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

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Abstract

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29 As COVID-19 cases exceed hundreds of millions globally, it is clear that many survivors face

30 cognitive challenges and prolonged symptoms. However, important questions about the

31 cognitive impacts of COVID-19 remain unresolved. In the present online study, 485 volunteers

32 who reported having had a confirmed COVID-positive test completed a comprehensive cognitive

33 battery and an extensive questionnaire. This group performed significantly worse than pre-

34 pandemic controls on cognitive measures of reasoning, verbal, and overall performance, and

35 processing speed, but not short-term memory – suggesting domain-specific deficits. We

36 identified two distinct factors underlying health measures: one varying with physical symptoms

37 and illness severity, and one with mental health. Crucially, cognitive deficits were correlated

38 with physical symptoms, but not mental health, and were evident even in cases that did not

39 require hospitalisation. These findings suggest that the subjective experience of "long COVID"

40 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-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

67   to provide a comprehensive picture of cognitive performance[16–20]. For example, in one study,

68   28% of recovered COVID-19 patients scored below the established cut off of 26 (for dementia)

69   on the MoCA, compared to only 17% of controls, although median MoCA scores in the patients

70   were not statistically different from those of the controls[20]. Other studies have suggested a

71   specific domain of cognitive impairment; however, this has varied across studies from primary

72   deficits in attention[21] to visuospatial deficits[20]. Most studies report multidomain cognitive

73   impairments, although there appears to be a high degree of disagreement about which domains

74   are most affected[1,16–19,22–25].

75   Second, how does the emergence of cognitive deficits following COVID-19 infection relate to

76   the severity of the primary infection? Several preliminary studies have suggested that, in patients

77   who required hospitalised treatment, cognitive deficits following COVID-19 infection are

78   dependent on the level of medical assistance received[1,22] and the degree of inflammation[21] with

79   severe infections being associated with significant cognitive deficits[17,18,23] although cognitive

80   impairments have also been reported in asymptomatic patients[16], and one small study reported no

81   correlation with hospitalization and cognitive impairments[24]. Given current knowledge about

82   long-lasting cognitive deficits from post ICU syndrome, we might expect a worse cognitive

83   outcome with more severe COVID-19 illness[7–9]. Alternatively, perhaps the longstanding and

84   untreated hypoxia reported in asymptomatic COVID-19 patients[26,27] may lead to long lasting

85   cognitive decline, as has been shown to be the case in other conditions that cause longstanding

86   hypoxia[28,29].

87   Third, how does the pattern of cognitive deficits observed following COVID-19 infection relate

88   to aspects of mental health such as anxiety, depression and fatigue that may be a consequence of

89   the disease process itself, or a more general effect of living during the time of a global

90   pandemic? Research conducted prior to the worldwide spread of COVID-19 clearly established

91   that associations exist between impaired cognitive function and both anxiety disorders[30], and

92   depression[31], although the relationship between fatigue and specific cognitive deficits seems

93   rather less clear[32,33]. Several recent studies have reported an increased risk of psychiatric

94   disturbance in patients recovering from COVID-19[20,34–36], although others have reported no

95   association between cognitive outcomes and psychiatric symptoms[25], including anxiety[17,24]

96   depression[17,24] and fatigue[24].

97   To fully address these questions, large numbers of patients need to be examined in order to

98   mitigate the effects of infection severity, stage of recovery and concomitant mental health issues.

99   To date, most studies have focused on single-case reports, or relatively small (< 25) cohorts[17–

100   19,23,24,37], confounding these issues. With many countries in virtual lockdown, opportunities for

101   face-to-face testing are limited, resulting in the widespread use of telephone screening and/or

102   self-reported cognitive status, which have obvious limitations[23,24,37].

103   In this study, we report data from a cohort of 485 patients who self-reported having had

104   confirmed positive COVID-19 test, who were assessed using a comprehensive and widely

105   validated battery of cognitive tests, measuring aspects of memory, attention, problem-solving

106   and reasoning. Every patient also completed an extensive questionnaire to fully document their

107   COVID-19 experience, infection severity, extent of recovery, health status (physical and

108   emotional health, including functioning, pain, energy and fatigue; SF-36[38]), and mental health

109   status, assessed using standard measures of anxiety (GAD2[39]) and depression (PHQ2[40]). While

110   this cohort will be followed longitudinally for the next 12 months to investigate the trajectory of

111   cognitive sequelae following COVID-19 infection, here we report the results of our initial

112   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.

(Tables 1 & 2)

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 (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. < 0.005; 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)

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

159   Strong correlations were observed between health-related questionnaire variables from the

160   COVID+ group (Figures 1B, S2). Bartlett's test of sphericity ($\chi^2_{(45)} = 2199$, $p < 0.001$) and a

161   Kaiser-Meyer-Olkin value of 0.88 confirmed that the multivariate data were factorable. A

162   subsequent factor analysis revealed a two-factor structure underlying these data (i.e., two factors

163   had eigenvalues greater than 1.0), which we interpreted as broadly representing overall physical

164   health including COVID severity (henceforth referred to as F1; Figure 1B, inner ring), and

165   mental health & wellness (henceforth referred to as F2; Figure 1B, outer ring). Illness severity

166   (WHO_COVID_severity) correlated most strongly (and negatively) with the SF-36 measures of

167   physical functioning, physical-role limitations, energy & fatigue, and pain scales, and the two

168   subjective measures of cognition (Figures 1B, S2). The approximate elapsed time since infection

169   demonstrated negligible correlations with all measures (Figures 1B, S2). Descriptive statistics of

170   each heath variable, along with their loadings on F1 and F2, can be found in Table S2.

