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

Conor Wild (cwild@uwo.ca)
University of Western Ontario
Loretta Norton
King's University College at Western University
David Menon
University of Cambridge https://orcid.org/0000-0002-3228-9692
David Ripsman
University of Ottawa
Richard Swartz
Sunnybrook HSC, University of Toronto
Adrian Owen
Department of Psychology, Brain and Mind Institute, Western University

Article

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Abstract

As COVID-19 cases exceed hundreds of millions globally, it is clear that many survivors face cognitive challenges and prolonged symptoms. However, important questions about the cognitive impacts of COVID-19 remain unresolved. In the present online study, 485 volunteers who reported having had a confirmed COVID-positive test completed a comprehensive cognitive battery and an extensive questionnaire. This group performed significantly worse than pre-pandemic controls on cognitive measures of reasoning, verbal, and overall performance, and processing speed, but not short-term memory – suggesting domain-specific deficits. We identified two distinct factors underlying health measures: one varying with physical symptoms and illness severity, and one with mental health. Crucially, cognitive deficits were correlated with physical symptoms, but not mental health, and were evident even in cases that did not require hospitalisation. These findings suggest that the subjective experience of "long COVID" or "brain fog" relates to a combination of physical symptoms and cognitive deficits.

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-solving[1]. 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-19[2–5], as well as signs of microvascular damage[6] 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 (MMSE[14]) and the Montreal Cognitive Assessment (MOCA[15]) 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 controls[20]. Other studies have suggested a specific domain of cognitive impairment; however, this has varied across studies from primary deficits in attention[21] to visuospatial deficits[20]. 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 inflammation[21] with severe infections being associated with significant cognitive deficits[17,18,23] although cognitive impairments have also been reported in asymptomatic patients[16], and one small study reported no correlation with hospitalization and cognitive impairments[24]. 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 disorders[30], and depression[31], 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 symptoms[25], including anxiety[17,24] depression[17,24] and fatigue[24].

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 485 patients who self-reported having had 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-36[38]), and mental health status, assessed using standard measures of anxiety

(GAD2[39]) and depression (PHQ2[40]). 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 485 volunteers who reported having a confirmed-positive case of COVID-19 (i.e., the COVID + group) 67 required treatment in a hospital for their illness, and of those: 35 required supplemental oxygen therapy, 17 were in the Intensive Care Unit (ICU), and 11 were on a ventilator. Cases that were not hospitalised (N = 418) were asked about their daily functioning, and 287 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 severity[41], 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; Figure S1, Table S1). Participants also indicated the year and month of their most recent positive test for COVID-19 to approximate the elapsed time since infection (*median* = 3 months, *SD* = 2 months). It is also worth noting that 160 (33%) and 158 (31.5%) of participants met the criterion for a suspected generalized anxiety disorder (i.e., GAD2 > = 3) or major depressive disorder (i.e., PHQ2 > = 3) respectively.

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 confounding variables from cognitive scores. This 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.

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 = 485). 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	457 (94.2%)	28 (5.8%)	.	485 (100%)
Selected at least one of: "*cough", "fever", "difficulty breathing", "pneumonia", or "loss of smell"*				
Hospital	67 (13.8%)	418 (86.2%)	.	485 (100%)
Daily Routine	131 (27.0%)	287 (59.2%)	.	418 (86.2%)
Supplemental O_2	35 (7.2%)	31 (6.4%)	1 (0.3%)	67 (13.8%)
Intensive Care	17 (3.5%)	50 (10.3%)	.	67 (13.8%)
Ventilator	11 (2.3%)	6 (1.2%)	.	17 (3.5%)

Table 2
Descriptive statistics for the (unmatched) COVID+ (N = 485) and control (CTRL; N = 8,815) groups.

