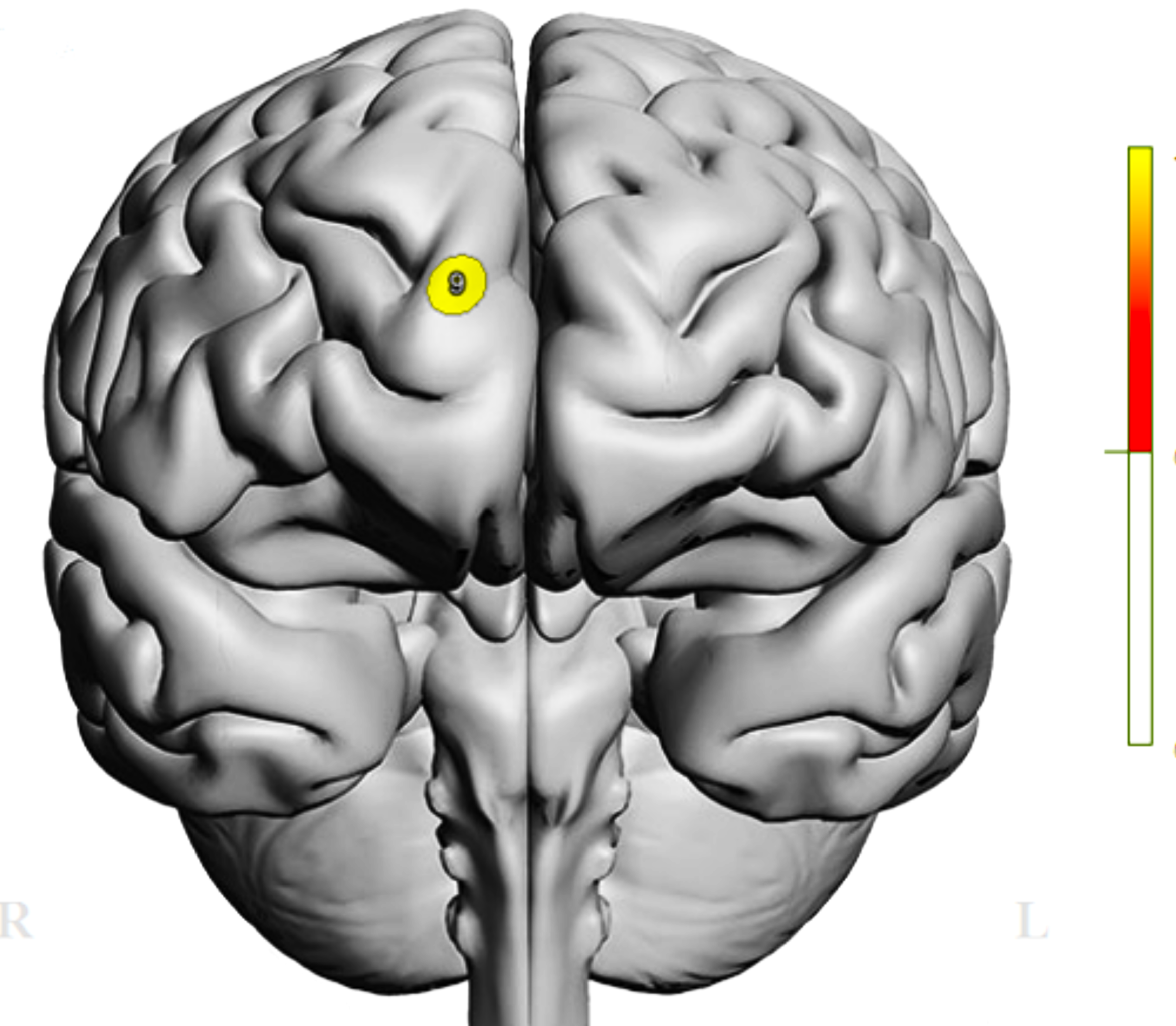
Highlights

- Using data from the Canadian COVID-19 Experiences Project, we examined associations between COVID-19 and several indicators of cognitive dysfunction, brain oxygen saturation, and psychiatric symptoms.
- COVID-19 was associated with greater self-reported symptoms of cognitive dysfunction, worse performance on computer-based tests of executive function, and reduced task-related oxygenation within the superior frontal gyrus of the PFC.
- In population based prospective analyses, COVID-19 at baseline predicted increased levels of psychiatric symptoms >6 months later. This prospective association appeared to be statistically accounted for by symptoms of cognitive dysfunction.
- COVID-19 may influence cognitive and psychiatric function in a causal manner.

Citation:

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CONCLUSION

COVID-19 is associated with self-reported symptoms of cognitive dysfunction and psychiatric symptoms >6 months after infection. Similar associations are evident when performance based cognitive tasks are used. Oxygen uptake within the prefrontal cortex during task performance appears to be negatively impacted, particularly among older adult women.

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