Executive dysfunction following SARS-CoV-2 infection: A cross-sectional examination in a population-representative sample

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Abstract

Objective: To determine whether SRS-CoV-2 infection and COVID-19 symptom severity are associated with executive dysfunction among members of the general population, including those not hospitalized or exposed to intubation.
Design: Cross-sectional observation study with data from an ongoing national cohort study of young and middle-aged adults. The Canadian COVID-19 Experiences Survey (CCES) involves 1,958 adults with equal representation of vaccinated and vaccine hesitant adults between the ages of 18 and 54 years.
Setting: Population-based survey of community dwelling adults, representative of the broader Canadian population.
Participants: Men and women between 18 and 54 years of age from English and French speaking provinces. The sample comprised 1,958 adults with a mean age of 37 years (*SD*=10.4); 60.8% were female.
Exposures: SARS-CoV-2 infection with COVID-19 symptoms of any severity, ranging from negligeable to life-threatening infection requiring hospitalization.
Primary Outcome: Symptoms of cognitive dysfunction assessed via an abbreviated form of the Barkley Deficits in Executive Functioning Scale (BDEFS).
Results: Those who reported a prior SARS-CoV-2 infection regardless of COVID-19 symptom severity (M_{adj}=1.89, *SE*=0.08, *CI*: 1.74, 2.04; n=175) reported a significantly higher number of symptoms of executive dysfunction than their non-infected counterparts (M_{adj}=1.63, *SE*=0.08, *CI*: 1.47,1.80; *n*=1,599; β=0.26, *p*=.001). Among those infected, there was a dose-response relationship between COVID-19 symptom severity and level of executive dysfunction, with moderate (β=0.23, *CI*: 0.003-0.46) and very/extremely severe (β= 0.69, *CI*: 0.22-1.16) COVID-19 symptoms being associated with significantly greater dysfunction. These effects remained reliable and of similar magnitude after removing those who had been received intubation.
Conclusions: Positive SARS-CoV-2 infection history and COVID-19 symptom severity are associated with executive dysfunction among young and middle-aged adults with no history of medically induced coma.

Key words: SARS-CoV-2, COVID-19, brain, cognition, executive function

Introduction

Cognitive dysfunction is one of the potential adverse consequences of SARS-CoV-2 infection. It is understood that SARS-CoV-2 could impact the brain through a number of non-exclusive, indirect mechanisms including hypoxia, thrombosis, coagulopathy, cytokine storm, and megakaryocyte invasion[1-6] .Studies of hospitalized patients have revealed cognitive deficits in the areas of memory, spatial navigation, attention, short-term memory, and executive function[5,7] Further, the cognitive impairments following SARS-Cov-2 infection may persist after the acute phase of infection [5], a phenomenon known as "long covid"[8,9].

Several studies have reported reliable evidence of cognitive dysfunction among those previously infected with SARS-CoV-2.[7, 10-14] However, some of these studies are limited by non-representative samples and lack of comparison to non-infected controls in the general population. Examination of a population-based sample including asymptomatic and minimally symptomatic individuals, coupled with a control sample of non-infected individuals from the same population facilitates quantification of the reliability and magnitude of SARS-CoV-2 infection impacts on cognition, if they do indeed exist. Beyond the above, relatively little is known about the extent to which cognitive deficits are predicted by age or sex, as demographic moderators.

The current study reports findings from a population survey of 1,958 adults in the general population, who reported cognitive status, SARS-CoV-2 infection history, and COVID-19 symptom severity. It was hypothesized based on prior research[7, 10-14] that (1) SARS-CoV-2 infection history would be associated with greater symptoms of executive dysfunction, and (2) severity of COVID-19 symptoms would be positively correlated with severity of cognitive dysfunction, in a dose response manner. Based on the increased sensitivity of higher cognitive functions to environmental and systemic insults, it was expected that older adults would be more susceptible to infection-related executive dysfunction than younger adults.

1. Methods

Participants

Participants were recruited as part of the Canadian COVID-19 Experiences Project (CCEP15), a multi-study project which includes a national cohort survey of 1,958 adults aged 18 to 54. One research objective was to examine differences between fully vaccinated and vaccine-hesitant individuals on a broad set of demographic, psychosocial, and experiential variables. Thus, the cohort was recruited to have an equal proportion of fully vaccinated and vaccine-hesitant Canadians: 50.2% received two vaccine shots, 43.3% had received no shots, and 5.5% received one vaccine shot, but were not intending to receive a second shot). The mean age was 37 (SD=10.4) and 60.8% were female.