Variable		COVID+		CTRL	
		N	**%**	**N**	**%**
Sex	Female	341	70.30	5539	62.84
	Male	144	29.70	3276	37.16
Post-Secondary	FALSE	85	17.53	2150	24.39
	TRUE	400	82.47	6665	75.61
SES	At or above poverty level	449	92.58	8226	93.32
	Below poverty level	36	7.42	589	6.68
Age (in years)		*M* = 43.41		*M* = 42.76	
		(*SD* = 13.17)		(*SD* = 14.44)	

Differences in cognitive performance 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 work[42], we interpreted the resulting components as generally describing cognitive performance in three domains: visuospatial short-term memory (STM), reasoning, and verbal domains (Fig. 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 *p*s. < 0.005; Table 3), such that COVID + participants performed, on average, worse than the controls by 0.18, 0.17, 0.29, and 0.15 *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 50 times more likely to occur given the model that included a difference between groups (i.e., all BF_{10}s > 50; 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

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	*t*	*df*	p_{adj}	CI	BF_{10}
STM	0.05	1.20	557.04	1.000	(-0.072, 0.169)	0.11
reasoning	**-0.18**	**-4.01**	**540.84**	**0.001**	**(-0.319, -0.049)**	**153.69**
verbal	**-0.17**	**-3.84**	**544.28**	**0.002**	**(-0.303, -0.040)**	**79.14**
processing_speed	**-0.29**	**-6.71**	**546.17**	**< 0.001**	**(-0.424, -0.165)**	**> 1000**
overall	**-0.15**	**-3.75**	**556.00**	**0.003**	**(-0.275, -0.033)**	**55.84**

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

Two dissociable health-related factors associated with COVID-19 infection

Strong correlations were observed between health-related questionnaire variables from the COVID + group (Figs. 1B, S2). Bartlett's test of sphericity ($\chi^2_{(45)} = 2199$, $p < 0.001$) and a Kaiser-Meyer-Olkin value of 0.88 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; Fig. 1B, inner ring), and mental health & wellness (henceforth referred to as F2; Fig. 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 (Figs. 1B, S2). The approximate elapsed time since infection demonstrated negligible correlations with all measures (Figs. 1B, S2). Descriptive statistics of each heath variable, along with their loadings on F1 and F2, can be found in Table S2.

The two health factors (F1 and F2) were dissociable with respect to their relationships with demographic variables (Fig. 2). Linear regression models (Table S4) showed that the overall physical health factor (F1) was negatively correlated with age ($t_{(480)} = -3.17$, $p_{adj} < 0.05$, $f^2 = 0.021$, $BF_{10} = 6.86$) with an average decline of approximately 0.1 SDs per decade, whereas mental health & wellness (F2) increased with age ($t_{(480)} = 2.84$, $p_{adj} < 0.05$, $f^2 = 0.017$, $BF_{10} = 2.60$) by 0.1 SDs per decade. Completion of post-secondary education was also associated with significantly better (F2) mental health ($t_{(480)} = 3.27$, $p_{adj} < 0.05$, $d = 0.38$, $BF_{10} = 9.53$) but not (F1) physical health, and males reported better (F1) physical health ($t_{(480)} = 5.91$, $p_{adj} < 0.001$, $d = 0.56$, $BF_{10} > 1000$) 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.

Delineating the relationships between health factors and cognitive domains

Figure 3 describes cognitive performance of COVID + participants relative to controls ($Y = 0$) as a function of overall physical health (F1; Fig. 3A) and mental health & wellness (F2; Fig. 3B); to simplify this visualization and reduce the number of comparisons, participants were grouped into tercile bins for each health factor (i.e., percentiles that each contained 1/3rd of the sample – corresponding to below average, average, and above average). Figure 3A shows that COVID + participants who had better than average physical health (white bars) performed similarly to controls in all cognitive domains. In contrast, those participants with worse than average physical health (darkest bars) exhibited significant impairments relative to controls (Table S5) on the four cognitive scores already identified as being impaired 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 (Fig. 3B).

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 ps < 0.05; Table 4) – when controlling for F2. BFs suggested positive to strong evidence in favour of these relationships (BF_{10} of 9.33, 21.60, 8.97 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 was associated with better verbal and overall performance and faster processing speed, consistent with the results depicted in Fig. 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 ps $= 1.0$ and BF_{10}s < 1; Table 4).