171   (Figure 1)

172   The two health factors (F1 and F2) were dissociable with respect to their relationships with

173   demographic variables (Figure 2). Linear regression models (Table S4) showed that the overall

174   physical health factor (F1) was negatively correlated with age ($t_{(480)} = -3.17$, $p_{adj} < 0.05$, $f^2 = 0.021$,

175     $BF_{10} = 6.86$) with an average decline of approximately 0.1 SDs per decade, whereas mental

176   health & wellness (F2) increased with age ($t_{(480)} = 2.84$, $p_{adj} < 0.05$, $f^2 = 0.017$, $BF_{10} = 2.60$) by

177   0.1 SDs per decade. Completion of post-secondary education was also associated with

178   significantly better (F2) mental health ($t_{(480)} = 3.27$, $p_{adj} < 0.05$, $d = 0.38$, $BF_{10} = 9.53$) but not

179   (F1) physical health, and males reported better (F1) physical health ($t_{(480)} = 5.91$, $p_{adj} < 0.001$, $d =$

180   0.56, $BF_{10} > 1000$) yet there was no difference between males and females in terms of (F2)

181   mental health & wellness. The fact that these measures were clearly dissociable in terms of the

182   demographic variables that they correlated with suggests that they represent two distinct and

183   separable, though not mutually exclusive, effects of COVID-19 infection.

184

185   Delineating the relationships between health factors and cognitive domains

186   (Figure 3)

187   Figure 3 describes cognitive performance of COVID+ participants relative to controls (Y=0) as a

188   function of overall physical health (F1; Figure 3A) and mental health & wellness (F2; Figure

189   3B); to simplify this visualization and reduce the number of comparisons, participants were

190   grouped into tercile bins for each health factor (i.e., percentiles that each contained 1/3rd of the

191   sample – corresponding to below average, average, and above average). Figure 3A shows that

192   COVID+ participants who had better than average physical health (white bars) performed

193   similarly to controls in all cognitive domains. In contrast, those participants with worse than

194   average physical health (darkest bars) exhibited significant impairments relative to controls

195   (Table S5) on the four cognitive scores already identified as being impaired in the COVID+

196   cohort compared relative to controls: reasoning, verbal, processing speed, and overall

197   performance. A similar pattern was not apparent when data were re-grouped by mental health &

198   wellness scores (Figure 3B).

199   Next, we constructed linear regression models to predict each composite cognitive score from the

200   two health factors and used Bayesian model comparison to quantify the unique contribution of

201   each factor in predicting cognitive performance. The physical factor exhibited strong and

202   statistically reliable linear associations with three cognitive scores – verbal, processing speed,

203   and overall performance (F1; all adjusted ps < 0.05; Table 4) – when controlling for F2. BFs

204   suggested positive to strong evidence in favour of these relationships (BF_{10} of 9.33, 21.60, 8.97

205   for verbal, processing speed, and overall performance; Table 4). The directions of these

206   coefficients in Table 4 revealed positive relationships; that is, better physical health was

207   associated with better verbal and overall performance and faster processing speed, consistent

208   with the results depicted in Figure 3. In contrast, mental health & wellness (F2) did not exhibit a

209   linear relationship with any measure of cognitive performance after accounting for physical

210   health (all adjusted ps = 1.0 and BF_{10}s < 1; Table 4).

211   (Table 4)

212   Figure 4 summarizes the COVID+ vs. control group comparisons and tests of health-factor

213   regression parameters – across all five cognitive domains. A supplementary analysis that

214   included socio-demographic covariates (despite these effects already having been removed)

215   yielded the same pattern of results (Table S6), suggesting that the observed relationships between

216   physical health (F1) and cognitive scores were not driven by residual effects of these factors.

217   (Figure 4)

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

219   We next examined whether the impairments observed in the COVID+ cohort were driven by the

220   more severe cases of COVID-19 that required hospitalisation. Comparisons of hospitalised and

221   non-hospitalised participants revealed significant differences in terms of F1 ($t_{(89.79)}$ = -3.89, p_{adj} <

222   0.001, d = 0.49, BF_{10} = 170.87) with hospitalised cases reporting worse overall physical health

223   than non-hospitalised cases (Figure 5A) – an unsurprising finding given that hospitalisation was

224   one of the criteria for the COVID severity score, which loaded on F1. However, these two

225   groups did not significantly differ in terms of their mental health (F2) or cognitive performance

226   (Figure 5B, Table S7). Despite the non-significant group differences in cognition at a corrected

227   level, it is worth noting that the hospitalised group trended towards having worse performance on

228   the scores that were significantly impaired in the non-hospitalised group; that is, the estimated

229   effect sizes were suggestive of larger impairments in the hospitalised group, as is visible in

230   Figure 5B.

231   Direct comparisons of each of these COVID+ subgroups against the controls showed that both

232   had significant cognitive impairments in some domains (Figure 5B). Specifically, the non-

233   hospitalised group were significantly impaired in the reasoning and verbal domains, and in terms

234   of speed of processing and overall performance (Figure 5B, Table S8). Meanwhile, the

235   hospitalised group only had significant impairments in the reasoning domain and in processing

236   speed (Figure 5B, Table S8). Although the verbal and overall performance scores for this group

237   did not differ significantly from the control sample at a corrected level, Bayesian statistics

238   suggested weak evidence (verbal $BF_{10} = 2.88$, overall $BF_{10} = 1.58$) in support of impairments on

239   these measures; a plausible explanation for the statistically weak differences between groups is

240   the small sample size of hospitalised patients (N=67). In contrast, the STM domain scores for

241   both groups were not significantly different from controls, and BFs instead supported the null

242   hypothesis (i.e., $BF_{10}s < 1.0$) that there was no difference between the control sample and these

243   two groups in this domain (Table S9).

244   Given that the hospitalised group reported significantly worse overall physical health and had

245   somewhat poorer cognitive performance than the non-hospitalised group, we included this

246   variable in our regression analyses to see if it explained away or reduced the observed

247   relationship(s) between physical health (F1) and cognitive performance. The pattern of results

248   (Figure 6, Table S9) remained consistent with Figure 3: we observed significant and positive

249   relationships between physical health (F1) and verbal domain performance, speed of processing,

250   and overall cognitive performance (all p-values < 0.05, corrected for 15 comparisons). Again, the

251   Bayesian statistics provided positive evidence ($BF_{10}s > 3.0$) for these relationships, showing that

252   physical health predicted cognitive performance even when accounting for mental health

253   measures and hospitalisation.

