Research article

Brain effects of mild COVID-19 in healthy young adults: A pilot study

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ABSTRACT

Rationale and objectives: This study examined the brain effects of mild severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection which are incompletely understood. Our objective was to ascertain within-person changes associated with mild coronavirus disease 2019 (COVID-19) in otherwise healthy adults.
Materials and methods: We leveraged existing pre-pandemic baseline neuroimaging and neurocognitive data, and collected follow-up data from uninfected controls and individuals with prior mild COVID-19, during December 2020 and January 2021, when vaccines were not yet available. We compared change during follow-up in patients (n = 5) versus controls (n = 15).
Results: We identified a decrease of intracellular volume fraction (ICVF), decrease of isotropic volume fraction (ISO) and decrease of orientation dispersion index (ODI) in multiple inferior frontal regions of interest in COVID-19 patients; this longitudinal change was significantly different from the control group which demonstrated increases in equivalent measures. This pattern suggests injury with neuronal loss and/or inflammation as underlying mechanisms. Neurocognitive studies identified a pattern of cognitive decline (processing speed, executive function, verbal learning, working memory) in patients, that did not reach significance.
Conclusion: Our pilot data suggests that mild COVID-19 may result in brain pathology and impact neurocognitive function in younger adults in a manner parallel to prior findings in older individuals. Though findings may not generalize to other SARS-CoV-2 variants, larger longitudinal studies of mild COVID-19 should be undertaken to understand the potential clinical implications of these findings over the longer term.

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1. Introduction

Severe COVID-19 effects on the brain include stroke, cerebritis and more (e.g, [1]). However, the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on the brain in mild disease is poorly understood. Within-person change in brain structure using pre-pandemic data have been reported in older adults with coronavirus disease 2019 (COVID-19) [2], but not in young healthy adults with mild or asymptomatic SARS-CoV-2 infection. Detection of mild or subclinical effects of SARS-CoV-2 infection is challenging due to potential confounding by socioeconomic status and poor pre-infection health status, which alter infection risk [3]. Pandemic-related stressors, including social isolation and socioeconomic impact, could adversely affect brain structure and function [4]. To understand the impact of mild infection we conducted an observational study using an existing pre-pandemic dataset in ethnically diverse healthy young adults from pre-2020 to early 2021, to identify changes in neuroimaging and neurocognitive function by COVID-19 status. We hypothesized that individuals with SARS-CoV-2 infection would exhibit decline of brain structure (MRI) and neurocognitive function compared to uninfected individuals when accounting for the pre-infection baseline.

2. Methods

2.1. Study design

To study the effect of mild COVID-19 using a pre- and post-event within-person change approach, we contacted 149 healthy young adults in August–November 2020 (a time period when vaccines were not yet available), who had participated in neuroimaging studies prior to the COVID-19 pandemic between 2014–January 2020 [5]. Participants recruited into the prepandemic studies from the New York City area through advertisements and through amateur soccer and other sport leagues. For this study, prior participants were contacted and asked to complete a brief web-based survey. Those who completed the survey were contacted by phone, in order of the survey completion to invite them to participate in this study. The first 20 of those who agreed were enrolled and proceeded to visit the laboratory for an assessment battery (below), which was completed on a single day.

To assess their infection status, study participants were asked to complete a survey addressing their medical history and history of symptoms related to COVID-19 (headache, dizziness, imbalance, fogginess, slowed thinking, difficulty speaking, difficulty understanding others, change of hearing, change of vision, sadness, depression, anxiousness, sleep disturbance, loss of coordination, poor concentration, trouble remembering, disorientation and confusion). SARS-CoV-2 treatment data were also collected and a blood sample for serology was taken. Study participants were classified into two groups, COVID-19 or control, based on clinical-epidemiological criteria [6]. Study subjects' status was confirmed with a SARS-CoV-2 spike protein serologic assay. The COVID-19 vaccine was not yet available, and thus a positive result indicated SARS-CoV-2 infection [7]. PCR testing contemporaneous with acute illness was not generally available early in the pandemic and was not used in our case definition. Hospitalization for COVID-19 or the presence of a comorbidity (ie. heart condition, stroke, lung disease, rheumatological condition, cancer, HIV/AIDS, kidney disease, blood disease, chronic viral infection, any neurological disorder other than headache, chronic headache, concussion, or traumatic brain injury) were exclusion criteria. We enrolled the first 20 respondents who completed a single in-person assessment during December 2020 through January 2021. The neuroimaging and neurocognitive tests were identical to the protocols employed in the pre-pandemic, baseline studies.