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	*t*	*df*	p_{adj}	CI	ΔR^2	f^2	BF_{10}
STM	F1	0.02	0.59	482	1.000	(-0.094, 0.141)	0.001	0.001	0.05
	F2	0.01	0.31	482	1.000	(-0.105, 0.129)	0.000	0.000	0.05
reasoning	F1	0.08	1.76	482	1.000	(-0.053, 0.210)	0.006	0.006	0.21
	F2	0.04	0.97	482	1.000	(-0.088, 0.175)	0.002	0.002	0.07
verbal	F1	**0.14**	**3.27**	**482**	**0.017**	**(0.014, 0.268)**	**0.022**	**0.022**	**9.33**
	F2	0.00	0.01	482	1.000	(-0.127, 0.128)	0.000	0.000	0.05
processing_speed	F1	**0.15**	**3.52**	**482**	**0.007**	**(0.024, 0.274)**	**0.025**	**0.026**	**21.60**
	F2	-0.06	-1.35	482	1.000	(-0.182, 0.068)	0.004	0.004	0.11
overall	F1	**0.13**	**3.26**	**482**	**0.018**	**(0.012, 0.245)**	**0.021**	**0.022**	**8.97**
	F2	0.04	0.91	482	1.000	(-0.081, 0.152)	0.002	0.002	0.07

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

Figure 4 summarizes the COVID + vs. control group comparisons and tests of health-factor regression parameters – across all five cognitive domains. A supplementary analysis that included socio-demographic covariates (despite these effects already having been removed) yielded the same pattern of results (Table S6), suggesting that the observed relationships between physical health (F1) and cognitive scores were not driven by residual effects of these factors.

Is the relationship between physical health and cognition explained by hospitalisation?

We next examined whether the impairments observed 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 ($t_{(89.79)}$ = -3.89, p_{adj} < 0.001, *d* =

0.49, BF_{10} = 170.87) with hospitalised cases reporting worse overall physical health than non-hospitalised cases (Fig. 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 (Fig. 5B, Table S7). 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 Fig. 5B.

Direct comparisons of each of these COVID + subgroups against the controls showed that both had significant cognitive impairments in some domains (Fig. 5B). Specifically, the non-hospitalised group were significantly impaired in the reasoning and verbal domains, and in terms of speed of processing and overall performance (Fig. 5B, Table S8). Meanwhile, the hospitalised group only had significant impairments in the reasoning domain and in processing speed (Fig. 5B, Table S8). 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 weak evidence (verbal BF_{10} = 2.88, overall BF_{10} = 1.58) 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_{10}s < 1.0) that there was no difference between the control sample and these two groups in this domain (Table S9).

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 (Fig. 6, Table S9) remained consistent with Fig. 3: 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_{10}s > 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 cognitive performance

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 (Figure S4A), and BF_{01}s suggested positive to strong evidence (Figure S4B, Table S10) in support of the null (H_0) hypotheses. This suggests

that: 1) using the control dataset to estimate and remove the effects of these potential confounders from cognitive scores was successful, and 2) the effects of these variables did not differ between the control and COVID + datasets. Simply, the cognitive impairments associated with COVID-19 infection did not differ between females and males or vary with age.

Discussion

In this study, we present data from a cohort of 485 individuals who 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 unequivocally confirm the existence of cognitive impairments in the aftermath of COVID-19 infection. There are several important novel findings here. First, there is striking domain specificity of the impairments. 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 taken into account, two distinct subjective symptom patterns 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.

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 (Figure S4) 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 (Table S4) 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 measures of mental health such as anxiety and depression were 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 participants[30] showed that generalized anxiety is associated with memory and verbal fluency deficits, particularly in young adults. Similarly, a systematic review and meta-analysis by Semkovska 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 detectible, 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 pandemic[43]. 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.

Based on our data it is not possible to disentangle the effects on mental health of COVID-19 infection and the pandemic more generally. Factors such as job security, financial instability, home-schooling, social isolation and an elevated sense of community fear have undoubtedly affected the mental well-being of people throughout the world, irrespective of whether they have received a positive COVID-19 diagnosis. Theoretically, the same argument could be made to explain some of our physical and cognitive outcome

measures; increased fatigue, poorer subjective memory, and even impaired reasoning and processing speed might occur, to some extent, even in the general non-COVID + ve population during the pandemic. However, two observations suggest otherwise: first, the fact that the severity of these deficits was tightly coupled to the severity of COVID-19 symptoms, whereas no such relationship existed between WHO severity ratings and mental-health scores, and second, participants who had better than average physical health scores (i.e., were relatively unaffected by the infection in physical terms) performed similarly to pre-pandemic controls in all cognitive domains, whereas cognitive impairments were only seen in those participants who reported poor physical health and more severe illness. Taken together, these results suggest that the physical/cognitive profile identified here is one that is specifically related to COVID-19 infection itself.

