

Seeing through brain fog: disentangling the cognitive, physical, and mental health sequelae of COVID-19.

Conor J. Wild^{1,2*}, Loretta Norton^{1,3}, David K. Menon⁴, David A. Ripsman⁵, Richard H. Swartz⁶⁺, & Adrian M. Owen^{1,7+}

1. The Brain & Mind Institute, Western University, London, Canada
2. Physiology and Pharmacology, Western University, London, Canada
3. Department of Psychology, King's University College, Western University, London, Canada
4. Division of Anaesthesiology, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
5. Department of Medicine, University of Ottawa, Ottawa, Canada
6. Department of Medicine (Neurology), Hurvitz Brain Sciences Program, Sunnybrook HSC, University of Toronto, Toronto, Canada
7. Department of Psychology, Western University, London, Canada

+ co-senior authors

* corresponding author:

Conor J. Wild

cwild@uwo.ca

(226) 926-9453

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27 Abstract

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29 As COVID-19 cases exceed hundreds of millions globally, many survivors face cognitive
30 challenges and prolonged symptoms. However, important questions about the cognitive impacts
31 of COVID-19 remain unresolved. In the present online study, 478 volunteers who self-reported a
32 confirmed COVID-positive test completed a comprehensive cognitive battery and an extensive
33 questionnaire. This group performed significantly worse than pre-pandemic controls on cognitive
34 measures of reasoning, verbal, and overall performance, and processing speed, but not short-term
35 memory – suggesting domain-specific deficits. We identified two distinct factors underlying health
36 measures: one varying with physical symptoms and illness severity, and one with mental health.
37 Crucially, within the COVID-positive group cognitive performance was correlated with physical
38 symptoms, but not mental health, and significant impairments were evident even in the subgroup
39 that did not require hospitalisation. These findings suggest that the subjective experience of “long
40 COVID” or “brain fog” relates to a combination of physical symptoms and cognitive deficits.

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Introduction

As the number of people recovering from the effects of COVID-19 infection continues to grow, it is becoming increasingly clear that many experience ongoing cognitive challenges, including problems with memory, attention, reasoning and simple problem-solving¹. These issues could be caused by direct viral effects on the brain (such as neuroinflammation, stroke, and autoimmune responses), as elevated cerebrospinal fluid autoantibodies and significant white matter changes have been reported in patients with neurological symptoms following infection with COVID-19²⁻⁵, as well as signs of microvascular damage⁶ have been reported. Indirect effects of infection may also be attributed to changes in cognition resulting from inflammation, blood clots, low oxygen levels, sedation and ventilation. In a recent prospective study of mechanically ventilated critical illness survivors, we reported that all patients emerged from the intensive care unit (ICU) with cognitive impairments, regardless of their aetiology at admission (sepsis, cardiac arrest, respiratory failure etc.)⁷⁻⁹.

Nevertheless, as the worldwide incidence rates of proven COVID-19 infections exceed 120M, many questions of importance for post COVID-19 treatment and recovery remain unanswered. First, are these cognitive deficits, where they occur, generalised or ‘domain-specific’; that is, do they affect certain cognitive systems more than others and, if so, which cognitive systems are most susceptible? This issue has gained import in recent months as poorly specified terms like ‘brain fog’ have entered both common parlance and the scientific literature describing ‘long COVID’ or COVID ‘long-haulers’¹⁰⁻¹³. Unfortunately, the widespread use of ‘blunt’ screening tools such as the Mini Mental State Examination (MMSE¹⁴) and the Montreal Cognitive Assessment (MOCA¹⁵) to evaluate the effects of COVID-19 infection only adds to this confusion, as both were designed to detect the emergence of dementia in the elderly, rather than

to provide a comprehensive picture of cognitive performance^{16–20}. For example, in one study, 28% of recovered COVID-19 patients scored below the established cut off of 26 (for dementia) on the MoCA, compared to only 17% of controls, although median MoCA scores in the patients were not statistically different from those of the controls²⁰. Other studies have suggested a specific domain of cognitive impairment; however, this has varied across studies from primary deficits in attention²¹ to visuospatial deficits²⁰. Most studies report multidomain cognitive impairments, although there appears to be a high degree of disagreement about which domains are most affected^{1,16–19,22–25}.

Second, how does the emergence of cognitive deficits following COVID-19 infection relate to the severity of the primary infection? Several preliminary studies have suggested that, in patients who required hospitalised treatment, cognitive deficits following COVID-19 infection are dependent on the level of medical assistance received^{1,22} and the degree of inflammation²¹ with severe infections being associated with significant cognitive deficits^{17,18,23} although cognitive impairments have also been reported in asymptomatic patients¹⁶, and one small study reported no correlation with hospitalization and cognitive impairments²⁴. Given current knowledge about long-lasting cognitive deficits from post ICU syndrome, we might expect a worse cognitive outcome with more severe COVID-19 illness^{7–9}. Alternatively, perhaps the longstanding and untreated hypoxia reported in asymptomatic COVID-19 patients^{26,27} may lead to long lasting cognitive decline, as has been shown to be the case in other conditions that cause longstanding hypoxia^{28,29}.

Third, how does the pattern of cognitive deficits observed following COVID-19 infection relate to aspects of mental health such as anxiety, depression and fatigue that may be a consequence of the disease process itself, or a more general effect of living during the time of a global

pandemic? Research conducted prior to the worldwide spread of COVID-19 clearly established that associations exist between impaired cognitive function and both anxiety disorders³⁰, and depression³¹, although the relationship between fatigue and specific cognitive deficits seems rather less clear^{32,33}. Several recent studies have reported an increased risk of psychiatric disturbance in patients recovering from COVID-19^{20,34–36}, although others have reported no association between cognitive outcomes and psychiatric symptoms²⁵, including anxiety^{17,24} depression^{17,24} and fatigue²⁴.

To fully address these questions, large numbers of patients need to be examined in order to mitigate the effects of infection severity, stage of recovery and concomitant mental health issues. To date, most studies have focused on single-case reports, or relatively small (< 25) cohorts^{17–19,23,24,37}, confounding these issues. With many countries in virtual lockdown, opportunities for face-to-face testing are limited, resulting in the widespread use of telephone screening and/or self-reported cognitive status, which have obvious limitations^{23,24,37}.

In this study, we report data from a cohort of 478 patients who self-reported having had a confirmed positive COVID-19 test, who were assessed using a comprehensive and widely validated battery of cognitive tests, measuring aspects of memory, attention, problem-solving and reasoning. Every patient also completed an extensive questionnaire to fully document their COVID-19 experience, infection severity, extent of recovery, health status (physical and emotional health, including functioning, pain, energy and fatigue; SF-36³⁸), and mental health status, assessed using standard measures of anxiety (GAD2³⁹) and depression (PHQ2⁴⁰). While this cohort will be followed longitudinally for the next 12 months to investigate the trajectory of cognitive sequelae following COVID-19 infection, here we report the results of our initial assessment, conducted in the first few months following a positive COVID-19 test.

Results

Participants

Of the 478 volunteers who reported having a confirmed positive case of COVID-19 (i.e., the COVID+ group) 66 required treatment in a hospital for their illness, and of those: 34 required supplemental oxygen therapy, 17 were in the Intensive Care Unit (ICU), and 11 were on a ventilator. Cases that were not hospitalised (N=412) were asked about their daily functioning, and 283 of them reported being negatively impacted by their illness. A COVID severity score, based on the World Health Organization's 8-point ordinal scale of COVID-19 severity⁴¹, was assigned to each participant based on their responses to these questions; scores ranged from unaffected (score = 0) to hospitalised with severe disease (score = 6; Supplementary Figure 1, Supplementary Table 1). Participants also indicated the year and month of their most recent positive test for COVID-19 to approximate the elapsed time since infection ($M = 3$ months, $SD = 2$ months). Also, 159 (33%) and 151 (31.6%) of participants met the criterion for a suspected generalized anxiety disorder (i.e., GAD2 ≥ 3) or major depressive disorder (i.e., PHQ2 ≥ 3) respectively. 112 participants indicated having one more pre-existing medical conditions prior to COVID-19: diabetes (N=23), obesity (N=80), hypertension (N=47), stroke (N=4), heart attack (N=1), or memory problems (N=2).