Procedure

The survey was conducted from 28 September to 21 October 2021, when the predominant SARS-CoV-2 variant in Canada was Delta (4 weeks prior to the appearance of Omicron16). Participants were contacted by email with an invitation to participate in the survey. A link to the survey was provided for eligible participants, and all measures were completed online following provision of informed consent. A quota target of equal number of vaccinated and vaccine hesitant was applied to obtain a balanced sample with respect to both vaccinated and vaccine-hesitant populations. Within each quota target, the sample was recruited from ten Canadian provinces through an online survey panel (Leger Opinion, the largest nationally representative probability-based panel in Canada). The survey firm and University of Waterloo monitored survey response in the sample of each quota to achieve the final representative sample. This study was reviewed and received ethics clearance from the institutional research ethics board of the University of Waterloo.

Measures

Executive dysfunction. Symptoms of executive dysfunction were assessed using four "self-restraint" subscale items from the Deficits in Executive Functioning Scale, short form (BDEFS-SF).[15] Respondents were asked how often they have experienced each the four problems during the past 6 months, including "I am unable to inhibit my reactions or responses to events or to other people", "I make impulsive comments to others", "I am likely to do things without considering the consequences for doing them", and "I act without thinking". Responses were indicated on a numerical scale where 1= never or rarely, 2=sometimes, 3=often, and 4=very often. Cronbach's alpha for the 4 items was 0.89, indicating acceptable reliability. The four executive dysfunction items were averaged for this analysis to create a composite executive dysfunction measure.

SARS-CoV-2 infection status: Infection status was assessed using the question "What best describes YOUR experience with [SARS-CoV-2] infection?" where 1= I have NOT been infected, 2 =I have been infected, and 3= not stated.

Symptom severity: COVID-19 symptom severity was assessed among those who have been infected by SARS-CoV-2 using two questions. (1) "How do you know that you HAVE BEEN infected with [SARS-CoV-2]?" responses were given the answers of 1= had symptoms but did not get tested, 2= had symptoms and tested positive, and 3 = had no symptoms but tested positive. (2) "How severe was your [SARS-CoV-2] illness?" The five-point response scale was 1=not at all severe, 2=slightly severe, 3=moderately severe, 4=very severe, 5=extremely severe. Those reporting "had no symptoms but tested positive" were incorporated into the second question as 1=not at all severe.

Statistical analysis

Samples were post stratified by sampling regions: Alberta, British Columbia, Manitoba + Saskatchewan, Ontario, Quebec English, and Quebec French, and the Atlantic

provinces (Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland and Labrador). Sampling weights were computed using a ranking procedure and calibrated to target marginal joint population distributions of sampling regions x SARS-CoV-2 infection status, and gender x age groups x SARS-CoV-2 infection status based on the 2016 Canadian census data and the disposition code data in the survey, thus allowing generalization to the Canadian population. Survey linear regression models incorporating survey strata and weights were applied to estimate composite executive dysfunction scores and their associations with SARS-CoV-2 infection status and COVID-19 symptom severity. Regression models controlled for respondents' gender and age groups (18-24, 25-39 and 40-54). All models were conducted in SAS with SUDAAN V11. All confidence intervals (CI) and statistical significance were assessed at the 95% confidence level.

2. Results

Baseline characteristics of the sample are presented in Table 1. The majority of the participants were female (60%) and from the 25-39 (40%) and 40-54 (43%) age groups (Table 1). 84% of participants reported that they had not been infected; those who reported having been infected reported symptoms to be "not at all severe" (3%), "slightly severe" (2.4%), "moderately severe" (2.7%), with relatively few experiencing "very/extremely severe" (1%; Table 1).

Those who reported a prior SARS-CoV-2 infection regardless of COVID-19 symptom severity (M_{adj}=1.89, *SE*=0.08, *CI*: 1.74, 2.04; n=175) reported a significantly higher number of symptoms of cognitive dysfunction than their non-infected counterparts (M_{adj}=1.63, *SE*=0.08, *CI*: 1.47,1.80; *n*=1,599; β=0.26, *p*=.001). Men were likely to experience more cognitive dysfunction than women (β= 0.15, *p*<.001); younger adults (25-39 years) were more likely to experience cognitive dysfunction than middle aged adults (40-54 years; β= 0.30, *p*<.001).

