Multivariate profile and acute-phase correlates of cognitive deficits in a COVID-19 hospitalised cohort

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Summary

Background Preliminary evidence has highlighted a possible association between severe COVID-19 and persistent cognitive deficits. Further research is required to confirm this association, determine whether cognitive deficits relate to clinical features from the acute phase or to mental health status at the point of assessment, and quantify rate of recovery.

Methods 46 individuals who received critical care for COVID-19 at Addenbrooke's hospital between 10th March 2020 and 31st July 2020 (16 mechanically ventilated) underwent detailed computerised cognitive assessment alongside scales measuring anxiety, depression and post-traumatic stress disorder under supervised conditions at a mean follow up of 6.0 (± 2.1) months following acute illness. Patient and matched control ($N = 460$) performances were transformed into standard deviation from expected scores, accounting for age and demographic factors using $N = 66,008$ normative datasets. Global accuracy and response time composites were calculated (G_SScore & G_RT). Linear modelling predicted composite score deficits from acute severity, mental-health status at assessment, and time from hospital admission. The pattern of deficits across tasks was qualitatively compared with normal age-related decline, and early-stage dementia.

Findings COVID-19 survivors were less accurate (G_SScore=-0.53SDs) and slower (G_RT=+0.89SDs) in their responses than expected compared to their matched controls. Acute illness, but not chronic mental health, significantly predicted cognitive deviation from expected scores (G_SScore (p=0.0037) and G_RT (p = 0.0366)). The most prominent task associations with COVID-19 were for higher cognition and processing speed, which was qualitatively distinct from the profiles of normal ageing and dementia and similar in magnitude to the effects of ageing between 50 and 70 years of age. A trend towards reduced deficits with time from illness (r~=0.15) did not reach statistical significance.

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Interpretation Cognitive deficits after severe COVID-19 relate most strongly to acute illness severity, persist long into the chronic phase, and recover slowly if at all, with a characteristic profile highlighting higher cognitive functions and processing speed.

Keywords: COVID-19; Cognition; Cognitive assessment; Attention; Memory; Reasoning; Planning

Research in context

Evidence before this study

A PubMed search for articles using the terms 'COVID-19', 'chronic' and 'cognitive impairment' returns 85 results between 2020 and 2022, reflecting growing concern that people may suffer persistent cognitive problems after SARS-CoV-2 infection. However, most of these studies have built on either subjective report of cognitive problems or brief pen-and paper assessment scales that lack sensitivity to mild deficits and precision regarding affected cognitive domains.

Added value of this study

Using precision computerised cognitive assessment tools, we observed that 46 COVID-19 patients matched for age, gender, education and first language, 6−10 months after admission for care at Addenbrookes hospital perform less well than controls in terms of cognition. Critically, the scale of their cognitive deficits correlated with acute illness severity as recorded during the hospital stay, but not fatigue or mental health status at the time of cognitive assessment.

Implications of all the available evidence

These results suggest that the patients who have recovered from severe COVID-19 may need longer term support for cognitive deficits that persist into the chronic phase. More research is required to understand the basis of these deficits. Future work will be focused on mapping these cognitive deficits to underlying neural pathologies and inflammatory biomarkers, and to longitudinally track recovery into the chronic phase.

Introduction

There is growing evidence that COVID-19 can cause lasting cognitive and mental health problems. Recovered patients reporting psychological symptoms including fatigue, cognitive difficulties ("brain fog" and "problems finding the words"), sleep disturbances breathlessness and psychiatric disorders months after infection.[1] In the UK alone, 13.7% of 20,000 individuals reported having symptoms inclusive of cognitive difficulties 12 weeks after a positive COVID-19 test (UK Office for National Statistics, April 2021). Mild cases can report persistent cognitive symptoms; however, prevalence is higher in severe cases,[2] with ∼33−76% of patients suffering cognitive symptoms 3−6 months post hospitalisation.[3,4]

The neurobiological and psychological bases of these deficits remain unclear. Imaging biomarker studies indicate multiple likely candidates. Indeed, drawing parallels with serious acute respiratory syndrome (SARS), middle eastern respiratory syndrome (MERS) and post-critical illness/intensive care syndrome, a range of neurological/ central nervous system (CNS) complications can arise from infection.[5,6] Most notably, encephalitis, ischaemia, haemorrhage, microstructural and functional changes and cerebrovascular disease (CVD) have been observed in COVID-19 patients, and more recently, evidence of brainstem inflammation using 7 Tesla magnetic resonance imaging (MRI) has been reported.[7] There has been concern regarding whether cognitive deficits will remain for years as a chronic syndrome, and whether patients who develop CVD as a result of infection will experience neurodegeneration and dementia in the long-term,[7−9] despite recovery of other acute and sub-acute symptoms.[10]

Key limitations for much of this early work include a reliance on self-report as opposed to objective assessment of cognitive deficits, the application of neuropsychological scales that lack sensitivity to detect subtle deficits in the formerly unimpaired or precision to differentiate deficits across cognitive domains, and uncertainty regarding longevity of deficits. Furthermore, depression, anxiety, fatigue and post-traumatic stress are elevated post COVID-19 illness,[11] which might mediate the association with cognitive sequelae.