3. Data collection and processing

3.1. Neuroimaging

MRI**:** 3.0T Elition scanner and 32-channel head coil (Philips Healthcare, Best, The Netherlands); 3D T1-weighted (MP-RAGE, 1 mm^3 voxels); Diffusion (2 mm^3 voxels, 10 b = 0, 6 directions @b = 300, 32 directions @b = 800 and 60 directions @b = 2000).

Image processing used our previously reported processing pipelines [8]. Regional gray and white matter volume and cortical thickness were extracted using FreeSurfer [9–11]. Diffusion (Neurite Orientation Dispersion Density Imaging (NODDI [12]) data were fit (AMICO [13]) to generate orientation dispersion index (ODI), intracellular volume fraction (ICVF) and isotropic volume fraction (ISO). Based on the findings of prior studies [2], diffusion parameters were averaged over regions of interest (ROI) in frontal, temporal and limbic areas, including extended olfactory network components.

3.2. Neurocognitive testing

Cogstate (Cogstate, New Haven, CT) is a widely-used computer-administered battery of a range of cognitive functions that has demonstrated reliability and validity [14,15]. A full description of the test battery can be found on www.cogstate.com. Selected subtests included the Identification Task (IDN, a measure of processing speed and attention in which the participant indicates whether a playing card is red or not), the Groton Maze Task Chase Test (GMCT), a measure of processing speed and reaction time in which the participant chases a target through a maze, the International Shopping List (immediate (ISL) and 20-min delay (ISRL), a measure of episodic verbal learning and memory in which the participant is asked to recall a list of 12 words from a shopping list over three learning trials and one delayed recall trial) and the 1-Back (ONB) and 2-Back (TWOB) tests, measures of attention and working memory in which the participant indicates whether a playing card is the same as that presented on one card (ONB) or two cards (TWOB) previously.

3.3. Statistical analysis

We computed the change of imaging and cognitive measures from pre-pandemic to a post-pandemic assessment. Welch two-sample t-tests were used to compare the changes of SARS-CoV-2 cases to those of uninfected controls (two-sided p-values). The effect size was defined as $\frac{\overline{X}_{cases} - \overline{X}_{control}}{S_{pooled}}$ (Cohen's d). Analyses were performed in R (v4.2.1) [16]. We reported neuroimaging regions showing differences between cases and controls with the effect size exceeding 1 in either direction.

4. Results

Twenty individuals completed the study between Dec 2020 and Jan 2021, five of whom had COVID-19. Fifteen were uninfected controls. Demographics and infection status is shown in Table 1. Each of the five COVID-19 participants reported new neurological or cognitive symptoms. Of these five, two reported anosmia and ageusia. No control participant reported new neurological symptoms.

We report on findings with effect sizes (Cohen's d) exceeding 1 in either direction. No group differences of change in global or regional brain volume were identified. Cortical thickness in the left lateral anterior cingulate decreased in both control and patient groups but patient group cortical thickness decreased significantly more (p = 0.03). Gyrus rectus ICVF decreased in patients compared to minimal increase in controls (gray matter p = 0.006, white matter p = 0.04), and ISO decreased in the same location in patients, compared to minimal increase in controls (p = 0.05). ISO also decreased in the right middle orbitofrontal white matter (p = 0.07) compared to a minimal increase in control. Decrease of ODI was detected in left orbitofrontal regions (lateral orbitofrontal p = 0.06; middle orbitofrontal p = 0.04; middle orbitofrontal white matter p = 0.07), right entorhinal gray matter (p = 0.04), and right uncinate fasciculus (p = 0.02) in the patient group, compared to minimal increase in controls (Fig. 1). Similarly, compared to controls, ODI in the right inferior frontal gyrus increased less in the patient group (p = 0.05).

While controls exhibited improved performance on most tasks (IDN, GMCT, ISRL, ONB, and TWOB), consistent with expected practice effects, patients exhibited an adverse change in performance (IDN, GMCT, ONB and TWOB). Longitudinal change in cognitive performance (processing speed, executive function, verbal learning and working memory), although differing in directionality, was not statistically different between patients and controls (Table 2).