Details about the COVID+ participants and the pre-pandemic control group are shown in Table 2. Note that instead of performing a matched-sample analysis between the COVID+ and control groups, we employed a regression-based approach to estimate and remove the effects of potential confounding variables from cognitive scores; these ten variables were common to both datasets: 1) age, 2) sex, 3) level of education, 4) socio-economic status (growing up), 5) frequency of exercise, and consumption of 6) nicotine, 7) alcohol, 8) cannabis, or other 9) simulants, or 10)

depressants. Regressing out these variables, instead of matching on them, allowed us to retain all observations in both datasets, as discarding cases that could not be matched would result in a smaller sample size, and a loss of efficiency that would prohibit smaller sub-group analyses within the COVID+ cohort.

(Tables 1 & 2)

Cognitive differences between COVID+ and control participants

To investigate the effects of COVID-19 infection on cognitive functioning, we compared the COVID+ cohort to the control sample on 5 composite scores of cognitive performance, rather than examining each test in isolation. Three of these measures were derived from a principal components analysis of the 12 cognitive test scores in the control group; replicating our previous work⁴², we interpreted the resulting components as generally describing cognitive performance in three domains: visuospatial short-term memory (STM), reasoning, and verbal domains (Figure 1A). Two additional scores included overall performance across the cognitive task battery, and average processing speed (i.e., a reaction-time based measure across all tests).

We observed statistically significant differences between these groups on the reasoning domain, verbal domain, processing speed, and overall cognitive scores (all adjusted $ps. < 0.001$; Table 3), such that COVID+ participants performed, on average, worse than the controls by 0.20, 0.18, 0.29, and 0.16 SDs in these domains – respectively. Bayesian statistics supported these findings with strong evidence in favour of the group differences. In all four cases, the data were at least 120 times more likely to occur given the model that included a difference between groups (i.e., all $BF_{10S} > 120$; Table 3). The one exception was STM performance, which did not significantly differ between groups and had a Bayes Factor (BF) supporting the null hypothesis.

(Table 3)

Dissociable health factors associated with COVID-19 infection

Strong correlations were observed between health-related questionnaire variables from the COVID+ group (Figures 1B, S2). Bartlett's test of sphericity ($\chi^2_{(45)} = 2168, p < 0.001$) and a Kaiser-Meyer-Olkin value of 0.87 confirmed that the multivariate data were factorable. A subsequent factor analysis revealed a two-factor structure underlying these data (i.e., two factors had eigenvalues greater than 1.0), which we interpreted as broadly representing overall physical health including COVID severity (henceforth referred to as F1; Figure 1B, inner ring), and mental health & wellness (henceforth referred to as F2; Figure 1B, outer ring). Illness severity (WHO_COVID_severity) correlated most strongly (and negatively) with the SF-36 measures of physical functioning, physical-role limitations, energy & fatigue, and pain scales, and the two subjective measures of cognition (Figures 1B, S2). The approximate elapsed time since infection demonstrated negligible correlations with all measures (Figures 1B, S2). Descriptive statistics of each health variable, along with their loadings on F1 and F2, can be found in Supplementary Table 2.

(Figure 1)

The two health factors (F1 and F2) were dissociable with respect to their relationships with demographic variables (Figure 2). Linear regression models (Supplementary Table 6) showed that the overall physical health factor (F1) was negatively correlated with age ($t_{(473)} = -3.20, p_{\text{adj}} < 0.05, f^2 = 0.022, \text{BF}_{10} = 7.65$) with an average decline of approximately 0.1 SDs per decade, whereas mental health & wellness (F2) increased with age ($t_{(473)} = 2.82, p_{\text{adj}} < 0.05, f^2 = 0.017$,

BF₁₀ = 2.46) by 0.1 SDs per decade. Completion of post-secondary education was also associated with significantly better (F2) mental health ($t_{(473)} = 3.36$, $p_{\text{adj}} < 0.01$, $d = 0.40$, BF₁₀ = 12.94) but not (F1) physical health, and males reported better (F1) physical health ($t_{(473)} = 5.91$, $p_{\text{adj}} < 0.001$, $d = 0.57$, BF₁₀ > 1000) yet there was no difference between males and females in terms of (F2) mental health & wellness. The fact that these measures were clearly dissociable in terms of the demographic variables that they correlated with suggests that they represent two distinct and separable, though not mutually exclusive, effects of COVID-19 infection.

Within-group associations between health and cognition

(Figure 3)

Figure 3 describes cognitive performance of COVID+ participants relative to controls ($Y=0$) as a function of overall physical health (F1; Figure 3A); to simplify this visualization and reduce the number of comparisons, participants were grouped into tercile bins (i.e., percentiles that each contained 1/3rd of the sample – corresponding to worse, average, and better physical health). COVID+ participants who had better than average physical health (Figure 3, purple data) performed similarly to controls in all cognitive domains. In contrast, those participants with worse than average physical health (Figure 3, green data) exhibited significant differences relative to controls (Supplementary Table 7) on the four cognitive scores already identified as being significantly lower in the COVID+ cohort compared relative to controls: reasoning, verbal, processing speed, and overall performance. A similar pattern was not apparent when data were re-grouped by mental health & wellness scores.

Next, we constructed linear regression models to predict each composite cognitive score from the two health factors and used Bayesian model comparison to quantify the unique contribution of each factor in predicting cognitive performance. The physical factor exhibited strong and statistically reliable linear associations with three cognitive scores – verbal, processing speed, and overall performance (F1; all adjusted p s < 0.05; Table 4) – when controlling for F2. BF₁₀s suggested positive to strong evidence in favour of these relationships (BF₁₀ of 8.12, 18.69, 15.82 for verbal, processing speed, and overall performance; Table 4). The directions of these coefficients in Table 4 revealed positive relationships; that is, better physical health (and milder COVID severity) was associated with better verbal and overall performance and faster processing speed, consistent with the results depicted in Figure 3. In contrast, mental health & wellness (F2) did not exhibit a linear relationship with any measure of cognitive performance after accounting for physical health (all adjusted p -values = 1.0 and BF₁₀s < 1; Table 4).

(Table 4)

A supplementary analysis was performed that included all 10 nuisance variables that had been regressed out (socio-demographic covariates, exercise, and drug use), and an additional predictor that indicated the presence of a pre-existing medical condition (diabetes, obesity, hypertension, stroke, heart attack, or memory problems). These highly parameterized models yielded the same pattern of results (Supplementary Table 8), suggesting that the observed relationships between physical health (F1) and cognitive scores were not driven by residual effects of nuisance variables or the presence of a pre-existing health risk factor. Figure 4 summarizes the COVID+ vs. control group comparisons and tests of health-factor regression parameters – across all five cognitive domains.

(Figure 4)

Does hospitalisation explain physical/cognitive associations?

We next examined whether the pattern of results found in the COVID+ cohort were driven by the more severe cases of COVID-19 that required hospitalisation. Comparisons of hospitalised and non-hospitalised participants revealed significant differences in terms of F1 ($t_{(88.55)} = -3.92, p_{\text{adj}} < 0.001, d = 0.50, \text{BF}_{10} = 189.99$) with hospitalised cases reporting worse overall physical health than non-hospitalised cases (Figure 5A) – an unsurprising finding given that hospitalisation was one of the criteria for the COVID severity score, which loaded on F1. However, these two groups did not significantly differ in terms of their mental health (F2) or cognitive performance (Figure 5B, Supplementary Table 9). Despite the non-significant group differences in cognition at a corrected level, it is worth noting that the hospitalised group trended towards having worse performance on the scores that were significantly impaired in the non-hospitalised group; that is, the estimated effect sizes were suggestive of larger impairments in the hospitalised group, as is visible in Figure 5B.

Direct comparisons of each of these COVID+ subgroups against the controls showed that both had significantly lower performance in some domains (Figure 5B). Specifically, the non-hospitalised group was significantly worse than controls in the reasoning and verbal domains, and in terms of speed of processing and overall performance (Figure 5B, Supplementary Table 10). Meanwhile, the hospitalised group performed significantly lower than controls in the reasoning domain and in processing speed (Figure 5B, Supplementary Table 10). Although the verbal and overall performance scores for this group did not differ significantly from the control sample at a corrected level, Bayesian statistics suggested positive and weak evidence (verbal $\text{BF}_{10} = 5.14$, overall $\text{BF}_{10} = 1.91$) in support of impairments on these measures; a plausible explanation for the statistically weak differences between groups is the small sample size of

hospitalised patients (N=67). In contrast, the STM domain scores for both groups were not significantly different from controls, and BFs instead supported the null hypothesis (i.e., $BF_{10S} < 1.0$) that there was no difference between the control sample and these two groups in this domain (Supplementary Table 10).