254   Relationships between other variables and cognitive performance

255   A final set of exploratory analyses were used to examine whether any of the demographic

256   variables (age, sex, post-secondary education, and SES) were related to cognitive performance.

257   Given that the cognitive scores were already corrected for demographic factors using parameters

258   estimated from the control sample data, a significant effect of one of these variables would

259   suggest that its effect differed between the control and COVID+ groups (i.e., a group by

260   demographic-variable interaction). However, we found no correlations between any of these

261   variables and cognitive scores (Figure S4A), and $BF_{01}s$ suggested positive to strong evidence

262   (Figure S4B, Table S10) in support of the null (H_0) hypotheses. This suggests that: 1) using the

263   control dataset to estimate and remove the effects of these potential confounders from cognitive

264   scores was successful, and 2) the effects of these variables did not differ between the control and

265   COVID+ datasets. Simply, the cognitive impairments associated with COVID-19 infection did

266   not differ between females and males or vary with age.

267

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,

291 while no associations were found between these measures and the mental health & wellness

292 factor.

293 Given the global nature of the COVID-19 pandemic and the fact that it has disproportionately

294 (but not exclusively) affected the elderly and those from low educational and SES backgrounds,

295 it is of interest to explore how these factors interact with the physical and mental health

296 outcomes that we have identified. In our primary analyses, age, sex, post-secondary education,

297 and SES were accounted for by adjusting cognitive scores for the known effects of these

298 variables (estimated from a large control sample), yet even when these factors were included as

299 covariates in a supplementary analysis the same pattern of results was observed, confirming that

300 the observed relationships between physical health and cognitive scores were not driven by a

301 residual effect of any these factors. Furthermore, the lack of any correlations between these

302 socio-demographic variables and corrected cognitive scores (Figure S4) suggests that this

303 relationship is a core characteristic of COVID-19 infection, rather than a secondary effect related

304 to the demographic profile of those who have been most commonly infected.

305 It is important to understand that we are not describing two types of *people* in the post COVID-

306 19 infection population, but two distinct factors that contribute to and characterise the post

307 COVID-19 syndrome. Indeed, the fact that these measures were clearly dissociable in terms of

308 the demographic variables that they correlated with, suggests that they represent two distinct and

309 separable, though not mutually exclusive, effects of COVID-19 infection. For example, our

310 linear regression models (Table S4) showed that physical health was negatively correlated with

311 age (with an average decline of approximately 0.1 SDs per decade), whereas mental health &

312 wellness increased with age (by 0.1 SDs for every 10 years). While it is perhaps to be expected

313 that older COVID-19 survivors would be most affected in terms of their physical and cognitive

314 outcomes (given the greater likelihood of co-morbidities in that group), the fact that it is the

315 young that have been most severely affected in terms of their mental health and well-being is

316 surprising. Completion of post-secondary education was also associated with significantly better

317 mental health, but not physical health outcomes, and males reported better physical health, yet

318 there was no difference between males and females in terms of mental health & wellness. Again,

319 the differing patterns of correlations between socio-demographic variables and the physical and

320 mental health factors further confirm the existence of two distinct outcomes of COVID-19

321 infection that are dissociable in multiple ways.

322 The fact that measures of mental health such as anxiety and depression were not associated with

323 cognitive outcomes in the context of the COVID-19 pandemic is surprising, as numerous studies

324 have shown an association between anxiety, depression and cognition in the pre-pandemic era.

325 For example, one study of 4582 participants[30] showed that generalized anxiety is associated with

326 memory and verbal fluency deficits, particularly in young adults. Similarly, a systematic review

327 and meta-analysis by Semkovska et al.[31] confirmed that deficits in selective attention, working

328 memory and long-term memory persist in major depression and worsen with repeated episodes.

329 However, it is important to clarify that these, and most other studies that have examined the

330 relationship between mental health and cognition, have focussed on *clinical* populations; that is,

331 patients who have been diagnosed with a major mental health condition, such as depression or

332 anxiety. In our study, the fact that no association was observed between measures of mental

333 health and cognition may be due to a predominance of detectible, yet sub-clinical, mental health

334 issues among the COVID-19 survivors. For instance, we found that only about one third of our

335 participants had probable anxiety or depression, which is consistent with estimates of the

336 prevalence of these disorders in the general population during the COVID-19 pandemic[43].

337 Regardless, our study highlights the importance of carefully examining the relationship between

338 physical wellness, mental health and cognition in other patient populations, to determine what is

339 driving any observed cognitive impairments.

340 Based on our data it is not possible to disentangle the effects on mental health of COVID-19

341 infection and the pandemic more generally. Factors such as job security, financial instability,

342 home-schooling, social isolation and an elevated sense of community fear have undoubtedly

343 affected the mental well-being of people throughout the world, irrespective of whether they have

344 received a positive COVID-19 diagnosis. Theoretically, the same argument could be made to

345 explain some of our physical and cognitive outcome measures; increased fatigue, poorer

346 subjective memory, and even impaired reasoning and processing speed might occur, to some

347 extent, even in the general non-COVID +ve population during the pandemic. However, two

348 observations suggest otherwise: first, the fact that the severity of these deficits was tightly

349 coupled to the severity of COVID-19 symptoms, whereas no such relationship existed between

350 WHO severity ratings and mental-health scores, and second, participants who had better than

351 average physical health scores (i.e., were relatively unaffected by the infection in physical terms)

352 performed similarly to pre-pandemic controls in all cognitive domains, whereas cognitive

353 impairments were only seen in those participants who reported poor physical health and more

354 severe illness. Taken together, these results suggest that the physical/cognitive profile identified

355 here is one that is specifically related to COVID-19 infection itself.