5. Discussion

SARS-CoV-2 infection has been associated with neurological disease, including a decline in working memory [17], abnormal neuroimaging findings and long COVID syndrome [18]. A major limitation to studies of COVID-19-associated neuropathology is the lack of baseline data to inform robust conclusions in observational studies. Without pre-infection baseline data we cannot distinguish risk factors for infection from consequences of infection. In this study, we leveraged pre pandemic neurocognitive testing and neuroimaging to examine the effects of mild COVID-19 on the brain. Our preliminary findings show incident neurological symptoms, adverse microstructural brain changes and trends toward decline of cognitive function in diverse young adults with mild COVID-19 compared to uninfected controls. Even absent cognitive change, there could exist subclinical effects that warrant further investigation.

Diffusion MRI findings in prefrontal and limbic regions are consistent with "brain fog", a common post-COVID neurological complaint comprising slow information processing, inattentiveness, dysexecutive syndrome, and impaired memory. The MRI changes indicate alteration of brain network infrastructure affecting frontal, olfactory and limbic areas previously identified as predilection sites for SARS-CoV-2 infection [2], and central to cognitive performance. Our use of NODDI confers the ability to interrogate gray matter microstructure, leading to identification of multiple areas of change within prefrontal cortex. The consistent decline of diffusion measures over the period of the COVID-19 pandemic in patients, but not in controls, including decrease of intracellular water (ICVF), decrease of free water (ISO) and increase of fiber organization (decrease in ODI) may reflect a combination of underlying mechanisms. Decrease in ODI in cortical gray matter, for example, is consistent with loss of dendritic process complexity; decrease in ICVF similarly supports a loss of neurites. Decrease in ISO in the patient group, but an increase in ISO in the control group could indicate differing responses to the pandemic, with the control group exhibiting an inflammatory response which could be overshadowed by neurite loss in the patient group. The findings are thus consistent with neurite loss, which may arise from neurodegeneration, although co-occurring inflammation cannot be excluded.

Further work is necessary to confirm and characterize these preliminary findings, which point to the potential for persistent adverse

Table 1
Participant Characteristics by COVID-19 Status Data are presented as No. (%) unless otherwise indicated.

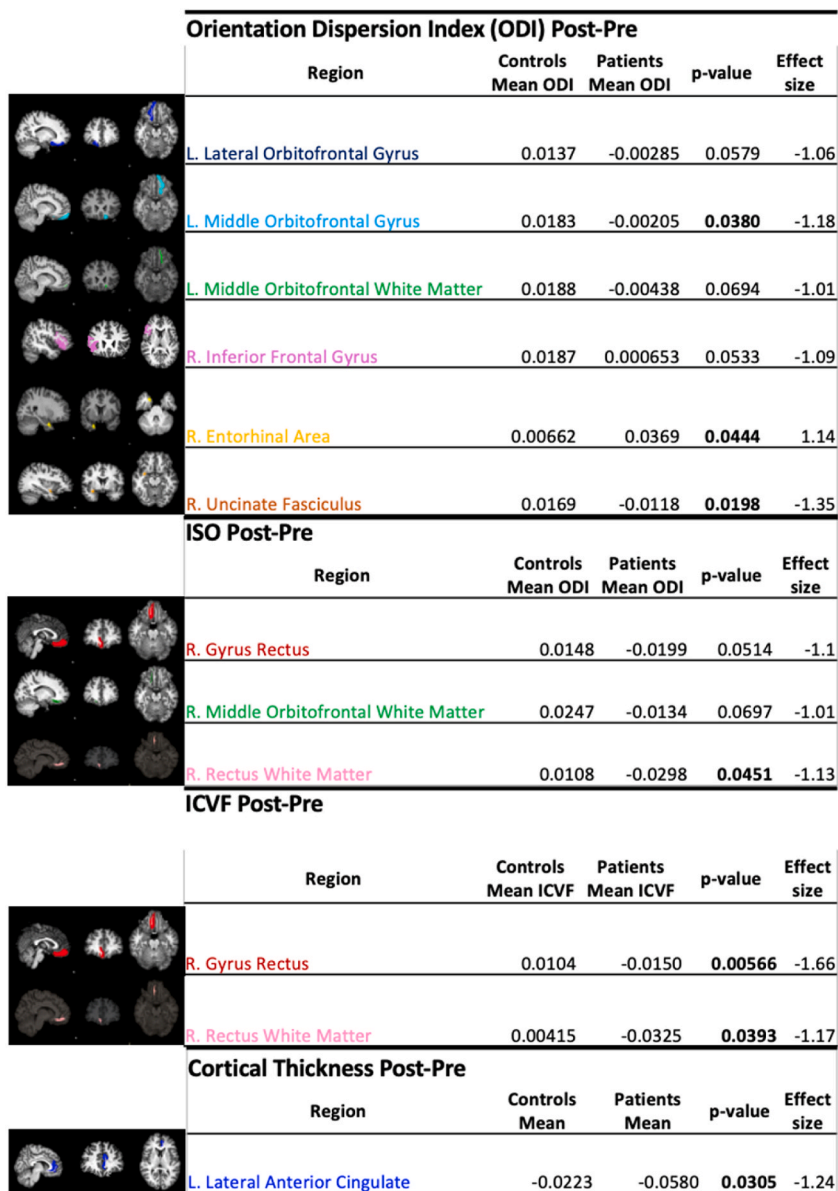| Characteristic	Total (n = 20)	COVID-19 (n = 5)	Control (n = 15)
Age **[years, Median (Range)]**	37 (24–57)	37 (25–56)	36 (24–57)
Male	9 (45)	2 (40)	7 (46.7)
Hispanic or Latino	4 (35)	1 (20)	3 (20)
RACE			
Asian	3 (15)	2 (40)	1 (6.7)
Black or African American	6 (30)	1 (20)	5 (33.3)
White	9 (45)	2 (40)	7 (46.7)
Mixed Race	2 (10)	0 (0)	2 (13.3)