Recently, we provided preliminary results addressing some of these limitations. Specifically, we used computerised cognitive assessment technology,[12,13] which has superior sensitivity and precision to gold-standard neuropsychological scales,[14] to investigate objectively measurable deficits across multiple cognitive domains in a large online cohort[15,16] that incidentally included people who reported infection with COVID-19 of varying severity.[17] Higher cognitive functions such as spatial planning and analogical reasoning appeared to be disproportionately impaired, especially in hospitalised patients. However, our earlier analyses lacked clinical-record corroboration of self-reported illness severity or hospital treatment. Furthermore, participants primarily were in the early chronic phase ~2−3 months post illness, which limited insight into the longevity of deficits.

Here, we use the same technology to assess patients at timepoints ranging from between ~1 and 10 months post admission to hospital for severe COVID-19. We sought to determine whether (i) the finding of higher cognitive deficits after COVID-19 infection can be replicated in a hospital confirmed cohort, (ii) the cognitive deficits relate to features of acute illness vs. mood, anxiety, tiredness or post-traumatic stress disorder (PTSD) at the point of assessment, (iii) the deficits negatively correlate with time since illness and (iv) the scale and profile of deficits is qualitatively comparable to that observed in normal age-related decline or dementia.

Methods

Data collection

All patients admitted to Addenbrookes Hospital with COVID-19 between 10th March 2020 and 31st July 2020, who survived and consented to take part were eligible for this cohort study. This comprised 489 patients, of whom 49 were consented to the NIHR COVID-19 BioResource to participate in the study and were administered the follow up battery. The study was approved by the Cambridge Central Research Ethics Committee (17/EE/0025 0025 & IRAS ID: 220277). Of these, 46 patients (27 females, 19 males, age mean=51 years standard deviation (SD)=14 years, range 28−83 years) completed the study protocol adequately to allow analysis (Tables S1−3). Based on the effect size observed in our previous citizen science dataset,[17] where people were assessed using the same technology, expected effect size for critically ill hospitalised patients would be >0.5 standard deviations. At n-46, power was sufficient to detect with one-tailed alpha at $p < 0.05$ a 0.5SD effect size difference as gauged by DfE scores from the linear model at 96% relative to zero and at 94% relative to the matched control group. There was statistical power of 95% to detect medium strength correlations of $r = 0.50$ at two tailed alpha $p < 0.05$. Participants completed a custom computerised cognitive assessment battery under supervised conditions via the Cognitron platform,[17,18] comprising 8 tasks deployed on an iPad (Supplemental Methods), as well as standard mood, anxiety and post-traumatic stress scales, specifically, the Generalized Anxiety Disorder 7 (GAD-7),[19] the Patient Health Questionnaire 9 (PHQ-9)[20,21] and the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders 5 (PCL-5)[22] in a return visit to the hospital on average 179 days after illness onset (SD=62 interquartile range=81).

Statistical methods

All analyses were conducted in MATLAB R2020a. To enable correlation of deficit magnitude with clinical and mental health measures whilst accounting for population variables, accuracy and median reaction times were extracted for each task, comprising 16 measures (Table S4), were transformed to deviation from expected (DfE) scores (see below definition) relative to $N = 66,008$ normative datasets (Table S5), comprising individuals who had performed the same set of tasks. Specifically, to calculate DfE scores, linear models were trained to predict performance for each task within the normative dataset from age decade, sex (male, female, other), education level, handedness (left, right ambidextrous) and first language (English, other). The trained models were then applied to the patient demographics, to which they were naive, providing expected scores for each individual. DfE score was quantified as the difference between observed minus predicted score divided by the control standard deviation. Non-compliant individuals from the normative dataset already had been identified and removed based on responding unfeasibly fast given the response time distribution; applying the same threshold identified no non-compliant participants within the patient dataset. Four patients could not complete Verbal Analogies and one could not complete Spatial Planning as they found them too challenging. Control and patient datasets were concatenated, and composites were then calculated by taking the first unrotated principal component (Table S6) across the eight summary score measures (G_SScore), focused on accuracy, and across the eight response time scores (G_RT), focussing on speed of response. Component scores were calculated for each subject via regression of

the component loadings matrix across the above measures, excluding any unavailable datapoints, and transformed to DfE score as described above. For further comparison, a set of matched controls was identified from within the normative database and processed in the same manner as the patients. Specifically, for each patient, ten unique control datasets were randomly selected who exactly matched them in terms of age decade, sex, handedness, first language and education level.