Given that the hospitalised group reported significantly worse overall physical health and had somewhat poorer cognitive performance than the non-hospitalised group, we included this variable in our regression analyses to see if it explained away or reduced the observed relationship(s) between physical health (F1) and cognitive performance. The pattern of results (Figure 6, Supplementary Table 11) remained similar: we observed significant and positive relationships between physical health (F1) and verbal domain performance, speed of processing, and overall cognitive performance (all p -values < 0.05 , corrected for 15 comparisons). Again, the Bayesian statistics provided positive evidence ($BF_{10S} > 3.0$) for these relationships, showing that physical health predicted cognitive performance even when accounting for mental health measures and hospitalisation.

Relationships between other variables and cognition

A final set of exploratory analyses were used to examine whether any of the demographic variables (age, sex, post-secondary education, and SES) were related to cognitive performance. Given that the cognitive scores were already corrected for demographic factors using parameters estimated from the control sample data, a significant effect of one of these variables would suggest that its effect differed between the control and COVID+ groups (i.e., a group by demographic-variable interaction). However, we found no correlations between any of these variables and cognitive scores (Supplementary Figure 5A), and BFs suggested positive to strong evidence (Supplementary Figure 5B, Supplementary Table 12) in support of the null (H_0)

272 hypotheses. This suggests that: 1) using the control dataset to estimate and remove the effects of
273 these potential confounders from cognitive scores was successful, and 2) the cognitive
274 differences associated with these variables did not differ between the control and COVID+
275 datasets, suggesting that the impact of COVID-19 infection on cognition did not differ between
276 males and females, or depend on age.

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Discussion

In this study, we present data from a cohort of 478 individuals who self-reported having a confirmed positive COVID-19 test, and who were assessed using a comprehensive and widely validated battery of cognitive tests that measures aspects of memory, attention, verbal abilities, problem-solving and reasoning. Cognitive scores in multiple broad domains were related to participants' self-reported COVID-19 physical and mental health experiences, including infection severity, extent of recovery, and measures of anxiety and depression.

The results support the existence of cognitive impairments in the aftermath of COVID-19 infection, and include several important additional findings. First, there is striking specificity in the domains that were affected. Speed of processing was most markedly impaired, with verbal abilities, reasoning and global cognition scores also impaired, whereas a measure of memory performance was unaffected. Second, when all physical, cognitive, and mental health factors were considered, two distinct patterns of subjective symptoms emerged. On the one hand, there exists a collection of 'physical symptoms', including fatigue, pain and limitations in performing everyday physical activities, that tend to vary together and are strongly associated with COVID-19 infection severity. Thus, unsurprisingly, more severe disease and older age are associated with poorer physical well-being post-infection. On the other hand, there exists a second set of 'mental health' symptoms that include depression, anxiety and self-reported limitations in emotional well-being that tend to co-occur and are unrelated to disease severity. Third, the cognitive deficits are strongly and consistently associated with the *physical* sequelae of the disease, rather than the *mental health* symptoms. That is, better physical health was correlated with faster processing speed, better verbal ability, and overall cognitive performance, while no associations were found between these measures and the mental health & wellness factor.

It is possible that some unmeasured confounding factor – such as job security, financial instability, home-schooling, social isolation, an elevated sense of community fear, or anything that undoubtedly affects the well-being of people throughout the world, irrespective of whether they have received a positive COVID-19 diagnosis – could underlie the cognitive differences observed between the COVID+ and pre-pandemic controls. However, two critical observations suggest otherwise. First, we also found cognitive differences within the infected group that were tightly coupled to illness severity and physical symptoms. Second, the subgroup of participants with better-than-average physical health (relative to the entire COVID+ group) performed similarly to controls on all cognitive measures. We further showed that these within-group correlations between cognition and physical health were not explained by the presence of a pre-existing medical condition, or residual effects of socio-demographic variables. The mutually reinforcing nature of these results – specifically, between-group differences that were replicated within the patient group along a dimension tied to illness severity – strongly suggests that these cognitive differences, and the physical/cognitive associations identified here, are specifically related COVID-19 infection itself.

Given the global nature of the COVID-19 pandemic and the fact that it has disproportionately (but not exclusively) affected the elderly and those from low educational and SES backgrounds, it is of interest to explore how these factors interact with the physical and mental health outcomes that we have identified. In our primary analyses, age, sex, post-secondary education, and SES were accounted for by adjusting cognitive scores for the known effects of these variables (estimated from a large control sample), yet even when these factors were included as covariates in a supplementary analysis the same pattern of results was observed, confirming that the observed relationships between physical health and cognitive scores were not driven by a residual effect of

any these factors. Furthermore, the lack of any correlations between these socio-demographic variables and corrected cognitive scores (Supplementary Figure 4) suggests that this relationship is a core characteristic of COVID-19 infection, rather than a secondary effect related to the demographic profile of those who have been most commonly infected.

It is important to understand that we are not describing two types of people in the post COVID-19 infection population, but two distinct factors that contribute to and characterise the post COVID-19 syndrome. Indeed, the fact that these measures were clearly dissociable in terms of the demographic variables that they correlated with, suggests that they represent two distinct and separable, though not mutually exclusive, effects of COVID-19 infection. For example, our linear regression models (Supplementary Table 4) showed that physical health was negatively correlated with age (with an average decline of approximately 0.1 SDs per decade), whereas mental health & wellness increased with age (by 0.1 SDs for every 10 years). While it is perhaps to be expected that older COVID-19 survivors would be most affected in terms of their physical and cognitive outcomes (given the greater likelihood of co-morbidities in that group), the fact that it is the young that have been most severely affected in terms of their mental health and well-being is surprising. Completion of post-secondary education was also associated with significantly better mental health, but not physical health outcomes, and males reported better physical health, yet there was no difference between males and females in terms of mental health & wellness. Again, the differing patterns of correlations between socio-demographic variables and the physical and mental health factors further confirm the existence of two distinct outcomes of COVID-19 infection that are dissociable in multiple ways.

The fact that a measure of mental health, including anxiety and depression, was not associated with cognitive outcomes in the context of the COVID-19 pandemic is surprising, as numerous

studies have shown an association between anxiety, depression, and cognition in the pre-pandemic era. For example, one study of 4582 participants³⁰ showed that generalized anxiety is associated with memory and verbal fluency deficits, particularly in young adults. Similarly, a systematic review and meta-analysis by Semkowska et al.³¹ confirmed that deficits in selective attention, working memory and long-term memory persist in major depression and worsen with repeated episodes. However, it is important to clarify that these, and most other studies that have examined the relationship between mental health and cognition, have focussed on *clinical* populations; that is, patients who have been diagnosed with a major mental health condition, such as depression or anxiety. In our study, the fact that no association was observed between measures of mental health and cognition may be due to a predominance of detectable, yet sub-clinical, mental health issues among the COVID-19 survivors. For instance, we found that only about one third of our participants had probable anxiety or depression, which is consistent with estimates of the prevalence of these disorders in the general population during the COVID-19 pandemic⁴³. Nonetheless, this result is based on a single factor construct (i.e., “overall mental health & wellness”) that encompasses anxiety, depression, fatigue, etc. It is possible that more specific and sensitive measures of anxiety and depression could reveal a relationship between psychopathology and cognitive performance; though, we are led to wonder about the size of those hypothesized effects if more data (e.g., from a longer questionnaire) are required to detect them. Regardless, our study highlights the importance of carefully examining the relationship between physical wellness, mental health, and cognition in other patient populations, to determine what is driving any observed cognitive impairments.

We further explored whether the observed pattern of cognitive deficits was explained by the more severe cases of illness that required hospitalisation. Several preliminary studies have suggested

that cognitive impairments following COVID-19 infection are dependent on the level of medical assistance received^{1,22} although at least one study has reported no correlation between hospitalisation and cognitive impairments²⁴. This is an important issue because long-lasting cognitive deficits have been reported in non-COVID-19 patients following treatment in the ICU, suggesting that factors such as mechanical ventilation, sedation, drug therapy and disturbed sleep may all contribute to the emergent cognitive profile, independent of infection⁷. In the current study, direct comparisons of the hospitalised and non-hospitalised post COVID-19 subgroups against the controls showed that both groups had significant cognitive impairments. Moreover, the groups did not differ significantly on any measure of cognitive outcome, although numerically the hospitalised group performed worse than the non-hospitalised group in terms of reasoning, verbal ability, processing speed and overall cognitive performance (Figure 5b). Given this trend, we included hospitalisation in our regression analyses to see if it explained away or reduced the observed relationship(s) between physical health and cognitive performance. The results showed that physical health predicted cognitive performance even when mental health measures and hospitalisation were accounted for, highlighting that the effects of COVID-19 on cognition are not entirely driven by hospitalisation. This is an important observation, given that most studies of the prolonged effects of COVID-19 have focused on hospitalised cohorts.