356 We further explored whether the observed pattern of cognitive deficits was explained by the

357 more severe cases of illness that required hospitalisation. Several preliminary studies have

358 suggested that cognitive impairments following COVID-19 infection are dependent on the level

359 of medical assistance received[1,22] although at least one study has reported no correlation between

360   hospitalisation and cognitive impairments[24]. This is an important issue because long-lasting

361   cognitive deficits have been reported in non-COVID-19 patients following treatment in the ICU,

362   suggesting that factors such as mechanical ventilation, sedation, drug therapy and disturbed sleep

363   may all contribute to the emergent cognitive profile, independent of infection[7] In the current

364   study, direct comparisons of the hospitalised and non-hospitalised post COVID-19 subgroups

365   against the controls showed that both groups had significant cognitive impairments. Moreover,

366   the groups did not differ significantly on any measure of cognitive outcome, although

367   numerically the hospitalised group performed worse than the non-hospitalised group in terms of

368   reasoning, verbal ability, processing speed and overall cognitive performance (Figure 5b). Given

369   this trend, we included hospitalisation in our regression analyses to see if it explained away or

370   reduced the observed relationship(s) between physical health and cognitive performance. The

371   results showed that physical health predicted cognitive performance even when mental health

372   measures and hospitalisation were accounted for, highlighting that the effects of COVID-19 on

373   cognition are not entirely driven by hospitalisation. This is an important observation, given that

374   most studies of the prolonged effects of COVID-19 have focused on hospitalised cohorts.

375   Although the current study provides clear evidence for a broad pattern of cognitive impairment

376   following COVID-19 infection, the effect was, at least to some extent, domain specific. That is

377   to say, notable impairments were found relative to controls in speed of processing and in the

378   reasoning and verbal domains, but not in STM performance. It is important to point out that this

379   relationship is not absolute, due to the nature of the three main factors that were extracted from

380   performance across a diverse range of 12 cognitive tests. Specifically, we use the term STM

381   descriptively to refer to a single factor derived from performance across the entire battery of

382   tests, and this will include some contributions from tests that do not ostensibly measure aspects

383   of STM. Nevertheless, as we have shown previously[42], and convincingly replicate here (Figure

384   1A, Table S3), this factor is driven primarily by tests such as 'spatial span', 'monkey ladder',

385   'token search' and 'paired associates', all of which are derived from standard measures of STM

386   (for details, including references for the original forms of the tasks on which the computerized

387   versions are based, see Hampshire et al.[42] or Wild et al.[44]). This finding sheds some light on the

388   nature and extent of the subjective experience of COVID-19 survivors, often called 'long

389   COVID' or 'brain fog' - the expression now used widely to describe the subjective sense of

390   cognitive impairment following COVID-19 infection. Specifically, that 'brain fog' in this

391   context includes processing (or 'thinking') speed, reasoning and verbal abilities, but leaves short

392   term memory relatively spared.

393   We are hesitant to draw conclusions about the underlying neural systems responsible for this

394   pattern of impairments post COVID-19 infection, but an fMRI-based brain parcellation based on

395   the same 12 tests used in this study may shed some preliminary light on this question. Hampshire

396   et al. (2012) found that the STM factor, which was resilient to the effects of COVID-19 infection

397   in the current study, had a brain network analogue that included the insula/frontal operculum, the

398   superior frontal sulcus, and the ventral portion of the anterior cingulate cortex/ presupplementary

399   motor area. The reasoning and verbal factors – which, in contrast, *did* show impaired

400   performance in the COVID+ sample – were associated with two non-overlapping networks,

401   composed of: (reasoning) the inferior frontal sulcus, the inferior parietal cortex, and the dorsal

402   portion of the anterior cingulate cortex/ presupplementary motor area, and (verbal) the left

403   inferior frontal gyrus and bilateral superior temporal regions. Although there is no obvious

404   explanation for why these two particular networks might be affected by COVID-19 infection

405   while others are spared, future work could use neuroimaging to investigate the hypothesis that

406 some brain regions or networks, and the cognitive systems they support, are more susceptible to

407 damage from COVID-19 infection.

408 Regardless of the underlying neuropathological substrates, the functional dissociation observed

409 in this study is important for understanding how COVID-19 related 'brain fog' differs from other

410 conditions and circumstances that have been described using similar terms, such as post-

411 chemotherapy cognitive dysfunction ('chemo brain'), cognitive impairment following heart

412 bypass surgery ('pump head') and disturbed cognition after sleep deprivation. Regarding the

413 latter, in a recent study of more than 10,000 participants assessed using the same battery of 12

414 tests used in the current study (and from which the current control sample was drawn) we

415 showed that typical sleep duration also had no bearing on short-term memory performance,

416 unlike reasoning and verbal skills, which were impaired by both too little, or too much, sleep on

417 a regular basis[45].

418 A key unanswered question remains the longitudinal nature of these problems. In those patients

419 who are most affected, are these cognitive disturbances temporary, permanent, or do they signal

420 the onset of a neurodegenerative cascade that results in a deteriorating pattern of impairment

421 over time? While it is too early to answer this question in full, some preliminary clues can be

422 gleaned from our data analysis. For example, the approximate time since infection demonstrated

423 negligible correlations with all measures (Figures 1B, S2), suggesting that cognitive impairments

424 do not get better or worse over the short term. The current cohort will be followed and retested

425 regularly for at least a year, and possibly longer, and until that process is complete the

426 longitudinal trajectory of post COVID-19 cognitive impairment will remain unclear.

427 Finally, this study illustrates that is possible to acquire comprehensive, high quality cognitive

428 assessments remotely without any inter-personal contact, which is essential in a pandemic

429   situation involving a highly contagious virus. Online data collection also allowed us to reach a

430   broader population than would have been possible by approaching patients from associated

431   health networks and will afford us the opportunity to easily follow our cohort longitudinally.

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

433   These are likely not the result of a "global" impact on cognitive processing, as STM performance

434   was relatively preserved. Crucially, in the domains that were affected, cognitive performance

435   was related to measures of physical health, including COVID severity, but not mental health.

436   This has implications from a clinical viewpoint, as survivors who exhibit increased anxiety or

437   depression may or may not have cognitive deficits, whereas these are much more likely in

438   patients who experience a greater physical toll from the illness. Our findings underscore the fact

439   that the physical, emotional, mental, and cognitive sequelae of COVID-19 are not bound together

440   as a single neurocognitive syndrome.