All statistical analyses applied a prior significance cut-off set to $p < 0.05$. T-tests, performed one-tailed with family wise error (FWE) correction for multiple comparisons, evaluated whether patient composite and individual task DfE scores were consistently poorer than expected relative to the matched normative group. Multiple regression determined whether G_SScore and G_RT DfE scores could be predicted from clinical features during the acute hospital stay or mental health measures at the time of assessment. Clinical features were World Health Organisation (WHO) COVID-19 severity score,[23] highest C-reactive protein (CRP), mechanical ventilation, extrapulmonary support, days ventilated, tracheostomy, and highest D-dimer; as well as age, sex and time since illness. Mental health scores were the GAD7, PHQ9 and PCL5. Due to high correlations between some of these clinical features, the feature matrix was reduced by applying Principal Component Analysis with varimax rotation, where the number of components was defined according to the Kaiser convention of retaining components with eigenvalues >1. The relationship between G_SScore and G_RT to time since illness was further examined in isolation using bivariate correlations with one-tailed significance.

To qualitatively gauge whether the profile of COVID-19 related cognitive deficits was similar in pattern or scale to age-related decline, standard deviation differences were extracted from the normative models (that is, accounting for the other population variables listed above) for each task between people at ages aged 70−79 minus those 20−29 or 50−59 within the control dataset. For further qualitative comparison, performance data from a previously collected group of 28 early-mid stage dementia patients were submitted to the same DfE pipeline as described above and effect sizes plotted (clinical and demographic details provided in Table S7).

Role of the funding source

Results
T-tests of global summary score and response time composites (Figure 1a) confirmed that participants who had been hospitalised due to COVID-19 scored significantly lower and were slower in their responses than would be expected given the control population as gauged by DfE scores (G_SScore estimate=-0.538 SDs, t=-4.214 $p < 0.0001$; G_RT estimate=0.726SDs, $t = 4.507$, $p < 0.0001$). Repeating the analysis for the 43 chronic-phase patients >90 days post symptom onset showed a similar result (G_SScore estimate=-0.524 SDs, t=-3.875 $p = 0.0004$; G_RT estimate=0.715SDs, $t = 4.194$, $p < 0.0001$). Contrasting the DfE scores directly against 460 precisely matched individuals (Figure 2), 10 per patient, from the control database reinforced this observation (mean difference in G_SScore estimate=-0.525SDs, t=-4.327, $p < 0.0001$; mean difference in G_RT estimate=0.887SDs, $t = 5.803$, $p < 0.0001$).

Application of Principal Component Analysis to the matrix of clinical and mental health features identified three components with eigenvalues >1 capturing 74% of the variance (Figure 1b). After varimax rotation, Component 1 captured variance pertaining to general severity of acute illness, including heavy positive loadings from WHO COVID-19 severity score, highest CRP, and requirement for mechanical ventilation, extrapulmonary organ support and days ventilated, moderate positive loading with age and requirement of tracheostomy and moderate negative loading for days since illness. Component 2 had heavy positive loading of requirement for tracheostomy and days ventilated, moderate positive loading for highest D-dimer and mechanical ventilation and extrapulmonary support, and moderate negative loading for females vs. males and time from illness onset. Component 3 had heavy positive loadings for the three mental health scales.

Multiple regression of the component scores onto DfE performance composites (Figure 1c) showed a significant negative correlation between G_SScore and Component 1 (Estimate=-0.346, $F_{(1,42)}= 9.392$ $p = 0.00380$), but not Component 2 (Estimate=0.140, $F_{(1,42)}=1.841$ $p = 0.18208$) or Component 3 (Estimate=-0.153, $F_{(1,42)}=1.855$ $p = 0.18041$). There was also a threshold level negative correlation between G_RT and Component 1 (Estimate=0.305, $F_{(1,42)}=4.008$ $p=0.05178$), but not Component 2 (Estimate=-0.177, $F_{(1,42)}=1.791$ $p = 0.21044$) or Component 3 (Estimate=0.111, $F_{(1,42)}=0.592$ $p = 0.46861$).