Although the current study provides clear evidence for a broad pattern of cognitive impairment following COVID-19 infection, the effect was, at least to some extent, domain specific. That is to say, significant differences were found relative to controls in speed of processing and in the reasoning and verbal domains, but not in STM performance. It is important to point out that this relationship is not absolute, due to the nature of the three main factors that were extracted from performance across a diverse range of 12 cognitive tests. Specifically, we use the term STM

descriptively to refer to a single factor derived from performance across the entire battery of tests, and this will include some contributions from tests that do not ostensibly measure aspects of STM. Nevertheless, as we have shown previously⁴², and convincingly replicate here (Figure 1A, Supplementary Table 3), this factor is driven primarily by tests such as ‘spatial span’, ‘monkey ladder’, ‘token search’ and ‘paired associates’, all of which are derived from standard measures of STM (for details, including references for the original forms of the tasks on which the computerized versions are based, see Hampshire et al.⁴² or Wild et al.⁴⁴). This finding sheds some light on the nature and extent of the subjective experience of COVID-19 survivors, often called ‘long COVID’ - the expression now used widely to describe the subjective symptoms that include a sense of cognitive impairment following COVID-19 infection. Specifically, that the cognitive sequelae of COVID-19 in this context includes processing (or ‘thinking’) speed, reasoning and verbal abilities, but leaves short term memory relatively spared.

We are hesitant to draw conclusions about the underlying neural systems responsible for this pattern of impairments post COVID-19 infection, but an fMRI-based brain parcellation based on the same 12 tests used in this study may shed some preliminary light on this question. Hampshire et al. (2012) found that the STM factor, which was resilient to the effects of COVID-19 infection in the current study, had a brain network analogue that included the insula/frontal operculum, the superior frontal sulcus, and the ventral portion of the anterior cingulate cortex/ presupplementary motor area. The reasoning and verbal factors – which, in contrast, did show impaired performance in the COVID+ sample – were associated with two non-overlapping networks, composed of: (reasoning) the inferior frontal sulcus, the inferior parietal cortex, and the dorsal portion of the anterior cingulate cortex/ presupplementary motor area, and (verbal) the left inferior frontal gyrus and bilateral superior temporal regions. Although there is no obvious explanation for why these

two particular networks might be affected by COVID-19 infection while others are spared, future work could use neuroimaging to investigate the hypothesis that some brain regions or networks, and the cognitive systems they support, are more susceptible to damage from COVID-19 infection.

Regardless of the underlying neuropathological substrates, the functional dissociation observed in this study is important for understanding how COVID-19 related ‘brain fog’ differs from other conditions and circumstances that have been described using similar terms, such as post-chemotherapy cognitive dysfunction (‘chemo brain’), cognitive impairment following heart bypass surgery (‘pump head’) and disturbed cognition after sleep deprivation. Regarding the latter, in a recent study of more than 10,000 participants assessed using the same battery of 12 tests used in the current study (and from which the current control sample was drawn) we showed that typical sleep duration also had no bearing on short-term memory performance, unlike reasoning and verbal skills, which were impaired by both too little, or too much, sleep on a regular basis⁴⁵.

A key unanswered question remains the longitudinal nature of these problems. In those patients who are most affected, are these cognitive disturbances temporary, permanent, or do they signal the onset of a neurodegenerative cascade that results in a deteriorating pattern of impairment over time? While it is too early to answer this question in full, some preliminary clues can be gleaned from our data analysis. For example, the approximate time since infection demonstrated negligible correlations with all measures (Figures 1B, S2), suggesting that cognitive impairments do not get better or worse over the short term. Continuing work (e.g., following these participants over time) is required to understand the longitudinal trajectory of post-COVID-19 symptomology.

Finally, this study illustrates that it is possible to acquire comprehensive, high quality cognitive assessments remotely without any inter-personal contact, which is essential in a pandemic situation involving a highly contagious virus. Online data collection also allowed us to reach a broader

population than would have been possible by approaching patients from associated health networks and will afford us the opportunity to easily follow our cohort longitudinally.

There are, of course, limitations to this study that are common to observational research. Primarily, we cannot conclusively demonstrate a causal link between COVID-19 infection and cognitive outcomes. As described earlier, there may be some unmeasured confounding factor or bias underlying the pattern of results that we observed, but we feel that this is unlikely given the number of potential confounders that we controlled for – such as socio-demographic variables, hospitalization status, and pre-existing medical conditions – and the three converging observations of: 1) cognitive differences between control and COVID+ groups, 2) strong associations between cognitive performance and physical symptoms *within* the latter group, and 3) similar performance in all cognitive domains between controls and the subgroup of COVID+ participants with good physical health. Along similar lines, there are many other outcomes of COVID-19 that we did not measure, such as post-traumatic stress disorder (PTSD), that might be interrelated with the sets of symptoms described here. However, regardless of whether cognitive impacts are directly caused by COVID-19 or indirectly through another factor, such as PTSD, the fact remains that these impairments *are* symptoms experienced by survivors of COVID-19 in the weeks to months following infection. Finally, some might be skeptical of the data quality in an internet-based study, but research has shown that cognitive data collected online – i.e., from unsupervised, anonymous, self-selected, and uncompensated individuals – can be as reliable as that collected in the laboratory^{46,47}. And, while we must rely on self-report of a COVID-positive test, we have no reason to believe that volunteers would be purposefully deceitful when there was no benefit or incentive to do so. We would also like to point out that data were discarded from participants who indicated

that they had not received a positive test for COVID-19, even if they had indicated symptoms and/or risks for exposure, due to the uncertainty of their diagnosis.

In conclusion, we have shown clear cognitive impairments following COVID-19 infection.

These are likely not the result of a “global” impact on cognitive processing, as STM performance was relatively preserved. Crucially, in the domains that were affected, cognitive performance was related to measures of physical health, including COVID severity, but not mental health.

This has implications from a clinical viewpoint, as survivors who exhibit increased anxiety or depression may or may not have cognitive deficits, whereas these are much more likely in patients who experience a greater physical toll from the illness. Our findings underscore the fact that the physical, emotional, mental, and cognitive sequelae of COVID-19 are not bound together as a single neurocognitive syndrome.

Materials and Methods

Participants and Materials

Data for this study were collected entirely online from June 23rd 2020 to February 2nd 2021. The study was advertised through a number of online social media channels (e.g., Facebook, Twitter, and Reddit) and mainstream media outlets and reached potential participants around the world. Visitors to our website (www.covidbrainstudy.com) learned about the study and could sign up if interested. There was no compensation for volunteering. Participants had to be older than 18 years of age, have had a confirmed case of COVID-19 (self-reported positive test), and be fluent in either French, English, or Spanish – all study materials including the cognitive tests were available in these three languages. The study procedures and materials were approved by Western University's Health Sciences Research Ethics Board, and participants could withdraw at any point. After reading the study letter of information and consenting to participate, volunteers completed an online questionnaire followed by 12 cognitive tasks (the order of which was randomized across participants) using a laptop or desktop computer. Cognitive testing was administered via the Cambridge Brain Sciences platform (cambridgebrainsciences.com), which we have used for other online studies of cognition^{42,45}. A control sample consisted of participants who had participated in a similar study in 2017 (that is, before the onset of the COVID-19 pandemic) which included the same 12 cognitive tasks and a subset of the same questions – detailed in Wild et al. (2018).