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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

468   score outliers were filtered in two iterative passes. First, extreme outliers more than 6 *SDs* from

469   the mean (e.g., technical/database errors) were removed to obtain reasonable estimates of the test

470   means and *SDs*; three participants had at least one score greater than this threshold. Then, outlier

471   scores were identified as being more than 4 *SD*s from the re-calculated mean, and 20 participants

472   were excluded for having at least one outlier. 211 cases were excluded because of missing test

473   scores or incomplete (i.e., optionally omitted) questionnaire responses. Finally, only participants

474   who indicated having a confirmed positive test for COVID-19 were retained for analysis,

475   resulting in a final dataset of 485 COVID-positive cases (i.e., the COVID+ group). The control

476   data were preprocessed in a similar way. From 26,256 datasets, 7,832 were removed for using a

477   mobile device, 1,831 indicated an age less than 18 or greater than 100 years, and 6,437 had

478   missing test scores or questionnaire items. Cases with outliers were removed (N=331 with a

479   score > 6 *SDs*, followed by N=1,010 with a score > 4 *SDs* from the mean), yielding a final

480   control sample 8,815 participants.

481   Health Measures

482   Participants were asked about their COVID-19 history (Table 1), including: presentation of

483   symptoms (according to common screening tools used at that time), the month and year of their

484   most recent positive COVID-19 test, and whether they required hospitalisation. If they did not

485   require treatment in the hospital, they indicated whether they could go about their daily routine

486   as usual. In cases where hospitalisation was required, participants were also asked if: they were

487   on supplemental oxygen therapy, in the intensive care unit (ICU), and (if in the ICU) on a

488   ventilator. Measures of physical and mental health were captured using the RAND Short-Form

489   Health Survey (SF-36) – specifically, the physical functioning, role functioning (physical), role

490   functioning (emotional), energy & fatigue, and pain scales – and the GAD-2 & PHQ-2 anxiety

491   and depression screeners [39,40]. The GAD-2 and PHQ-2 scales were reversed during analysis to

492   make them consistent with the other scales where higher scores were representative of "better"

493   health. Finally, two questions were included for subjective evaluations of cognitive functioning:

494   1) *"Do you feel that you are back to your baseline level of cognitive functioning?"*

495   (subj_baseline) and 2) *"How would you rate your memory?"* on a 5-point scale from "miserable"

496   to "excellent" (subj_memory).

497   Cognitive Test Battery

498   Detailed descriptions of the 12 CBS tasks can be found in the supplementary materials of some

499   of our previous studies [42,45], but briefly they are: 1) Spatial Span (SS; short-term memory); 2)

500   Monkey Ladder (ML; visuospatial working memory), 3) Paired Associates (PA; episodic

501   memory), 4) Token Search (TS; working memory and strategy), 5) Digit Span (DS; verbal

502   working memory), 6) Odd One Out (OOO; deductive reasoning), 7) Rotations (RT; mental

503   rotation), 8) Feature Match (FM; feature-based attention and concentration), 9) Spatial Planning

504   (SP; planning and executive function), 10) Interlocking Polygons (PO, visuospatial processing),

505   11) Grammatical Reasoning (GR, verbal reasoning), and 12) Double Trouble (DT; a modified

506   Stroop task). For tasks 1-5, the primary outcome measure was the number of items in the hardest

507   problem correctly solved, whereas scores for tasks 6-12 were variations of the sum of correct,

508   minus incorrect, answers within the given time window. Each task, except for SP, also provided

509   an aggregate measure of reaction time which was the average duration of correctly answered

510   trials; for tasks 1-5, the individual trial durations were first normalized by the number of items in

511   the problem.

512 ## Data Analysis

513 All data preprocessing and analysis was done in Python (v3.7.7, https://www.python.org/).

514 Specific packages included: pandas (v1.1.0) for data preprocessing and manipulation, scikit-learn

515 (v0.22.2) for estimating and applying data transformations, statsmodels (v0.11.0) for building

516 and fitting general linear models and calculating related statistics, pingouin (v.0.3.9) for

517 performing Bayesian t-tests, factor analyzer (v0.3.2) for performing principal component and

518 factor analyses, numpy (v1.18.2) for all mathematical operations, and plotly (v4.5.2) and

519 matplotlib (v.3.2.1) to support figure creation. A viewable notebook detailing the entire analysis,

520 including all custom code, can be viewed at (https://github.com/TheOwenLab/2021-Wild-et-al-

521 COVID-Cognition).

522 ## Health Factor and Compositive Cognitive Scores

523 Rather than examine every pairwise relationship between individual heath variables and all 12

524 cognitive test scores, we reduced the number of measures (of both independent and dependent

525 variables) using factor analyses. Each multivariate dataset (health measures and cognitive tests)

526 was decomposed into a smaller number of statistically independent underlying, or "latent",

527 factors that summarized the major modes of covariation amongst the variables. This approach

528 allowed us to simplify interpretations, reduce the total number of model parameters, and avoid

529 multicollinearity between predictors.

530 The set of health-related measures (i.e., SF-36 scales, GAD2, PHQ2, WHO COVID severity, and

531 subjective measures of cognition) from the COVID+ group was summarized using factor

532 analysis with a Varimax rotation. Factors with eigenvalues greater than 1.0 were retained for

533 further analysis, and their scores were calculated for each participant by transforming

534   questionnaire responses using the factor loadings matrix. The resulting factor scores were mean

535   centred (M=0.0) and had $SD = 1.0$.

536   A similar process was applied to the 12 cognitive tests scores. First, we performed a PCA

537   analysis on the 12 primary CBS scores in the control group, specifying three components and a

538   Varimax rotation; the solution was consistent with our previous findings[42], and these components

539   were interpreted as broadly representing short-term memory (STM), reasoning, and verbal ability

540   (Figure 1b, Table S4). Composite scores representing performance in these three domains were

541   calculated by transforming participants' 12 test scores using the PCA loadings[42,45]. We also

542   calculated an "overall" score of cognitive performance (the mean of the 12 z-scored primary

543   outcomes) and a measure of "processing speed" (the 1st principal component of the 11 reaction-

544   time based features). Inspection of composite score loadings confirmed that higher test scores

545   were indicative of better performance; that is, composite scores were positively correlated with

546   higher individual test scores and faster responses.