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 impairments[24]. 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 infection[7] 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 (Fig. 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, notable impairments 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 previously[42], and convincingly replicate here (Fig. 1A, Table S3), 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' or 'brain fog' - the expression now used widely to describe the subjective sense of cognitive impairment following COVID-19 infection. Specifically, that 'brain fog' 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 basis[45].

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 (Figs. 1B, S2), suggesting that cognitive impairments do not get better or worse over the short term. The current cohort will be followed and retested regularly for at least a year, and possibly longer, and until that process is complete the longitudinal trajectory of post COVID-19 cognitive impairment will remain unclear.

Finally, this study illustrates that 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.

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 1,379 completed the cognitive tests. One dataset was removed for using an unsupported (i.e., mobile) device and 190 datasets were omitted for indicating an age less than 18 years (no volunteers reported being older than 100 years). As we have done previously[45], 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*; three participants had at least one score greater than this threshold. Then, outlier scores were identified as being more than 4 *SD*s from the re-calculated mean, and 20 participants were excluded for having at least one outlier. 211 cases were excluded because of missing test scores or incomplete (i.e., optionally omitted) questionnaire responses. Finally, only participants who indicated having a confirmed positive test for COVID-19 were retained for analysis, resulting in a final dataset of 485 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 6,437 had missing test scores or questionnaire items. Cases with outliers were removed (N = 331 with a score > 6 *SDs*, followed by N = 1,010 with a score > 4 *SDs* from the mean), yielding a final control sample 8,815 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.

Data Analysis

All data preprocessing and analysis was done in Python (v3.7.7, https://www.python.org/). Specific packages included: pandas (v1.1.0) for data preprocessing and manipulation, scikit-learn (v0.22.2) for estimating and applying data transformations, statsmodels (v0.11.0) for building and fitting general linear models and calculating related statistics, pingouin (v.0.3.9) for performing Bayesian t-tests, factor analyzer (v0.3.2) for performing principal component and factor analyses, numpy (v1.18.2) for all mathematical operations, and plotly (v4.5.2) and matplotlib (v.3.2.1) to support figure creation. A viewable notebook detailing the entire analysis, including all custom code, can be viewed at (https://github.com/TheOwenLab/2021-Wild-et-al-COVID-Cognition).

Health Factor and Compositive Cognitive Scores

Rather than examine every pairwise relationship between individual heath variables and all 12 cognitive test scores, we reduced the number of measures (of both independent and dependent variables) using factor analyses. Each multivariate dataset (health measures and cognitive tests) 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 findings[42], and these components were interpreted as broadly representing short-term memory (STM), reasoning, and verbal ability (Fig. 1b, Table S4). 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

transformation[46] 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.

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 demographic variables: age (as a 2nd -order polynomial), and sex, post-secondary education, & SES as binary predictors. The estimated parameters were then used to regress out the expected effects of these variables from the COVID + 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 sizes[47]. 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 · 3 parameters = 15 statistical tests). Effects 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 size[48]. 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 hypothesis[49]. 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 factor[50], 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 Figure S3).

Declarations

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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.