Bivariate correlations (Table S8) showed significant associations between G_SScore and Severity WHO COVID-19 ordinal scale, mechanical ventilation, extrapulmonary organ dysfunction support and highest CRP during admission at the one tailed uncorrected threshold. However, the hypothesised trends towards reduced underperformance over time were of small effect size and were statistically non-significant (G_SScore $r = 0.15$
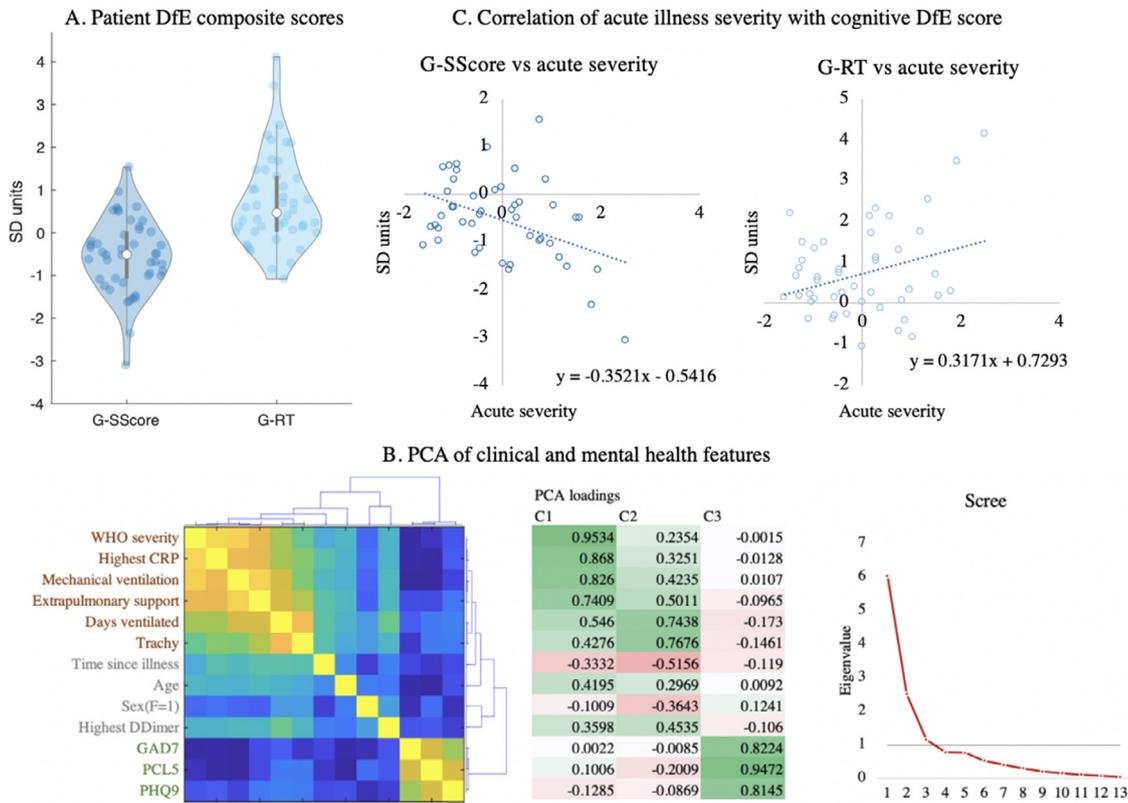
Figure 1. Analysis of composite deviation from expected cognitive performance scores A. Analysis of DfE composite scores showed that COVID-19 survivors were on average less accurate and slower to respond than expected given their age and demographic profiles. Scale is standard deviation units relative to the control population. **B.** Left. Clinical features from the acute phase, age, sex and mental health and time from illness at the point of assessment showed strong correlations with a clear natural clustering of acute clinical severity vs mental health scores at the time of cognitive assessment. Colour represents bivariate correlation strength where yellow = 1 and dark blue = -1. Right. Principal Component Analysis identified three components with eigenvalues greater than 1. Centre. After varimax rotation one general component included heavy loadings from acute illness severity, a second component more heavily loaded towards respiratory support features and a third component included high loadings from depression, anxiety and PTSD questionnaires. **C.** Acute clinical severity (component 1) showed statistically significant correlations with DfE composite scores that were of medium effect size. (X axis is clinical component score. Y axis is DfE score in SD units relative to the control population).

$p = 0.1542$, G_RT $r=-0.16$ $p = 0.1486$ one tailed and uncorrected). Reanalysing the data focusing exclusively on either those who were or were not ventilated relative to their respective controls showed significant cognitive deficits in both sub-groups (Fig. S1 & Table S9).

Finally, DfE scores were examined at the individual task level. There was a broad pattern of reduced accuracy and slowed response compared to the 460 matched controls (Table 1, Figure 2a), with multiple tasks surviving the $p < 0.05$ one-tailed and family wise error (FWE) corrected for multiple comparisons threshold. As predicted,[17] underperformance was more substantial for tasks challenging higher cognitive functions such as Analogical Reasoning (score -0.85SDs RT +1.34SDs) and Spatial Planning (score +0.28SDs RT +0.89SDs), as well as 2D Manipulations (score -0.58SDs RT +0.57SD) and word recall (immediate score -0.43SDs RT +0.43SDs delayed score -0.051SDs RT +0.46SDs).