In total, 3,243 people registered to participate in this study. Of those, 1,745 progressed through the questionnaire and 1,456 completed the cognitive tests. One dataset was removed for using an unsupported (i.e., mobile) device and 265 datasets were omitted for indicating an age less than 18 years (no volunteers reported being older than 100 years). As we have done previously⁴⁵, test

score outliers were filtered in two iterative passes. First, extreme outliers more than 6 *SDs* from the mean (e.g., technical/database errors) were removed to obtain reasonable estimates of the test means and *SDs*; four participants had at least one score greater than this threshold. Then, outlier scores were identified as being more than 4 *SDs* from the re-calculated mean, and 18 participants were excluded for having at least one outlier. 222 cases were excluded because of missing test scores or incomplete (i.e., optionally omitted) questionnaire responses. Finally, only participants who self-reported a confirmed positive test for COVID-19 were retained for analysis, resulting in a final dataset of 478 COVID-positive cases (i.e., the COVID+ group). The control data were preprocessed in a similar way. From 26,256 datasets, 7,832 were removed for using a mobile device, 1,831 indicated an age less than 18 or greater than 100 years, and 7,594 had missing test scores or questionnaire items. Cases with outliers were removed (N=289 with a score > 6 *SDs*, followed by N=877 with a score > 4 *SDs* from the mean), yielding a final control sample 7,832 participants.

Health Measures

Participants were asked about their COVID-19 history (Table 1), including: presentation of symptoms (according to common screening tools used at that time), the month and year of their most recent positive COVID-19 test, and whether they required hospitalisation. If they did not require treatment in the hospital, they indicated whether they could go about their daily routine as usual. In cases where hospitalisation was required, participants were also asked if: they were on supplemental oxygen therapy, in the intensive care unit (ICU), and (if in the ICU) on a ventilator. Measures of physical and mental health were captured using the RAND Short-Form Health Survey (SF-36) – specifically, the physical functioning, role functioning (physical), role functioning (emotional), energy & fatigue, and pain scales – and the GAD-2 & PHQ-2 anxiety

and depression screeners^{39,40}. The GAD-2 and PHQ-2 scales were reversed during analysis to make them consistent with the other scales where higher scores were representative of “better” health. Finally, two questions were included for subjective evaluations of cognitive functioning: 1) *“Do you feel that you are back to your baseline level of cognitive functioning?”* (subj_baseline) and 2) *“How would you rate your memory?”* on a 5-point scale from “miserable” to “excellent” (subj_memory).

Cognitive Test Battery

Detailed descriptions of the 12 CBS tasks can be found in the supplementary materials of some of our previous studies^{42,45}, but briefly they are: 1) Spatial Span (SS; short-term memory); 2) Monkey Ladder (ML; visuospatial working memory), 3) Paired Associates (PA; episodic memory), 4) Token Search (TS; working memory and strategy), 5) Digit Span (DS; verbal working memory), 6) Odd One Out (OOO; deductive reasoning), 7) Rotations (RT; mental rotation), 8) Feature Match (FM; feature-based attention and concentration), 9) Spatial Planning (SP; planning and executive function), 10) Interlocking Polygons (PO, visuospatial processing), 11) Grammatical Reasoning (GR, verbal reasoning), and 12) Double Trouble (DT; a modified Stroop task). For tasks 1-5, the primary outcome measure was the number of items in the hardest problem correctly solved, whereas scores for tasks 6-12 were variations of the sum of correct, minus incorrect, answers within the given time window. Each task, except for SP, also provided an aggregate measure of reaction time which was the average duration of correctly answered trials; for tasks 1-5, the individual trial durations were first normalized by the number of items in the problem.

544 Data Analysis

545 All data preprocessing and analysis was done in Python (v3.7.7, <https://www.python.org/>).
546 Specific packages included: pandas (v1.1.0) for data preprocessing and manipulation, scikit-learn
547 (v0.22.2) for estimating and applying data transformations, statsmodels (v0.11.0) for building
548 and fitting general linear models and calculating related statistics, pingouin (v0.3.9) for
549 performing Bayesian t-tests, factor analyzer (v0.3.2) for performing principal component and
550 factor analyses, numpy (v1.18.2) for all mathematical operations. A viewable notebook detailing
551 the entire analysis, including all custom code, can be viewed at
552 (<https://github.com/TheOwenLab/2021-Wild-et-al-COVID-Cognition>).

553 Data Visualization

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555 All figures were created with custom code written in Python, supported by the Plotly (v4.5.2)
556 and Matplotlib (v3.2.1) packages. Instead of using conventional bar plots (with error bars) to
557 depict summary statistics of group data (e.g., the mean and standard error of a measure of
558 cognitive performance for each group), we have adopted “raincloud” plots⁴⁸ that provide a
559 visualisation of the raw data, the estimated probability density, and summary statistics (i.e.,
560 median, 1st, and 3rd quartiles). Raincloud plots convey key aspects of the data without obscuring
561 underlying patterns and distributions of the data (with minimal redundancy) and hence are a
562 statistically transparent way to visualize data.

563 Health Factor and Compositive Cognitive Scores

564 Rather than examine every pairwise relationship between individual health variables and all 12
565 cognitive test scores, we reduced the number of measures (of both independent and dependent
566 variables) using factor analyses. Each multivariate dataset (health measures and cognitive tests)
567 was decomposed into a smaller number of statistically independent underlying, or “latent”,

factors that summarized the major modes of covariation amongst the variables. This approach allowed us to simplify interpretations, reduce the total number of model parameters, and avoid multicollinearity between predictors.

The set of health-related measures (i.e., SF-36 scales, GAD2, PHQ2, WHO COVID severity, and subjective measures of cognition) from the COVID+ group was summarized using factor analysis with a Varimax rotation. Factors with eigenvalues greater than 1.0 were retained for further analysis, and their scores were calculated for each participant by transforming questionnaire responses using the factor loadings matrix. The resulting factor scores were mean centred ($M = 0.0$) and had $SD = 1.0$.

A similar process was applied to the 12 cognitive tests scores. First, we performed a PCA analysis on the 12 primary CBS scores in the control group, specifying three components and a Varimax rotation; the solution was consistent with our previous findings⁴², and these components were interpreted as broadly representing short-term memory (STM), reasoning, and verbal ability (Figure 1b, Supplementary Table 4). Composite scores representing performance in these three domains were calculated by transforming participants' 12 test scores using the PCA loadings^{42,45}. We also calculated an "overall" score of cognitive performance (the mean of the 12 z-scored primary outcomes) and a measure of "processing speed" (the 1st principal component of the 11 reaction-time based features). Inspection of composite score loadings confirmed that higher test scores were indicative of better performance; that is, composite scores were positively correlated with higher individual test scores and faster responses.

Prior to the PCA analysis and score calculations, cognitive test data for both groups were standardized ($M = 0.0$, $SD = 1.0$) using the means and standard deviations from the control group. A power transformation⁴⁹ was applied (again, using parameters estimated from the control

group) to reduce skewness and improve normality of the test score features. The models, parameters, and transformations for these composite score calculations were derived using only the control group data, and therefore: 1) had $M = 0.0$ and $SD = 1.0$ in the control group, and 2) for COVID+ participants represented performance relative to the controls in units of standard deviations.

The PCA analyses (including standardization of score features) were repeated using data from only the COVID+ group to determine whether their cognitive data had a similar underlying factor structure. Indeed, a visually similar pattern was observed for the 3-component domain model (Supplementary Figure 2; Supplementary Table 4). The similarity of the factor solutions from the two groups was quantified using Tucker's congruence coefficient^{50,51}, which was greater than 0.97 for all three domains, and 0.99 for the processing speed component (Supplementary Table 5) – indicating that the solutions were equivalent between groups.

Statistical Analysis

Data analysis proceeded in two stages. First, we leveraged the power of our larger control dataset to estimate the relationship between each composite cognitive score and confounding variables common to both datasets. A linear multiple regression model was constructed for each cognitive score that included the predictors: age as a 2nd-order polynomial, and sex (male / female), post-secondary education (none / some), SES (above or below poverty level), exercise (at least weekly or not), and consumption of nicotine (>1 unit per day), alcohol (>7 units per week), cannabis (>1 unit per day), other stimulants (in the past 4 weeks), or other depressants (in the past 4 weeks) as binary predictors – totalling 12 regressors. The estimated parameters were then used to regress out the expected effects of these variables from the COVID+ and control participants' data, and the corrected cognitive scores were carried forward to subsequent

analyses. This approach was taken to avoid over-fitting the effects of these nuisance variables on the smaller dataset. For example, if COVID-19 infection has a greater impact on cognition for older individuals, then simply controlling for age in an analysis of the COVID+ dataset would obscure or reduce this critical finding.