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Figures

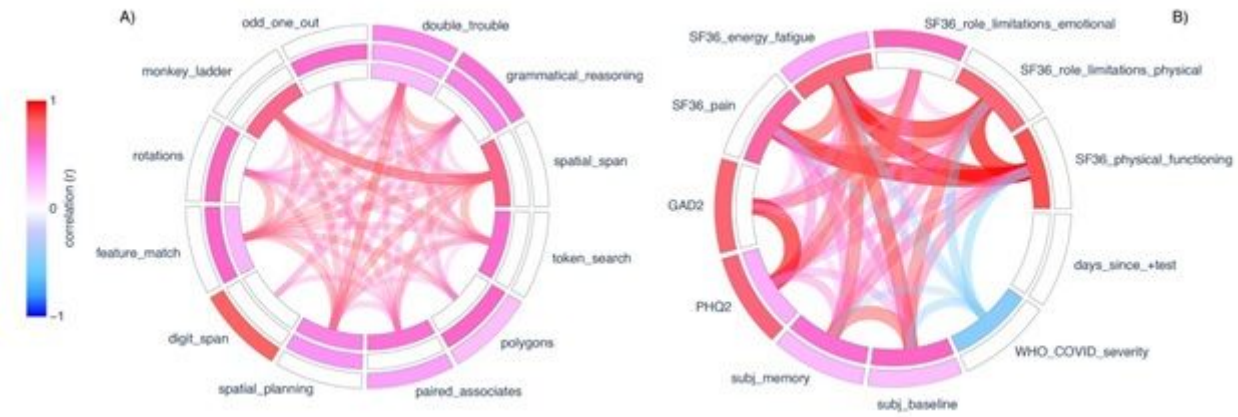

Figure 1

Factor analyses of A) (left) 12 cognitive test scores from control participants (N=8,815) and B) (right) health-related measures in COVID+ participants (N=485). 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. Correlations and loadings than 0.2 are masked. 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).

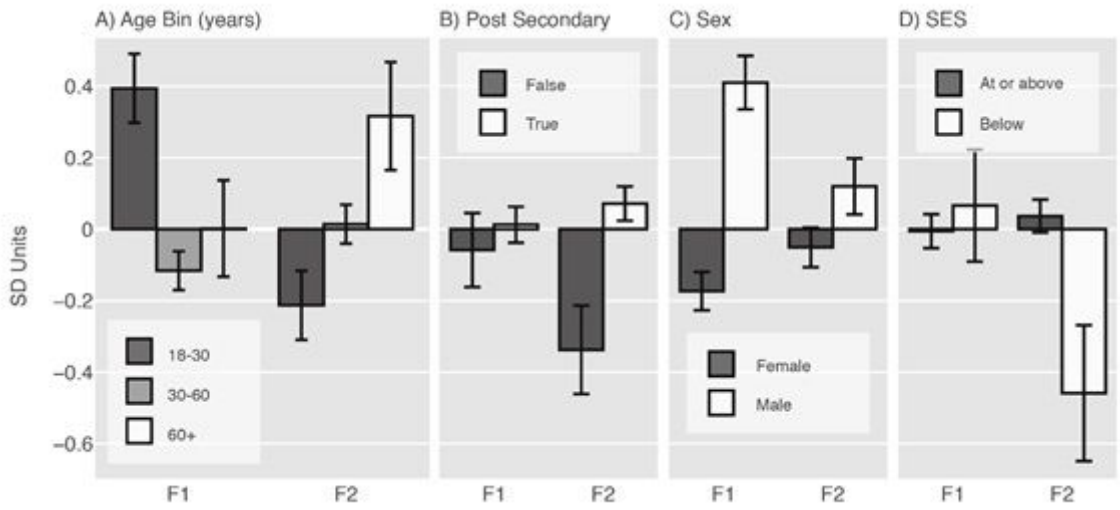

Figure 2

Average health factor scores — 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 poverty level) while growing up. Bar height is the average factor score for each subgroup (in units of standard deviations) and error bars depict the standard error the mean.