For comparison (Figure 2), the pattern of mean age-related differences in performance of people in their 70s minus 20s or 70s minus 50s was quite distinct, with age related differences being most pronounced for 2D Manipulations, Spatial Span and Target Detection as opposed to Spatial Planning or Verbal Analogies. Furthermore, the 28 dementia patients who undertook 6 of the tasks showed the greatest DfE score on the Word Memory task with notably higher effect size.

Discussion

Individuals who survive severe COVID-19 illness have objectively measurable cognitive deficits, lasting many months, with respect to age- and demographic-adjusted
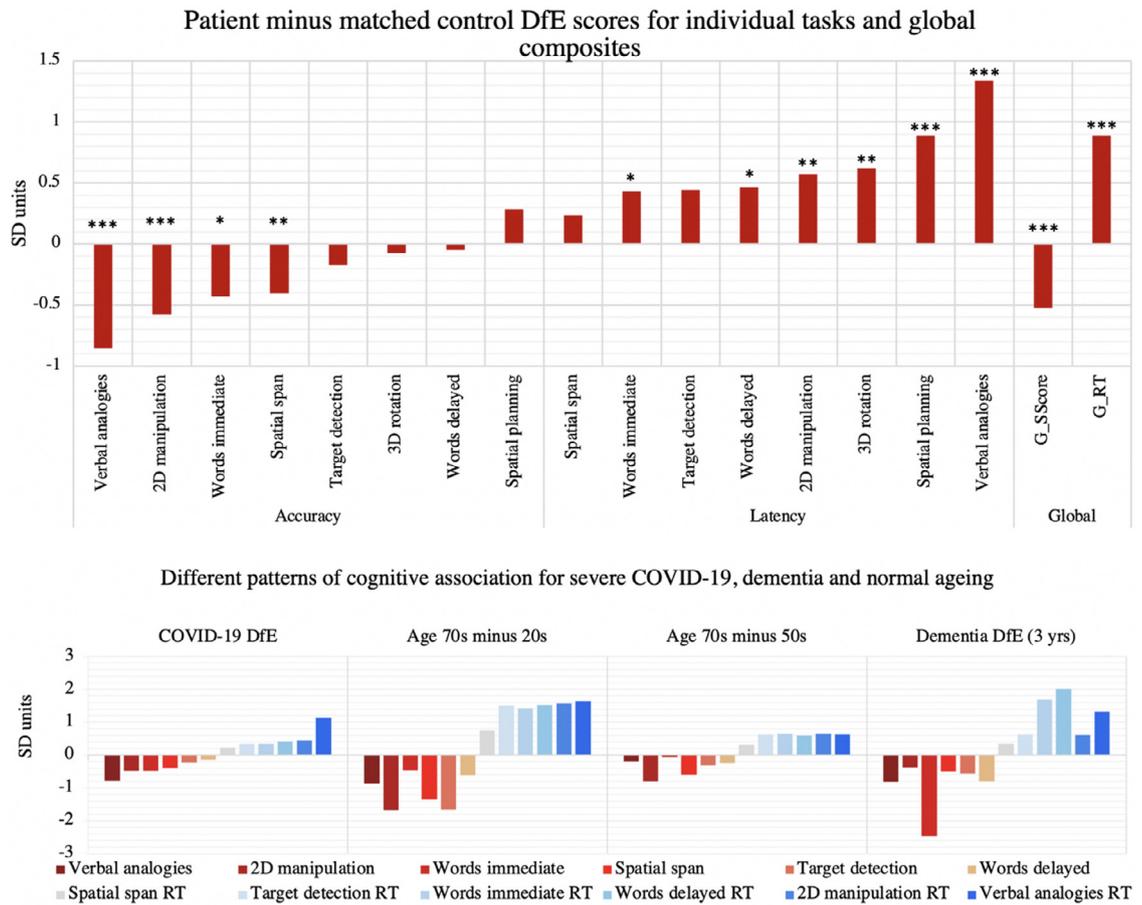
Figure 2. Multivariate profile of cognitive deficits after severe COVID-19 and relationship to age and dementia Upper. Patients showed a consistent pattern of cognitive underperformance in terms of reduced accuracy and slowed processing time that varied in magnitude across tasks. * $p < 0.05$, **$p < 0.01$, ***$p < 0.001$ one tailed FWE corrected for 18 multiple comparisons. Executive tasks tapping higher cognitive functions showed particularly strong associations, which was qualitatively different to the association with age-related decline or dementia. Y axis scale in standard deviation units relative to controls. **Lower.** The scale of DfE score for severe COVID-19 survivors was similar in scale to normal age-related decline in cognition between individuals in their seventies when compared to individuals in their fifties (but less than age related decline in cognition between 20 and 70 years of age), and less than cognitive problems in people with dementia 3 years post diagnosis. However, the pattern of deficits across cognitive domains was quite distinct to either of these comparisons. NB dementia patients had not undertaken Spatial Planning or 3D Perspective Rotation. Y axis scale is standard deviation units relative to controls.