In the second step a general linear model was used to estimate the relationship between each (corrected) composite score and the health-related factor scores, and t -tests of the parameter estimates were used to determine whether there was a linear relationship with each health factor. Instead of using the models' intercept statistics to determine whether the COVID+ differed significantly from zero, and hence the control group, we directly compared the two groups using Welch's t -test to account for unequal sample sizes⁵². All t -tests were two-tailed and reported p -values and confidence intervals were Bonferroni corrected across all scores and tests within each analysis set (e.g., 5 cognitive scores \times 3 parameters = 15 statistical tests). Effect sizes for continuous predictors included: ΔR^2 , the change in variance accounted for by adding the parameter, and Cohen's f^2 , a measure of local effect size⁵³. Given that the dependent variables were standardized in units of standard deviations (SDs), the parameter estimates for categorical variables, and differences between groups, amounted to standardized mean differences – analogous to Cohen's d .

We also performed Bayesian analyses to better characterize every statistical relationship. Given our reasonably large sample size, practically small effects might still be considered statistically significant using frequentist methods, whereas Bayesian methods guard against overfitting and a tiny effect size is less likely to result in a rejection of the null hypothesis⁵⁴. Therefore, we also report for every statistical test a Bayes Factor (BF) that quantifies the evidence in favour of the alternative hypothesis (BF_{10}). To obtain the BF_{10} for two-sample t -tests (e.g., group comparisons)

we employed the JZS Bayes factor⁵⁵, whereas we estimated the BF_{10} for parameters of regression models using the Bayesian Information Criterion approximation (Wagenmaker, 2007); that is, by comparing a “full” model that included the regressor of interest to a “restricted” model (i.e., a regression model *without* the predictor of interest, but that included other variables) or a “null” model (i.e., an intercept-only model). We interpreted BF magnitude using Wagenmakers’ heuristic, where BFs 1-3, 3-20, 20-150, and > 150 indicate weak, positive, strong, and very strong evidence, respectively, for the given hypothesis. The parametric statistics used in this study (both frequentist and Bayesian) assume the data or model residuals are normally distributed. Where appropriate, we used quantile-quantile plots (i.e., “*qq*” plots) to validate this assumption (e.g., see Supplementary Figure 3).

Data Availability

All anonymized data (i.e., cognitive testing and survey/questionnaire data) collected for this study are publicly available in the Scholar Portal Dataverse, as a part of this record⁵⁶ (<https://doi.org/10.5683/SP2/ZQR9QQ>), and can be used to recreate all statistics, tables, and figures in this manuscript. Source data for Tables 1 and 2, and Figures 2, 3, and 5 are provided along with this paper, whereas the data for Figure 1, 4, 6, are available in supplementary tables.

Code Availability

All custom code used for this study: data analyses, figure and table generation, etc. are publicly available at: <https://github.com/TheOwenLab/2021-Wild-et-al-COVID-Cognition>.

Figures

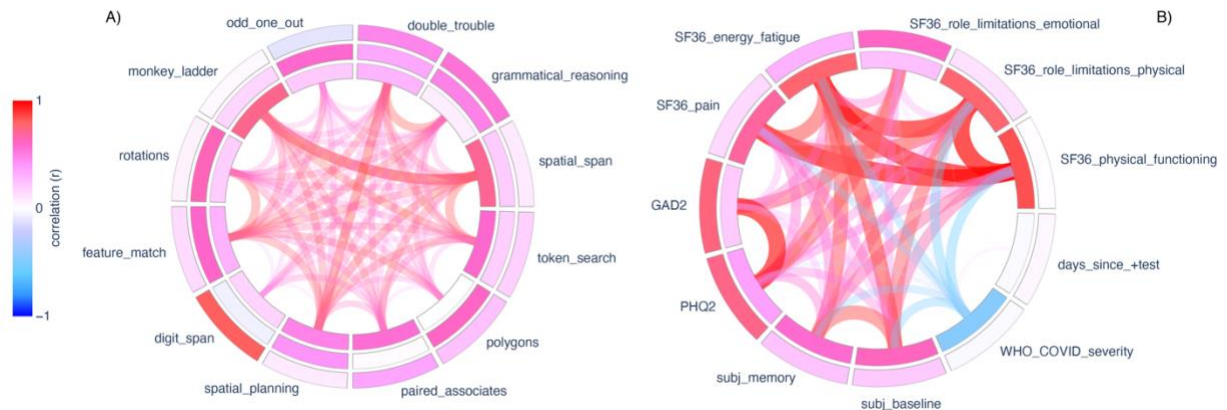
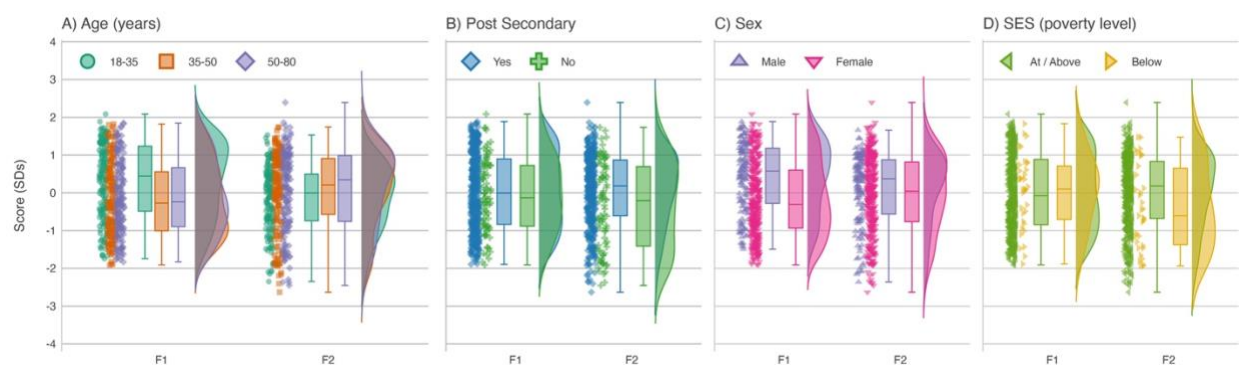


Figure 1. Factor analyses of cognitive test scores and health-related measures. **A)** (left) 12 cognitive test scores from control participants (N=7,832) and **B)** (right) health-related measures in COVID+ participants (N=478). Concentric rings represent factors, where inner rings (factors) explain more variance in the data than outer rings. Coloured cells show the loadings of observed variables, arranged around the ring, on each factor. Lines connecting observed variables indicate pairwise correlations. Pink colours indicate positive relationships, whereas blueish colours indicate negative correlations. **A)** Three (of five) composite cognitive scores analysed in this study were derived from a rotated factor analysis of the 12 cognitive tasks: STM (inner ring), reasoning (middle ring) and verbal (outer ring) domains. **B)** Two factors explained health-related questionnaire variables: overall physical health, including COVID severity (F1; inner ring), and mental health & wellness (F2; outer ring). Note that the GAD2 and PHQ2 scales were reversed to make higher scores correspond to better health, similar to other measures (except disease severity).

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Figure 2. Socio-demographic differences in health factor scores, within the COVID+ group. F1 (overall physical health, including COVID severity) and F2 (mental health & wellness) – as a function of: **A)** age (in three arbitrary bins), **B)** completion of post-secondary education, **C)** sex as assigned at birth, and **D)** Socio-economic status (relative to poverty level) while growing up. A raincloud summarizes the data in three ways: (left) stripe plots of individual data points; (middle) box plots that indicate median (middle line), 25th and 75th percentiles (box), and +/- 1.5 times the inter-quartile range (whiskers); and (right) overlapping probability density functions.