547   Prior to the PCA analysis and score calculations, cognitive test data for both groups were

548   standardized ($M = 0.0$, $SD = 1.0$) using the means and standard deviations from the control

549   group. A power transformation[46] was applied (again, using parameters estimated from the control

550   group) to reduce skewness and improve normality of the test score features. The models,

551   parameters, and transformations for these composite score calculations were derived using only

552   the control group data, and therefore: 1) had $M = 0.0$ and $SD = 1.0$ in the control group, and 2)

553   for COVID+ participants represented performance relative to the controls in units of standard

554   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*.

578   We also performed Bayesian analyses to better characterize every statistical relationship. Given

579   our reasonably large sample size, practically small effects might still be considered statistically

580   significant using frequentist methods, whereas Bayesian methods guard against overfitting and a

581   tiny effect size is less likely to result in a rejection of the null hypothesis[49]. Therefore, we also

582   report for every statistical test a Bayes Factor (BF) that quantifies the evidence in favour of the

583   alternative hypothesis (BF_{10}). To obtain the BF_{10} for two-sample *t*-tests (e.g., group comparisons)

584   we employed the JZS Bayes factor[50], whereas we estimated the BF_{10} for parameters of regression

585   models using the Bayesian Information Criterion approximation (Wagenmaker, 2007); that is, by

586   comparing a "full" model that included the regressor of interest to a "restricted" model (i.e., a

587   regression model *without* the predictor of interest, but that included other variables) or a "null"

588   model (i.e., an intercept-only model). We interpreted BF magnitude using Wagenmakers'

589   heuristic, where BFs 1-3, 3-20, 20-150, and > 150 indicate weak, positive, strong, and very

590   strong evidence, respectively, for the given hypothesis. The parametric statistics used in this

591   study (both frequentist and Bayesian) assume the data or model residuals are normally

592   distributed. Where appropriate, we used quantile-quantile plots (i.e., *"qq"* plots) to validate this
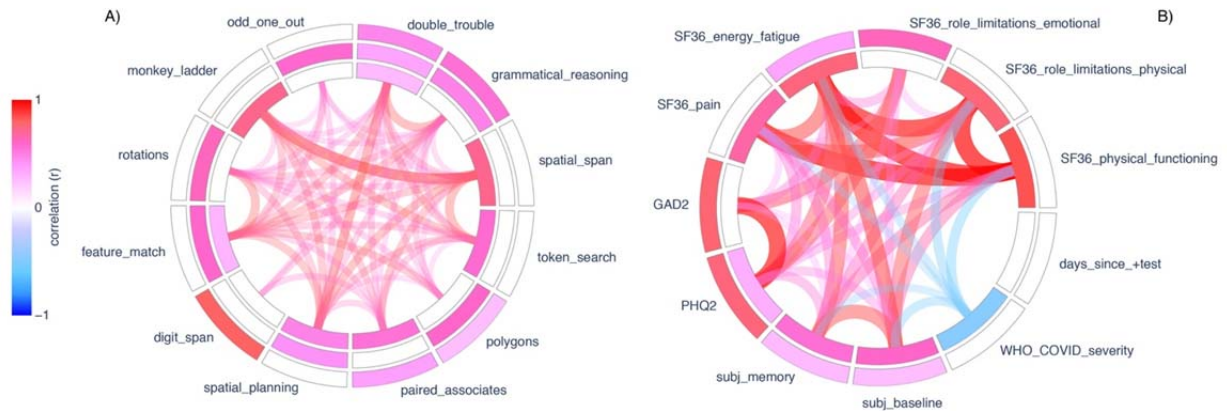
593   assumption (e.g., see Figure S3).

594

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).