norms.[17,24–30] Taking Cohen's notion of effect sizes as a gauge, the scale of those deficits was large; on average the 0.52SD and 0.89SD levels of underperformance on global accuracy and response time composite measures span the medium to large effect size range. For individuals who required mechanical ventilation, both composites were in the large range at 0.90SDs and 1.0 SDs, respectively, which is somewhat larger than our previous online study using the same assessment tools.[17] The deficits within specific cognitive domains were even greater, e.g., Verbal Analogies response times were 1.3SDs longer on average for all patients and 1.7SDs for those who had required mechanical ventilation. Notably, when analysing only those individuals for whom English was the native language, the same

pattern of deficits was still evident. Furthermore, our analyses accounted for both first language and education level. These results accord with self-reported problems 'finding words'[31] and neuropsychological case studies indicating verbal fluency deficits in severe COVID-19 patients post recovery.[32]

By using a large pre-existing normative dataset to correct for normal population variability in cognitive performance, we were able to begin the process of disentangling potential contributors to cognitive deficits post COVID-19. In particular, measures of mood, post-traumatic stress and mental health at the point of assessment were sufficiently dissociable from acute illness severity to be evaluated within the predictor matrix. This distinction is critical, because it is now well

		Effect size (DfE)	t	p (corrected)
Accuracy	Verbal analogies	-0.854	-6.205	<0.00001
	2D manipulation	-0.575	-4.221	0.00026
	Words immediate	-0.432	-2.869	0.03863
	Spatial span	-0.405	-3.605	0.00309
	Target detection	-0.176	-1.450	1.32876
	3D rotation	-0.076	-0.996	2.87946
	Words delayed	-0.051	-0.458	5.82405
	Spatial planning	0.283	1.510	1.18614
Latency	Spatial span	0.231	1.543	1.11135
	Words immediate	0.431	3.035	0.02276
	Target detection	0.444	2.568	0.09468
	Words delayed	0.463	2.942	0.03070
	2D manipulation	0.570	3.879	0.00107
	3D rotation	0.620	3.522	0.00421
	Spatial planning	0.888	4.779	0.00002
	Verbal analogies	1.337	7.018	<0.00001
Global	G_SScore	-0.525	-4.327	0.00016
	G_RT	0.887	5.803	<0.00001

Table 1: T-tests contrasting patients vs. 460 matched controls (one-tailed and FWE corrected for multiple comparisons).

established that people who have recovered from severe COVID-19 illness can have a broad spectrum of symptoms of poor mental health[11] as do those suffering from Long Covid,[1] which could conceivably contribute to both self-perceived and objectively measured cognitive deficits. These include problems with depression, anxiety post-traumatic stress, low motivation, fatigue, low mood, and disturbed sleep. Here, it was clearly the case that acute illness severity was the better predictor of objectively measurable global cognitive deficits during the chronic phase. At the level of individual clinical features, WHO COVID-19 severity score, highest CRP and the requirement for mechanical ventilation and multiple organ support were predictive of poorer cognitive performance.

All patients were recruited from the same hospital and following illness within a narrow timeframe, which given differences in patient treatment and virus variants across time limits our confidence when generalising these results. We believe that this limitation is somewhat mitigated by the concordance between the results presented here and our previous citizen science dataset, published in this journal.[17] Nonetheless, future research should seek to determine the relationship between variants, treatment strategies and cognitive outcomes at larger scale.

Regarding how representative the cohort was, the recruited population were younger, and more frequently female, and with a higher proportion of critical care admissions (WHO Ordinal Scale >6) than those who came through the centre (Tables S10−S14). A significant proportion, though not all, of these differences is attributable to the mortality of 24% in the overall

admitted population, since non-survivors were older (median age=80 inter quartile range =73−87), more often male (64%), and may have included patients in whom treatment limitation decisions may have been in place.

Our analysis of fatigue post COVID-19 illness was not in the original analysis plan. However, scores capturing self-report of fatigue in the months post illness were available for 38 patients (Tables S1−3) from the Post-Intensive Care Unit Presentation Screen, a brief functional screening tool to inform the rehabilitation needs after treatment in intensive care settings. 28 of them endorsed some level of fatigue. Fatigue score correlated robustly with the mental health composite score (r=-0.45 p = 0.005) but not with the acute illness composite score (r = 0.03 p = 0.852) or either of the cognitive composite scores (G_ACC r = 0.19 p = 0.240; G_RT r=-0.16 p = 0.343). These results indicate that although both fatigue and mental health are prominent chronic sequalae of COVID-19, their severity is likely to be somewhat independent from the observed cognitive deficits.