Fig. 1. – Regions of interest (ROI) are shaded in color on the left, with change of diffusion parameter from pre-to-post pandemic within each region for each group shown in corresponding rows.

Table 2
Cognitive performance by COVID-19 status.

Cognitive Test	Mean Change COVID-19	Controls	Effect Size	P-value
IDN (log$_{10}$ms)[a]	0.009	−0.046	0.534	0.365
GMCT (moves/sec) b	−0.050	0.218	−0.730	0.221
ISL (# correct) b	1.75	−0.923	0.604	0.308
ISRL (# correct) b	0.25	0.154	0.087	0.882
ONB (accuracy) b	−0.07	0.008	−0.341	0.560
TWOB (accuracy) b	−0.004	0.013	−0.102	0.861

IDN = Identification task; GMCT = Groton Maze Chase Task; ISL = International Shopping List immediate recall; ISRL= International Shopping List 20-min recall; ONB = One-Back task; TWOB = Two-Back task.

[a] Lower score = better function.

[b] Lower score = worse function.

brain effects in young previously individuals who experienced mild COVID-19 disease. Our longitudinal within-person design supports the attribution of effects to COVID-19, as opposed to baseline differences. Moreover, this approach at least partially accounts for adverse effects of the pandemic, such as stress and isolation, which were experienced by all, not only COVID-19 patients [4,19]. Limitations to our study include a small sample size, limitations of the standard clinical case definition we utilized to identify cases vs. controls, differential effects of SARS-CoV-2 variants which could add variance and limit our sensitivity, and lack of baseline measures for psychosocial status such as loneliness that were important features of the COVID-19 pandemic lockdowns. We were additionally not able to directly contrast our findings to those of more severe and overtly symptomatic long COVID cohorts, for which we did not have baseline data. Furthermore, SARS-CoV-2 has evolved since the beginning of the pandemic, and populations have gained immunity resulting in overall less severe disease [20]. These differences may limit the generalizability of our findings to patients infected with more recent variants of SARS-CoV-2 and to vaccinated patients.

Overall, this study expands knowledge on SARS-CoV-2 brain effects, finding changes within brain regions consistent with those of the larger UK Biobank study [2], but in a cohort two decades younger, with racial and ethnic diversity (40–50 % non-white) and putatively at lower risk for adverse effects. These preliminary findings may represent subclinical decline, which warrants further study to ascertain potential for future clinical implications [21].

Data availability statement

Data will be made available upon request from the corresponding authors JPD and MLL.

Ethics declarations

Ethics approval. This study was reviewed and approved by the Albert Einstein College of Medicine IRB on 7/24/2020 (IRB # 2020–12000) All participants provided written informed consent.

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CRediT authorship contribution statement

Michael L. Lipton: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Roman Fleysher:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Joan Y. Song:** Writing – review & editing, Visualization. **Kenny Ye:** Writing – review & editing, Writing – original draft, Visualization, Software, Formal analysis, Data curation. **Molly E. Zimmerman:** Writing – review & editing, Writing – original draft, Supervision. **Richard B. Lipton:** Writing – review & editing, Writing – original draft, Supervision. **Johanna P. Daily:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known completing financial interest of personal relationships that could have appeared to influence the work reported in this paper.

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