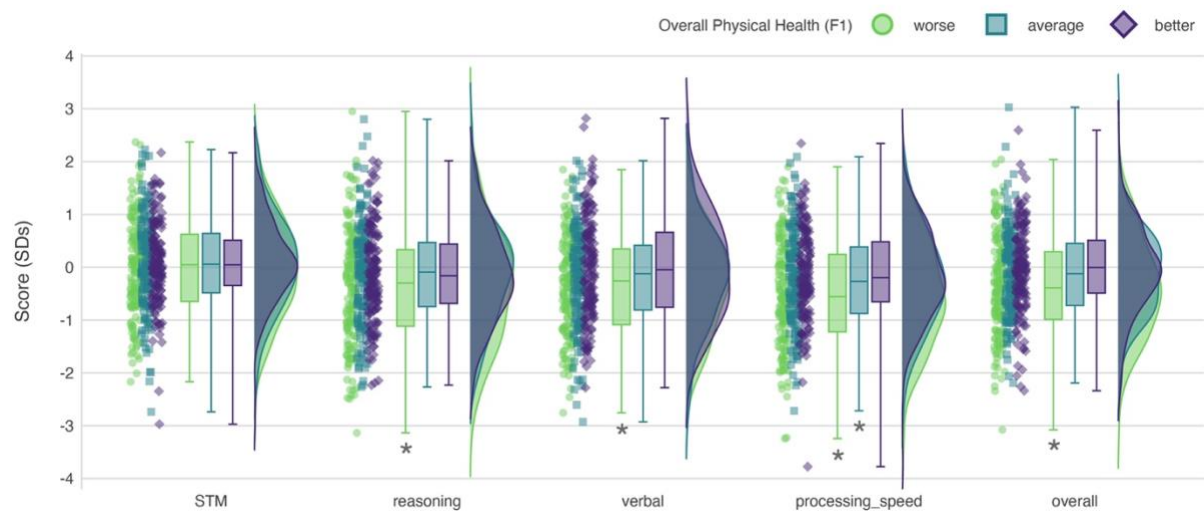


Figure 3. Cognitive scores for COVID+ participants as a function of overall physical health (F1). Participants were grouped into tercile bins based on their F1 scores: below average (“worse”; left group, green traces), “average” (middle group, blue traces), and above average (“better”; right group, purple traces) physical health (F1). Cognitive scores (corrected for nuisance variables) are relative to the control sample mean ($Y = 0.0$). Scores for each domain (along the x-axis) are depicted in three ways: (left) stripe plots of individual data points; (middle) box plots that indicate median (middle line), 25th and 75th percentiles (box), and +/- 1.5 times the inter-quartile range (whiskers); and (right) overlapping probability density functions. Subgroups (based on F1) are distinguishable by color, marker, and horizontal position. An asterisk below a box trace indicate a significant difference between that COVID+ subgroup and the control group ($p < 0.05$ corrected for 15 comparisons).

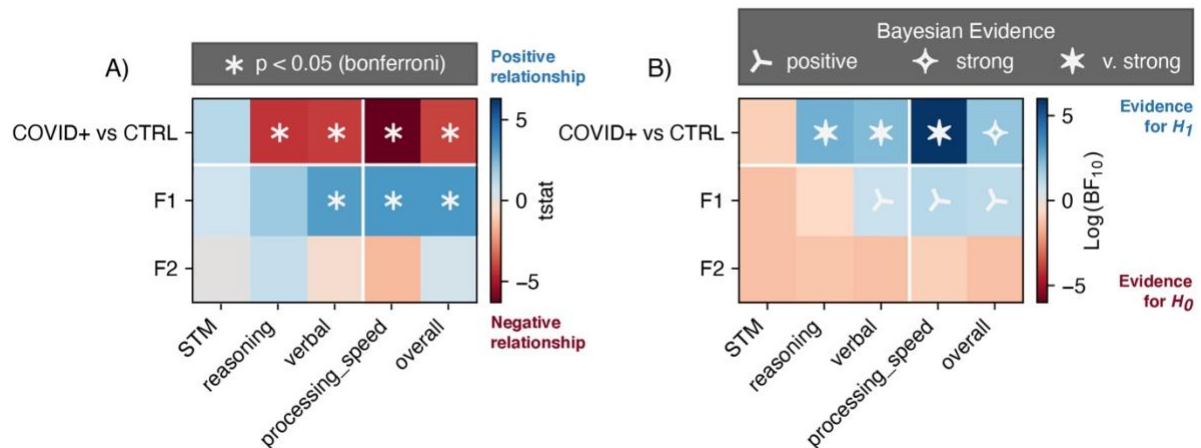
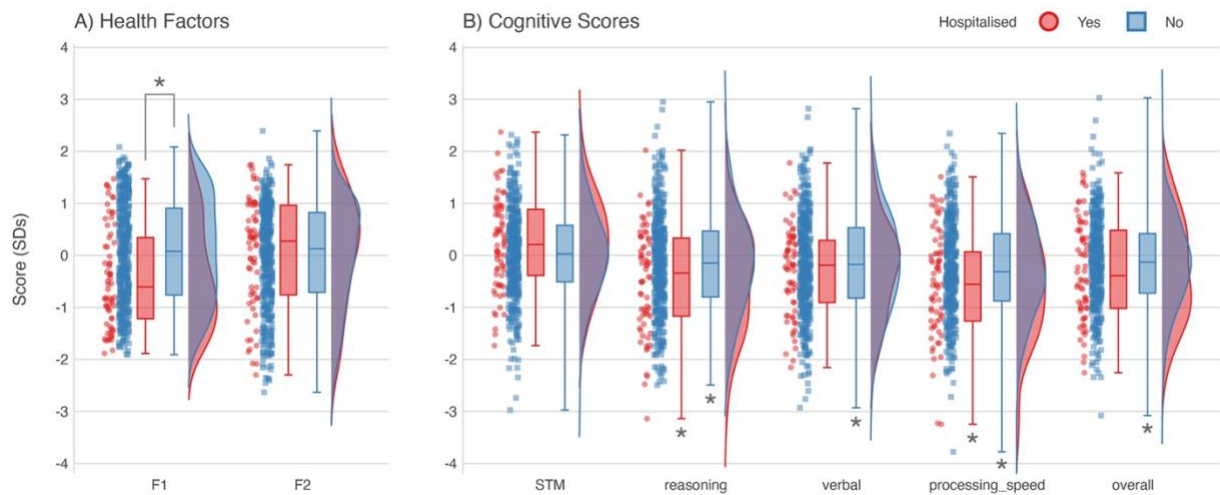


Figure 4. A visual summary of 15 statistical tests across 5 cognitive scores. A) frequentist and **B)** Bayesian statistics. In both panels the top row represents the two-sample t -test comparing COVID+ and control (CTRL) groups on each cognitive score. The 2nd and 3rd rows are tests of the regression parameters that predict cognitive scores from F1 (physical health), and F2 (mental health & wellness), while controlling for the other factor. **A)** T -statistics for each parameter estimate. Blue indicates a positive t -statistic (and a parameter > 0) whereas red indicates the converse. Stars indicate significant effects, $p < 0.05$ Bonferroni-corrected across all 15 comparisons. **B)** Bayes Factors for the same statistical tests. Blue indicates support for H_1 and red indicates support for H_0 . Symbols provide a heuristic interpretation for the given BF: positive (BF₁₀ 3-20), strong, (BF₁₀ 20-150), or very strong (BF₁₀ > 150) evidence for H_0 (labels not shown for interpretation of BF_{01s}).



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Figure 5. Differences between hospitalised (N=66) and non-hospitalised (N=412) COVID+ subgroups. A) Health factor scores: physical (F1) and mental (F2) health, where $Y=0$ corresponds to the COVID+ sample mean. The brace and asterisk indicate a significant group difference ($p < 0.001$). **B)** Cognitive scores (corrected for nuisance variables), where $Y=0$ indicates the control sample mean. Data for each score is presented in three ways: (left) stripe plots of individual data points; (middle) box plots that indicate median (middle line), 25th and 75th percentiles (box), and ± 1.5 times the inter-quartile range (whiskers); and (right) overlapping probability density functions. Asterisks below boxes indicate significant differences between the COVID+ subgroup and the control sample ($p < 0.05$ corrected for 10 comparisons). No cognitive differences between hospitalised and non-hospitalised groups were significant at a corrected level.