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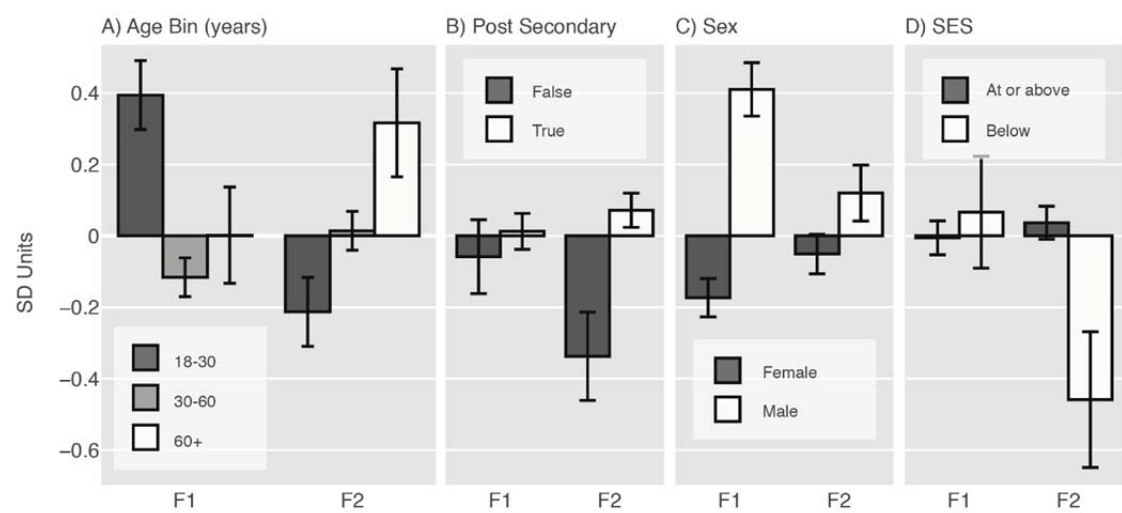
610 **Figure 2:** Average health factor scores — F1 (overall physical health, including COVID severity) and F2 (mental
611 health & wellness) – as a function of: **A)** age (in three arbitrary bins), **B)** completion of post-secondary education, **C)**
612 sex as assigned at birth, and **D)** Socio-economic status (relative poverty level) while growing up. Bar height is the
613 average factor score for each subgroup (in units of standard deviations) and error bars depict the standard error the
614 mean.
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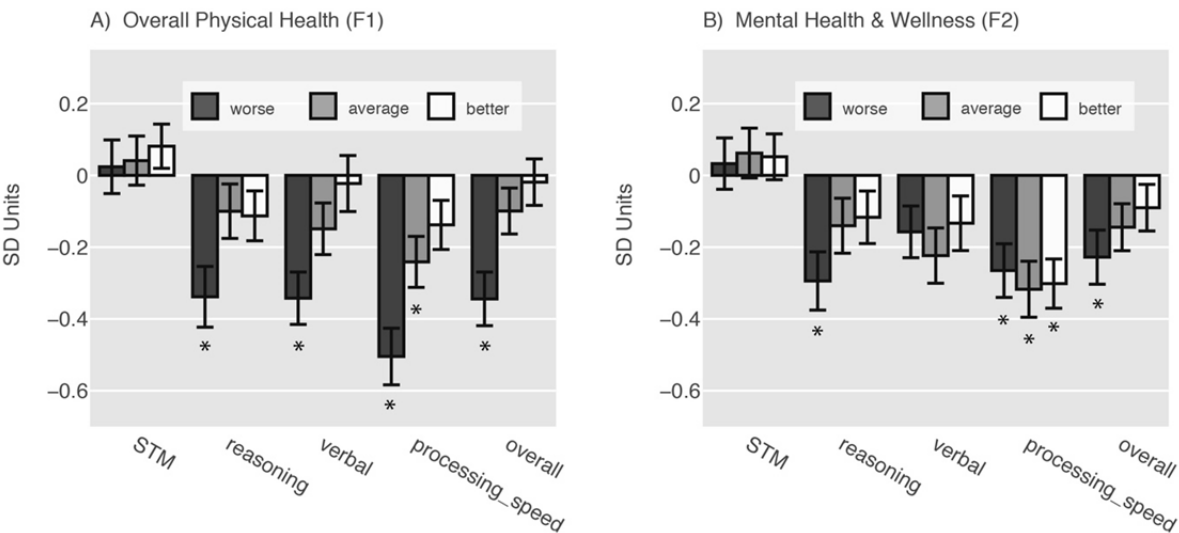
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618 **Figure 3:** Average cognitive scores for COVID+ participants grouped into tercile bins – below average ("worse)",
619 "average", and above average ("better") based on **A)** overall physical health (F1) *or* **B)** mental health & wellness
620 (F2) factor scores. Bar height is the average cognitive score (corrected for nuisance variables) relative to the control
621 sample mean (Y=0.0), error bars show SEM, and asterisks indicate a significant two-sample t-test vs the control
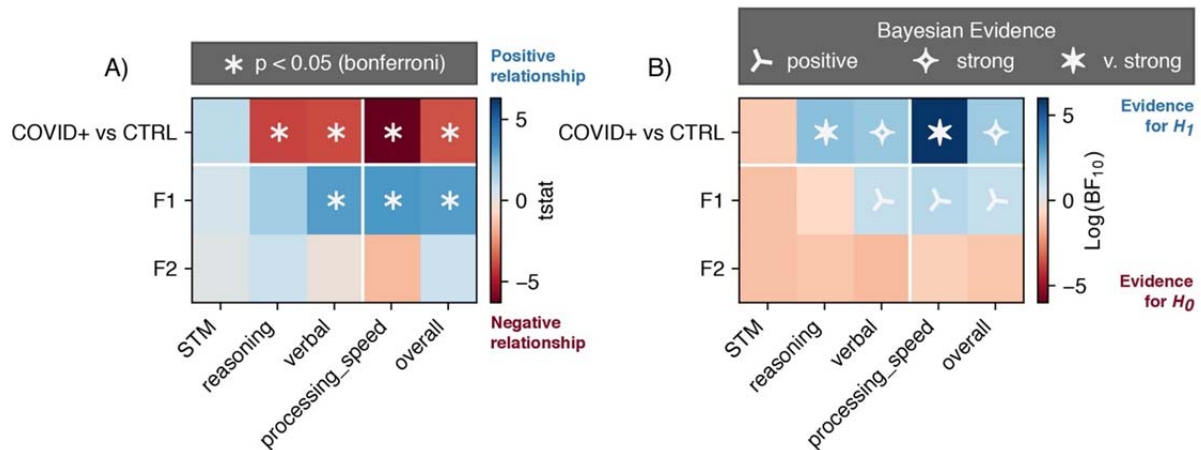622 group ($p < 0.05$ corrected for 15 comparisons).
623