A further limitation was that the acute clinical features were too highly correlated with each other to dissociate. All but two of the participants requiring mechanical ventilation also required multiple organ support, and the requirement for mechanical ventilation correlated with highest CRP, a measure of inflammation, at r∼=0.8. The observed correlation with a marker of acute inflammation may reflect a causal relationship beyond the severity of respiratory problems; however, given the high correlation to other clinical features of the acute phase, work seeking to disentangle underlying

clinical causes of the observed cognitive deficits will require either substantial sized cohorts with sufficient power to delineate highly correlated predictors or additional data types, such as brain imaging in order to detect associations with markers in specific types of neuropathology.

Some previous studies have observed significant recovery across time in terms of cognitive symptoms[18] and imaging measures of brain function.[33] In accordance with these studies, we did observe slow and non-significant trends towards reduced deficits in both accuracy and response latency as a function of time from illness. We conclude that any recovery in cognitive faculties is at best likely to be slow. It also is important to consider that trajectories of cognitive recovery may vary across individuals depending on illness severity and the neurological or psychological underpinnings, which are likely complex. Plotting recovery trajectories and untangling their multivariate relationships to clinical features will require multi-timepoint studies in larger cohorts.

At a finer multivariate grain, the profile of deficits replicates our previous report in an online cohort of disproportionate underperformance within certain cognitive domains. In concordance with a previous large scale online study this pattern includes tasks designed to assess performance accuracy of attention, memory, difficult word-based reasoning and planning.[17] However, we also observed slowed processing speed. On a neurological level, this pattern of impairment aligns with the observation of sub-acute phase hypometabolism within frontoparietal systems after COVID-19 illness[26] that are known to be recruited in different combinations and configurations during the performance of these tasks.[12,13,34]

In this latter respect, the application of an assessment battery that provides a dimensional profile spanning multiple cognitive domains is of value when offering interoperability across studies. Indeed, it was informative to note that this profile of cognitive dysfunction was quite distinct to the normal pattern of age-related decline and to the pattern of deficits observed in early-stage dementia patients. On average, the scale of deficits was most similar to that observed in normal cognitive decline between the ages of 50−70; however, when examined in more detail the pattern of cognitive deficits was most pronounced for different tasks than either age-related decline or the dementia group. These more detailed results highlight the potential value of cross comparing multivariate profile of COVID-19 cognitive deficits to a wider variety of populations in order to identify potential similarities to other neurological conditions. Future work should also expand the repertoire of disorders, especially populations who have recovered from other critical illnesses, and cross relate these detailed cognitive profiles to imaging and blood biomarker measures of neuropathology and tracking recovery and decline trajectories over a longer temporal scale.

In summary, severe COVID-19 illness is associated with significant objectively measurable cognitive deficits that persist into the chronic phase. The scale of the deficits correlates with clinical severity during the acute phase as opposed to mental health status at the time of assessment, shows at best a slow recovery trajectory and the multivariate profile of deficits is consistent with higher cognitive dysfunction as opposed to accelerated ageing or dementia.

Contributors

AH and DKM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: AH, JB, ETB, JBR, DKM

Acquisition, analysis, or interpretation of data: AH, DAC, AM, AJ, WT, PH, MDG, VFJN, JGG, JB, LP, AE, NS, JB, NK, SJS, DKM.

Drafting of the manuscript: AH.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: AH.

Obtained funding: JB, JBR, ETB, DKM.

Supervision: AH, ETB, JBR, DKM.

Data sharing statement

Requests for data should directed to the corresponding authors. Data will be available upon reasonable request.

Declaration of Interests

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi: 10.1016/j.eclinm.2022.101417.

References

1 Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601–615.

2 Huang D, Lian X, Song F, et al. Clinical features of severe patients infected with 2019 novel coronavirus: a systematic review and meta-analysis. *Ann Transl Med*. 2020;8(9):576.

3 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395 (10223):497–506.

4 Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-day outcomes among patients hospitalized with COVID-19. *Ann Intern Med*. 2021;174(4):576–578.

5 Inoue S, Hatakeyama J, Kondo Y, et al. Post-intensive care syndrome: its pathophysiology, prevention, and future directions. *Acute Med Surg*. 2019;6(3):233–246.

6 Lam MH, Wing YK, Yu MW, et al. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. *Arch Intern Med*. 2009;169(22):2142–2147.