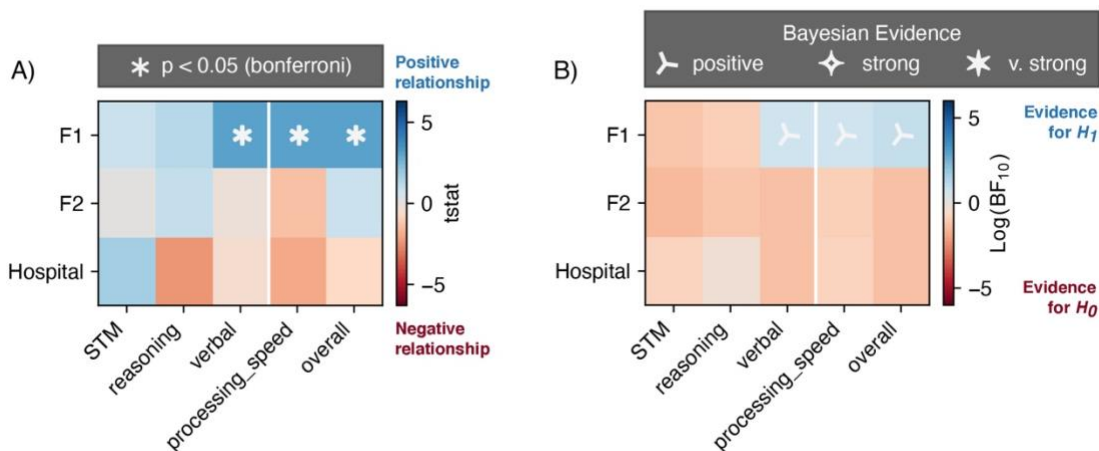


Figure 6: A summary of 15 statistical tests across 5 cognitive scores when accounting for the effects of hospitalisation, using A) frequentist and B) Bayesian statistics. In both panels, the rows represent tests of the regression parameters that predict cognitive performance from F1 (physical health), F2 (mental health & wellness), and hospitalisation status, while controlling for the other two factors. **A)** *T*-statistics for each parameter estimate. Blue indicates a positive *t*-statistic (and estimated parameter greater than 0.0) whereas red indicates the converse. Stars indicate significant effects, $p < 0.05$ (Bonferroni corrected, $N=15$). **B)** Bayes Factors from comparisons of the full model (including all three parameters) to a restricted model that did *not* contain the variable of interest. Blue cells indicate support for the alternative hypothesis ($BF_{10} > 1$), and warm cells indicate support for the null hypothesis ($BF_{10} < 1$). Symbols provide a heuristic interpretation for the given BF: positive (BF_{10} 3-20), strong, (BF_{10} 20-150), or very strong ($BF_{10} > 150$) evidence for H_1 (labels not shown for BFs that support the null hypotheses)

Tables

Table 1: Responses to questions about COVID-19 illness. Italicised text presents the questionnaire wording, and percentages are relative to the total COVID+ sample (N=478). Possible responses to each question, except the checklist of symptoms, included: “Yes”, “No”, and “I don’t know”.

Question	Yes	No	Don’t Know	# of Responses
Symptoms	450 (94.1%)	28 (5.9%)	.	478 (100%)
Selected at least one of: “cough”, “fever”, “difficulty breathing”, “pneumonia”, or “loss of smell”				
Hospital	66 (13.8%)	412 (86.2%)	.	478 (100%)
“Did you have to stay in the hospital for COVID-19 symptoms?”				
Daily Routine	129 (27.0%)	283 (59.2%)	.	412 (86.2%)
“Were you mostly able to go about your daily routine (e.g., mostly normal sleep, work, activity, etc.)?”				
Supplemental O ₂	34 (7.1%)	31 (6.5%)	1 (0.2%)	66 (13.8%)
“Did you require supplemental oxygenation (e.g., with a mask or nasal prongs) while in the hospital? (note, this does not include being on a ventilator)”				
Intensive Care	17 (3.6%)	49 (10.3%)	.	66 (13.8%)
“Were you in the ICU (Intensive Care Unit)?”				
Ventilator	11 (2.3%)	6 (1.3%)	.	17 (3.6%)
“Were you on a ventilator (breathing machine)?”				

Table 2: Descriptive statistics for the (unmatched) COVID+ and control groups.

		COVID+ (N = 478)		Control (N = 7,832)	
Age (in years)		$M = 42.6$ ($SD = 14.5$)		$M = 43.2$ ($SD = 13.0$)	
Sex - Female		336 (70%)		4857 (62%)	
Completed some post-secondary education		394 (82%)		5917 (76%)	
Grew up "At or above poverty level"		443 (93%)		7312 (93%)	
Languages spoken at home	English	368 (77%)		6387 (82%)	
	French	45 (9%)		485 (6%)	
	Spanish	23 (5%)		176 (2%)	
Location (top 5 countries)	1)	USA	202 (42.3%)	Canada	2453 (31.3%)
	2)	Canada	143 (29.9%)	U.K.	2420 (30.9%)
	3)	U.K.	42 (8.8%)	USA	607 (7.8%)
	4)	Spain	11 (2.3%)	Portugal	382 (4.9%)
	5)	Germany	7 (1.5%)	Australia	128 (1.6%)
Exercises at least once per week		335 (70%)		4777 (61%)	
One or more units of nicotine per day		40 (8%)		717 (9%)	
More than 7 units alcohol per week		17 (4%)		541 (7%)	
One or more units of cannabis per day		51 (11%)		553 (7%)	
other stimulants ⁺		7 (1%)		90 (1%)	
other depressants ⁺		4 (1%)		44 (1%)	

$M = \text{mean}; SD = \text{standard deviation}.$
⁺ consumed at least once in the past 4 weeks

Table 3: Results of comparisons between COVID+ and control groups on 5 composite cognitive scores. The cognitive measures were adjusted for nuisance covariates. The mean difference is between groups, COVID+ vs. controls, and measured in units of standard deviations (*i.e.*, analogous to Cohen's *d*). *P*-values and confidence intervals are Bonferroni-corrected for 15 comparisons. Bold entries indicate significant effects ($p_{adj} < 0.05$).

score	difference	<i>t</i>	<i>df</i>	p_{adj}	CI	BF ₁₀
STM	0.06	1.38	543.80	1.000	(-0.064, 0.177)	0.14
reasoning	-0.20	-4.26	530.10	< 0.001	(-0.334, -0.061)	424.92
verbal	-0.18	-4.07	540.49	< 0.001	(-0.318, -0.051)	194.48
processing_speed	-0.29	-6.67	527.97	< 0.001	(-0.423, -0.164)	> 1000
overall	-0.16	-3.96	532.52	0.001	(-0.284, -0.041)	124.22

t - *t*-statistic; *df* - degrees of freedom; p_{adj} - adjusted *p*-value; CI - confidence intervals

Table 4: Linear regression results from models that included both overall physical health (F1) and mental health & wellness (F2) factor scores as simultaneous predictors of cognitive scores. *P*-values and confidence intervals are Bonferroni-corrected for 15 comparisons. Intercept-related statistics are not included because the mean differences from zero are better described using two-sample *t*-tests against the control group (Table 3). Bold entries indicate significant effects ($p_{adj} < 0.05$).

DV	IV	β	<i>t</i>	<i>df</i>	p_{adj}	CI	ΔR^2	f^2	BF ₁₀
STM	F1	0.03	0.72	475	1.000	(-0.088, 0.146)	0.001	0.001	0.06
	F2	0.01	0.19	475	1.000	(-0.109, 0.125)	0.000	0.000	0.05
reasoning	F1	0.09	1.90	475	0.861	(-0.047, 0.219)	0.008	0.008	0.28
	F2	0.04	1.00	475	1.000	(-0.088, 0.178)	0.002	0.002	0.08
verbal	F1	0.14	3.23	475	0.020	(0.012, 0.269)	0.021	0.022	8.12
	F2	-0.02	-0.35	475	1.000	(-0.144, 0.114)	0.000	0.000	0.05
processing_speed	F1	0.15	3.48	475	0.008	(0.022, 0.273)	0.025	0.025	18.69
	F2	-0.06	-1.41	475	1.000	(-0.185, 0.065)	0.004	0.004	0.12
overall	F1	0.14	3.43	475	0.010	(0.019, 0.253)	0.024	0.025	15.82
	F2	0.03	0.69	475	1.000	(-0.090, 0.144)	0.001	0.001	0.06

DV - dependent variable, *IV* - independent variable, β - estimated coefficient; *t* - *t*-statistic; *df* - *t*-statistic degrees of freedom; p_{adj} - adjusted *p*-value; CI - confidence intervals; f^2 - Cohen's *f*

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Author Contributions

All authors conceived and designed the study. RHS and AMO supervised the project. CJW implemented the online data collection, analysed the data, and prepared figures, tables, etc. CJW and AMO wrote the paper. All authors provided valuable insights and suggestions, aided with data interpretation and manuscript revisions, and have approved the final version of the manuscript.

Corresponding Authors

Please send all correspondence to Conor J. Wild (cwild@uwo.ca) or Adrian M. Owen (uwocerc@uwo.ca)

Competing Interests

The cognitive tests used in this study are marketed by Cambridge Brain Sciences (CBS), of which AMO is the Chief Scientific Officer. Under the terms of the existing licensing agreement, AMO and his collaborators are free to use the platform at no cost for their scientific studies, and such research projects neither contribute to, nor are influenced by, the activities of the company. CJW provides consulting services to CBS. Consequently, there is no overlap between the current study and the activities of CBS, nor was there any cost to the authors, funding bodies, or participants who were involved in the study. The authors declared that there were no other potential conflicts of interest with respect to the authorship or the publication of this article.