624
625 **Figure 4:** A visual summary of 15 tests across 5 cognitive scores, using **A)** frequentist and **B)** Bayesian statistics. In
626 both panels the top row represents the two-sample *t*-test comparing COVID+ and control (CTRL) groups on each
627 cognitive score. The 2nd and 3rd rows are tests of the regression parameters that predict cognitive scores from F1
628 (physical health), and F2 (mental health & wellness), while controlling for the other factor.
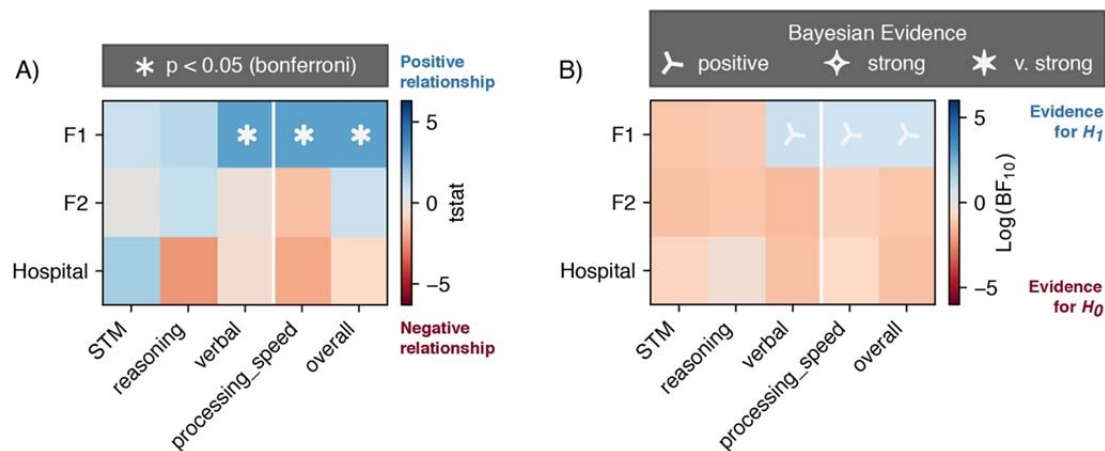
629
630 **A)** *T*-statistics for each parameter estimate. Blue indicates a positive *t*-statistic (and a parameter > 0) whereas red
631 indicates the converse. Stars indicate significant effects, $p < 0.05$ Bonferroni-corrected across all 15 comparisons.

632
633 **B)** Bayes Factors for the same statistical tests. Blue indicates support for H_1 and red indicates support for H_0.
634 Symbols provide a heuristic interpretation for the given BF: positive (BF_{10} 3-20), strong, (BF_{10} 20-150), or very
635 strong ($BF_{10} > 150$) evidence for H_0 (labels not shown for interpretation of BF_{01}s).

636

637
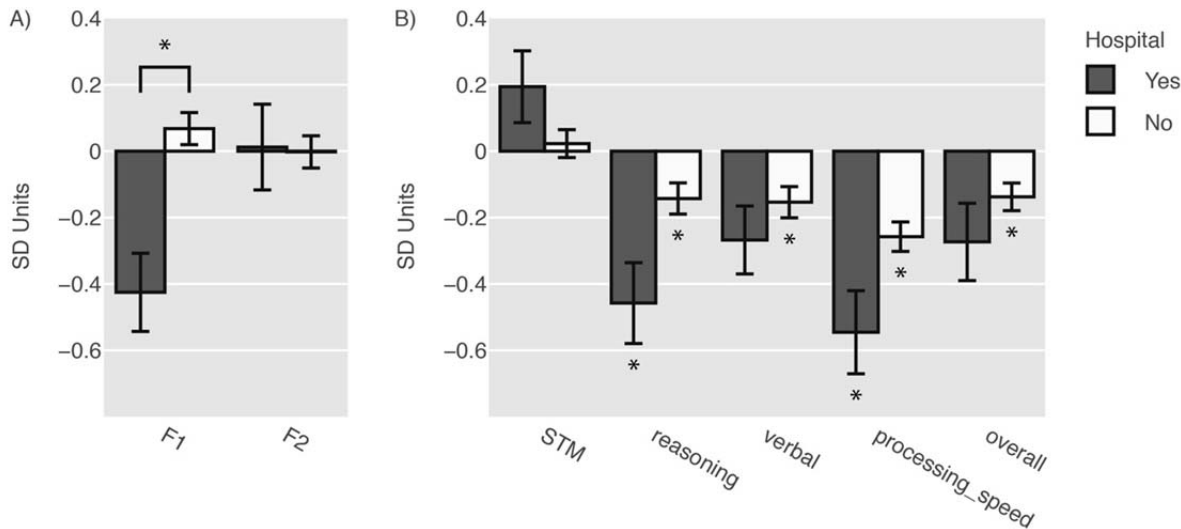
638
639 **Figure 5:** Average scores for hospitalised (N=67) and non-hospitalised (N=418) COVID+ subgroups. **A)** Health
640 factor scores: physical (F1) and mental (F2) health, where $Y=0$ corresponds to the COVID+ sample mean. The brace
641 and asterisk indicate a significant group difference ($p < 0.001$). **B)** Average (corrected) cognitive scores, where $Y=0$
642 indicates the control sample mean. Asterisks indicate bars that are significantly different than the control sample (p
643 < 0.05 corrected for 10 comparisons). No cognitive differences between hospitalised and non-hospitalised groups
644 were significant at a corrected level.

645

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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 ($BF_{10} > 1$), 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=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%)
"Did you have to stay in the hospital for COVID-19 symptoms?"				
Daily Routine	131 (27.0%)	287 (59.2%)	.	418 (86.2%)
"Were you mostly able to go about your daily routine (e.g., mostly normal sleep, work, activity, etc.)?"				
Supplemental O$_2$	35 (7.2%)	31 (6.4%)	1 (0.3%)	67 (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 (3.5%)	50 (10.3%)	.	67 (13.8%)
"Were you in the ICU (Intensive Care Unit)?"				
Ventilator	11 (2.3%)	6 (1.2%)	.	17 (3.5%)
"Were you on a ventilator (breathing machine)?"				

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 (*SD* = 13.17)		*M* = 42.76 (*SD* = 14.44)	

681 **Table 3:** Results of comparisons between COVID+ and control groups on 5 composite cognitive scores. The
682 cognitive measures were adjusted for nuisance covariates. The mean difference is between groups, COVID+ vs.
683 controls, and measured in units of standard deviations (*i.e.,* analogous to Cohen's *d*). *P*-values and confidence
684 intervals are Bonferroni-corrected for 15 comparisons. Bold entries indicate significant effects ($p_{adj} < 0.05$).
685

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

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691 **Table 4:** Linear regression results from models that included both overall physical health (F1) and mental health &
692 wellness (F2) factor scores as simultaneous predictors of cognitive scores. *P*-values and confidence intervals are
693 Bonferroni-corrected for 15 comparisons. Intercept-related statistics are not included because the mean differences
694 from zero are better described using two-sample *t*-tests against the control group (Table 3). Bold entries indicate
695 significant effects ($p_{adj} < 0.05$).
696
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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

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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.

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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.