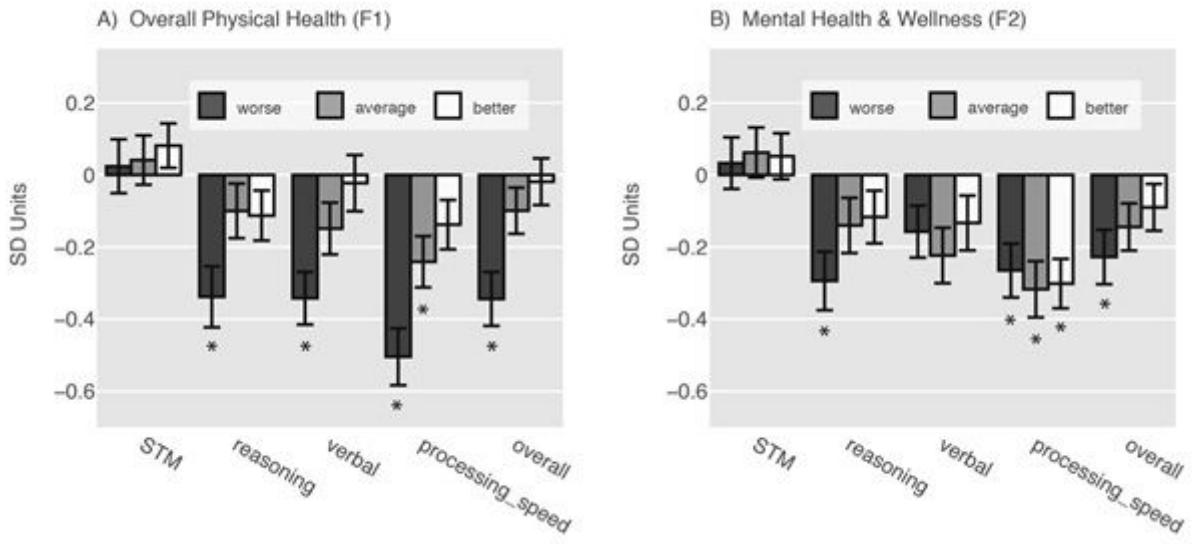

Figure 3

Average cognitive scores for COVID+ participants grouped into tercile bins – below average (“worse)”, “average”, and above average (“better”) based on A) overall physical health (F1) or B) mental health & wellness (F2) factor scores. Bar height is the average cognitive score (corrected for nuisance variables) relative to the control sample mean (Y=0.0), error bars show SEM, and asterisks indicate a significant two-sample t-test vs the control group ($p < 0.05$ corrected for 15 comparisons).

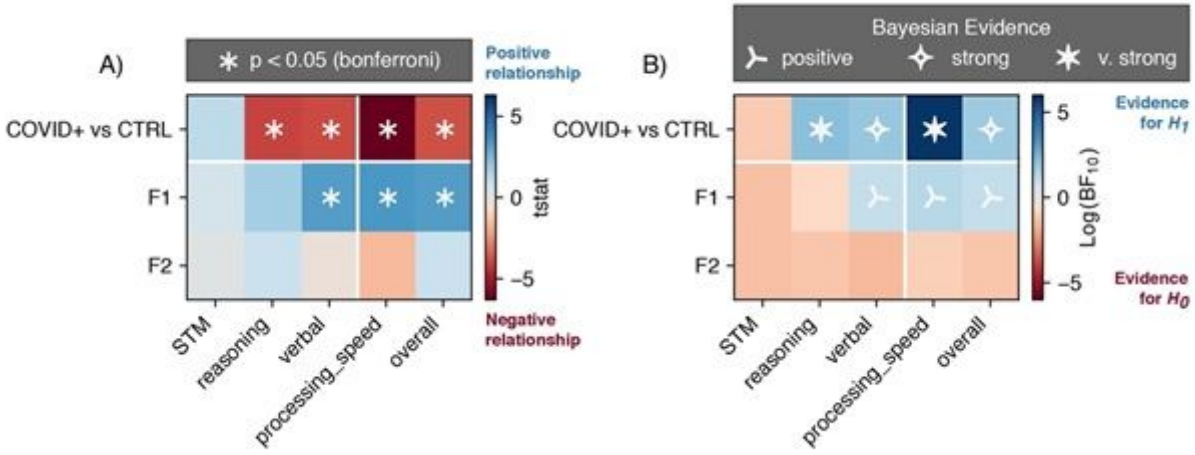

Figure 4

A visual summary of 15 tests across 5 cognitive scores, using 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 H1 and red indicates support for H0. Symbols provide a heuristic interpretation for the given BF: positive (BF10 3-20), strong, (BF10 20-150), or very strong (BF10 > 150) evidence for H0 (labels not shown for interpretation of BF01s).