Participants who reported "moderately severe" (M_{adj} = 1.85, 95% *CI* 1.63 – 2.08) and "very" or "extremely severe" (M_{adj} = 2.32, 95% *CI* 1.85 – 2.78) COVID-19 symptoms were significantly more likely to have higher levels of cognitive dysfunction compared to non-infected individuals (M_{adj} = 1.62, 95% *CI* 1.58 – 1.66) (Table 2).

A dose-response relationship between COVID-19 symptom severity and cognitive dysfunction was evident, with moderate (β=0.23, *CI*: 0.003-0.46) and very/extremely severe (β= 0.69, *CI*: 0.22-1.16) COVID-19 symptoms being associated with significantly greater degrees of cognitive dysfunction, compared to those not infected and those with asymptomatic infections (Figure 1). Identical findings emerged following removal of those who had reported receiving intubation.

3. Discussion

In this population-representative cohort of community-dwelling adults, those with a positive history of SARS-CoV-2 infection reported more symptoms of cognitive dysfunction than those with no such history. This effect was stronger for men than for women, and for younger versus older adults. A dose-response relationship between COVID-19 symptom severity and magnitude of cognitive dysfunction was evident such that increasing infection severity was associated with greater symptoms of cognitive dysfunction. Importantly, reliable effects of positive SARS-CoV-2 infection history and COVID-19 symptom severity on cognitive dysfunction were evident even in this sample of individuals not typically subject to age-related cognitive decline (ages 18 to 54) and not exposed to medically induced coma via hospital-based treatment for severe COVID-19. Our findings were similar to a prior report of executive dysfunction as correlated with COVID-19 symptom severity in a large population sample[13].

There are several hypothesized mechanisms by which SARS-CoV-2 infection may produce cognitive dysfunction, including encephalitis, coagulopathy, cytokine storm, hypoxia, and megakaryocyte invasion[4,5,6]. The current investigation cannot distinguish among these neurophysiological mechanisms, or others that may yet be identified. The current findings do not preclude the possibility that symptoms of cognitive dysfunction are influenced by reporting biases among those who are continuing to experience emotional distress following the measurement period. Given that the effects of negative mood on symptom reporting is causally established[18], and given that mood impacts of the COVID-19 pandemic are well-documented[19-23], this possibility cannot be definitively excluded. However, at least one prior population-based study has found similar dose-response effects using performance-based measures of cognitive function (i.e., cognitive tasks rather than reported symptoms).[7]

It is not clear why there appeared to be a stronger link between SARS-CoV-2 infection and cognitive dysfunction in younger- as compared with middled aged adults. It is possible that such deficits were more obvious to younger adults, given that a higher proportion would be in educational programs wherein lapses in attention and concentration may have been more salient to them. In either case, it is not clear how consequential symptoms of cognitive dysfunction would be expected to be, even if reliable across studies. It is not uncommon for other types of viral infections to cause symptoms of cognitive dysfunction, including the seasonal flu, herpes, MERS, Zika and Varicella (chickenpox)[24-28]. Documenting the stability and functional impact of any SARS-CoV-2 infection impairments in cognition will be important.

Finally, given that the predominant SARS-CoV-2 variant during the time of the survey was Delta, the findings are applicable only to the Delta and earlier variants. Moreover, the retrospective nature of the study does not allow us to determine with confidence which infections were attributable to Delta versus earlier variants. We also cannot conclude that the same associations would be observed with the Omicron variant, in particular because of the lower COVID-19 symptom severity apparent with

Omicron in comparison with earlier variants, at least based on early data[29-31]. In the current (pre-Omicron) sample, we found that only moderate and higher COVID-19 symptom severities were associated with significantly elevated symptoms of executive dysfunction. Further analyses of follow-up waves of the CCEP data will enable examination of the relative impact of the Omicron variant on symptoms of executive dysfunction.