7 Miners S, Kehoe PG, Love S. Cognitive impact of COVID-19: looking beyond the short term. *Alzheimers Res Ther*. 2020;12(1):170.

8 Bougakov D, Podell K, Goldberg E. Multiple neuroinvasive pathways in COVID-19. *Mol Neurobiol*. 2021;58(2):564–575.

9 Goldberg E, Podell K, Sodickson DK, Fieremans E. The brain after COVID-19: compensatory neurogenesis or persistent neuroinflammation? *EClinicalMedicine*. 2021;31: 100684.

10 Jason LA, Islam MF, Conroy K, et al. COVID-19 symptoms over time: comparing long-haulers to ME/CFS. *Fatigue Biomed Health Behav*. 2021.

11 Chamberlain SR, Grant JE, Trender W, Hellyer P, Hampshire A. Post-traumatic stress disorder symptoms in COVID-19 survivors: online population survey. *BJPsych Open*. 2021;7(2):e47.

12 Soreq E, Violante IR, Daws RE, Hampshire A. Neuroimaging evidence for a network sampling theory of individual differences in human intelligence test performance. *Nat Commun*. 2021;12 (1):2072.

13 Hampshire A, Highfield RR, Parkin BL, Owen AM. Fractionating human intelligence. *Neuron*. 2012;76(6):1225–1237.

14 Brooker H, Williams G, Hampshire A, et al. FLAME: a computerized neuropsychological composite for trials in early dementia. *Alzheimers Dement*. 2020;12(1):e12098. (Amst).

15 Hampshire A. Great British intelligence test protocol. Research Square. 2020.

16 Hampshire A, Hellyer PJ, Soreq E, et al. Associations between dimensions of behaviour, personality traits, and mental-health during the COVID-19 pandemic in the United Kingdom. *Nat Commun*. 2021;12(1):4111.

17 Hampshire A, Trender W, Chamberlain SR, et al. Cognitive deficits in people who have recovered from COVID-19. *EClinicalMedicine*. 2021 101044.

18 Zhao S, Shibata K, Hellyer PJ. et al. Rapid vigilance and episodic memory decrements in COVID-19 survivors. medrXiv 2021.

19 Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092–1097.

20 Kroenke K, Spitzer RL, Williams JB, Lowe B. The patient health questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. *Gen Hosp Psychiatry*. 2010;32(4):345–359.

21 Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient health questionnaire. *JAMA*. 1999;282(18):1737–1744.

22 Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): development and initial psychometric evaluation. *J Trauma Stress*. 2015;28 (6):489–498.

23 WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192.; -e7.

24 Beaud V, Crottaz-Herbette S, Dunet V, et al. Pattern of cognitive deficits in severe COVID-19. *J Neurol Neurosurg Psychiatry*. 2021;92 (5):567–568.

25 Hellmuth J, Barnett TA, Asken BM, et al. Persistent COVID-19-associated neurocognitive symptoms in non-hospitalized patients. *J Neurovirol*. 2021;27(1):191–195.

26 Hosp JA, Dressing A, Blazhenets G, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain*. 2021;144(4):1263–1276.

27 Jaywant A, Vanderlind WM, Alexopoulos GS, Fridman CB, Perlis RH, Gunning FM. Frequency and profile of objective cognitive

deficits in hospitalized patients recovering from COVID-19. *Neuropsychopharmacology*. 2021.

28 Miskowiak KW, Johnsen S, Sattler SM, et al. Cognitive impairments four months after COVID-19 hospital discharge: pattern, severity and association with illness variables. *Eur Neuropsychopharmacol*. 2021;46:39–48.

29 Raman B, Cassar MP, Tunnicliffe EM, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine*. 2021;31: 100683.

30 Woo MS, Malsy J, Pottgen J, et al. Frequent neurocognitive deficits after recovery from mild COVID-19. *Brain Commun*. 2020;2(2): fcaa205.

31 Seessle J, Waterboer T, Hippchen T, et al. Persistent symptoms in adult patients one year after COVID-19: a prospective cohort study. *Clin Infect Dis*. 2021.

32 Whiteside DM, Oleynick V, Holker E, Waldron EJ, Porter J, Kasprzak M. Neurocognitive deficits in severe COVID-19 infection: case series and proposed model. *Clin Neuropsychol*. 2021;35(4):799–818.

33 Blazhenets G, Schroeter N, Bormann T, et al. Slow but evident recovery from neocortical dysfunction and cognitive impairment in a series of chronic COVID-19 patients. *J Nucl Med*. 2021;62 (7):910–915.

34 Jolly AE, Scott GT, Sharp DJ, Hampshire AH. Distinct patterns of structural damage underlie working memory and reasoning deficits after traumatic brain injury. *Brain*. 2020;143(4):1158–1176.