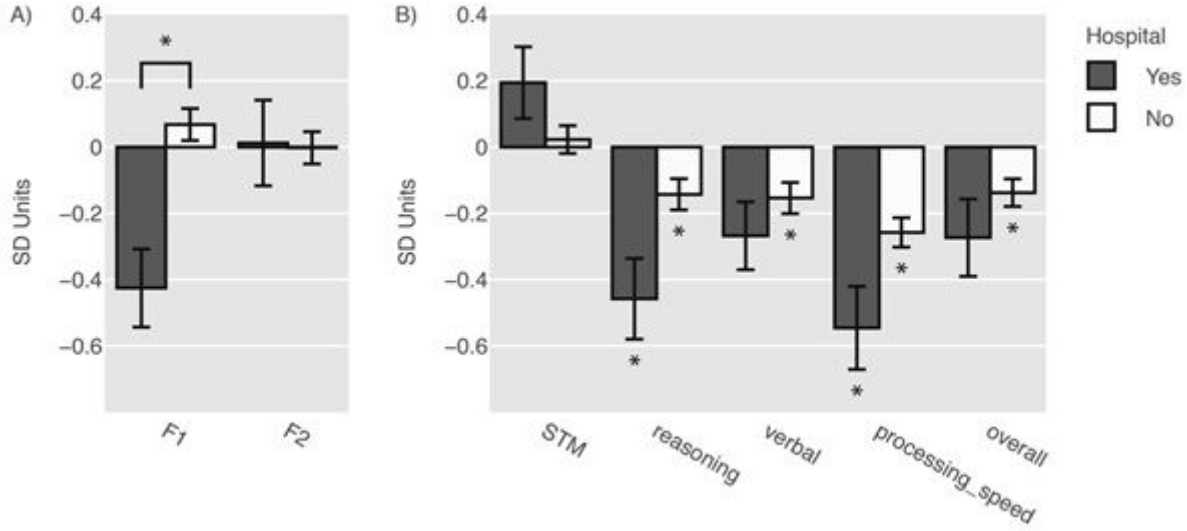

Figure 5

Average scores for hospitalised (N=67) and non-hospitalised (N=418) 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) Average (corrected) cognitive scores, where Y=0 indicates the control sample mean. Asterisks indicate bars that are significantly different than 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.

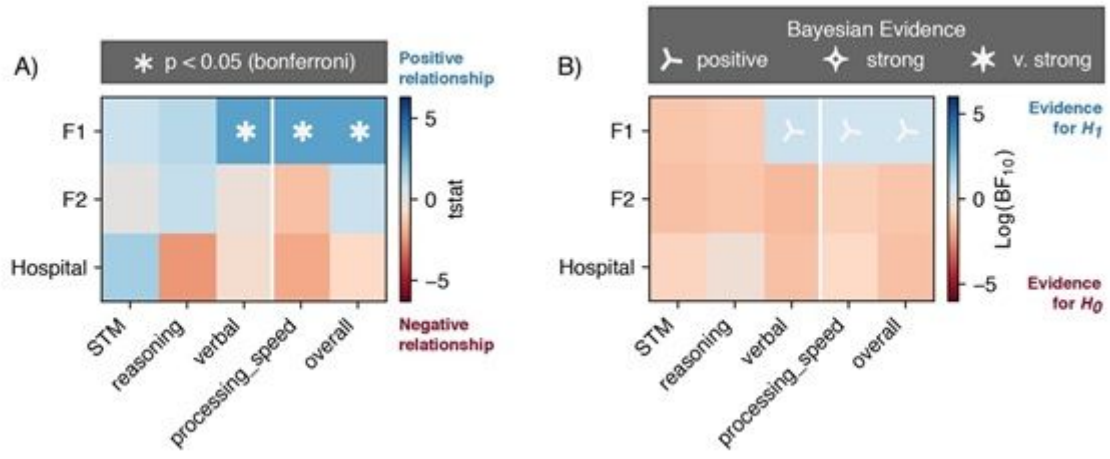

Figure 6

A summary of 15 statistical tests across 5 cognitive scores, 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 (BF10 > 1), and warm cells indicate support for the null hypothesis (BF10 < 1). Symbols provide a heuristic interpretation for the given BF: positive (BF10 3-20), strong, (BF10 20-150), or very strong (BF10 > 150) evidence for H1 (labels not shown for BFs that support the null hypotheses)

Supplementary Files

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- COVIDCognitionNCSupplementaryMaterialssubmissionready.docx