Strengths and Limitations

There are several strengths of the current study. One strength is the use of a large population-representative sample, consisting of infected individuals of a wide range of disease symptom severities—ranging from asymptomatic to hospitalized—as well as non-infected controls. Another strength is the use of a validated measure of subjective symptomology assessing everyday function rather than more sensitive but less ecologically valid performance-based measures. However, by virtue of the survey format, it was not possible to validate the infection status of individuals by testing. This may lead to under- or over-estimation of effect size and statistical significance of tests, vis-a-vis misreporting of infection status. This is a limitation of all survey studies of COVID-19 and cognitive dysfunction however. Finally, the cross-sectional design limits our ability to draw causal inference.

Future studies should examine the longevity of cognitive dysfunction symptoms over time, as well as the extent to which the dose-response and age gradients observed here are replicable across samples. Finally, additional studies examining neurological impacts at the level of the brain itself will be required, using functional brain imaging paradigms.

Conclusions

In summary, the current study used a population-representative sample consisting of a balanced proportion of infected and uninfected individuals to estimate the association between SARS-CoV-2 infection and symptoms of cognitive dysfunction. Findings indicated that individuals previously infected with SARS-CoV-2 reported significantly greater symptoms of cognitive dysfunction than non-infected individuals. Further, among those reporting an infection, a dose-response relationship between COVID-19 symptom severity and cognitive dysfunction was evident, such that those with moderate to severe symptoms were more likely to experience symptoms of cognitive dysfunction.

Research ethics statement

This study protocol was reviewed by and received approval from the University of Waterloo Office of Research Ethics.

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Data Availability Statement

Data will be available upon reasonable request to the corresponding author.

Conflicts of Interests

The authors declare no conflicts of interest.

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Figure 1 Legend

Effects of SARS-CoV-2 infection status and COVID-19 symptom severity on BDEFS scores; BDEFS=Barkley Deficits in Executive Functioning Scale.

Table 1: Sample characteristics.

Variables	***n***	**%**	**Executive function (unadjusted) Mean, 95% *CI***	**Executive function (adjusted) Mean, 95% *CI***
Gender				
Male	747	39.27	-	-
Female	1155	60.73	-	-
Age Group				
18-24	313	16.46	-	-
25-39	769	40.43	-	-
40-54	820	43.11	-	-
Infection Status				
Not infected	1599	84.07	1.62 (1.58, 1.66)	1.62 (1.58, 1.66)
Infected: Not at all severe	57	3.00	1.72 (1.52, 1.93)	1.73 (1.54, 1.91)
Infected: Slightly severe	46	2.42	1.78 (1.44, 2.11)	1.75 (1.45, 2.05)
Infected: Moderately severe	51	2.68	1.83 (1.60, 2.06)	1.85 (1.63, 2.08)
Infected: Very/extremely severe	21	1.10	2.29 (1.82, 2.76)	2.32 (1.85, 2.78)
Not stated	128	6.73	1.64 (1.46, 1.81)	1.63 (1.47, 1.80)

Note: Executive dysfunction mean is the average of the four BDEFS items. Participants who had no COVID-19 symptoms, but tested positive for SARS-CoV-2, were classified as “not at all severe”. The adjusted parameters are adjusted by sex and group. Table 1 includes the sample used in the current analysis (*N* = 1,902).

Table 2: Regression analysis predicting BDEFS scores from demographics, SARS-CoV-2 infection status and symptom severity.

Variables	**Beta (95% *CI*)**	***p***
Gender		
Male	0.15 (0.07, 0.22)	<0.001
Female	Ref	Ref
Age Group		
18-24	0.30 (0.19, 0.41)	<0.001
25-39	0.06 (-0.02, 0.14)	0.138
40-54	Ref	Ref
COVID-19 Infection Status		
Not infected	Ref	Ref
Infected: Not at all severe	0.10 (-0.09, 0.29)	0.284
Infected: Slightly severe	0.13 (-0.17, 0.42)	0.406
Infected: Moderately severe	0.23 (0.00, 0.46)	0.047
Infected: Very/Extremely severe	0.69 (0.22, 1.16)	0.004
Not stated	0.01 (-0.16, 0.18)	0.903

Author Contributions

PH, GF and SH conceived the study, planned and oversaw the statistical analyses, and wrote the final draft. GM planned and completed all statistical analyses and contributed to the writing of the final draft. MNS and AH contributed to the writing of the final draft.

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