Post-COVID cognitive deficits at one year are global and associated with elevated brain injury markers and grey matter volume reduction: national prospective study

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Abstract

The spectrum, pathophysiology, and recovery trajectory of persistent post-COVID-19 cognitive deficits are unknown, limiting our ability to develop prevention and treatment strategies. We report the one-year cognitive, serum biomarker, and neuroimaging findings from a prospective, national longitudinal study of cognition in 351 COVID-19 patients who had required hospitalisation, compared to 2,927 normative matched controls. Cognitive deficits were global and associated with elevated brain injury markers and reduced anterior cingulate cortex volume one year after admission. The severity of the initial infective insult, post-acute psychiatric symptoms, and a history of encephalopathy were associated with greatest deficits. There was strong concordance between subjective and objective cognitive deficits. Treatment with corticosteroids during the acute phase appeared protective against cognitive deficits. Together, these findings support the hypothesis that brain injury in moderate to severe COVID-19 is immune-mediated, and should guide the development of therapeutic strategies.

Main

Cognitive deficits have been widely reported in post-acute COVID-19 patients across the respiratory disease severity spectrum, however, their recovery trajectory and pathophysiology remain unknown (1, 2). The most severely impacted patients are likely to be those with symptoms of and clinical evidence for neurological or psychiatric complications secondary to COVID-19 (3). However, most previous studies have not included these patients despite such complications being present in up to one third of patients in the 6-months following COVID-19 diagnosis, including diagnoses such as stroke, movement disorders and psychosis (4). Early data suggested that the most common acute neurological complication of COVID-19 was encephalopathy, overlapping with delirium and subacute delirium in the context of COVID-19 (5, 6). The majority of the current literature uses suboptimal or domain-limited measures of cognitive performance and does not examine biological substrates. Few neuroimaging studies have assessed cognition across multiple cognitive domains utilising sensitive, precise, and objective assessments relative to appropriately matched controls, and there are scarce follow-up data to allow understanding of recovery trajectories and prognostic markers (7).

Early evidence suggested that COVID-19 patients primarily suffered from a dysexecutive syndrome during acute infection (8). However, the domain-specific pattern of cognitive impairment in the post-acute phase, commonly defined as beyond 3-months post COVID-19 symptom onset (9, 10), has not been well characterised (11, 12). Similarly, the biological basis of these objective cognitive deficits remains unclear, particularly the degree of brain injury and associated structural neuroimaging changes. Given that COVID-19 is very rarely neuroinvasive, with little robust evidence for SARS-Cov-2 virions in the brain (10), the impact on the brain is hypothesised to be via immune-mediated para- and post-infectious phenomena (13, 14), or else indirect effects via neuropsychiatric, psychological, and social consequences of illness and the pandemic more generally. The para-infectious brain insult demonstrated in COVID-19 is unlikely to be unique to SARS-CoV-2 infection given that similar findings have been demonstrated in other systemic infections and critical illness (15, 16, 17) and therefore improved understanding of post-acute cognitive impairment in this setting may be translatable to other clinical cohorts.

Ultimately, the current lack of evidence limits our ability to advise and manage patients with ongoing cognitive symptoms that can have a significant impact on quality of life and healthcare systems (18, 19, 20). There is an urgent need to comprehensively study COVID-19 patients including in-depth clinical, biological, and cognitive phenotyping, as well as longitudinal follow-up. The COVID-19 Clinical Neuroscience Study (COVID-CNS) is a prospective, national study of the neurological and psychiatric complications of COVID-19. This analysis aims to characterise post-acute cognitive impairment and explore the role of serum and neuroimaging biomarkers in adults hospitalised with COVID-19, with and

without acute clinical neurological and psychiatric complications. Analyses were conducted according to a pre-registered statistical analysis plan (21) to test the following hypotheses:

1. COVID-19 is associated with post-acute objectively measurable cognitive deficits.
2. Certain cognitive domains are more greatly impaired than others. Executive function will be disproportionately impaired in relation to accuracy and reaction time.
3. Cognitive deficits correlate with age, World Health Organization (WHO) COVID-19 disease severity, presence of an acute neurological or psychiatric complication, multimorbidity and mental health comorbidities, Rockwood clinical frailty scale, and acute serum inflammatory markers.
4. Educational attainment and prior treatment with dexamethasone during acute illness may be protective.
5. Post-acute cognitive deficits are associated with structural volumetric changes on magnetic resonance imaging (MRI).

Results

Study population

The analysis included 351 COVID-CNS participants and a normative comparator group of 2,927 subsampled age, sex, and education level matched community controls (Fig. 1). Participants were identified if they did not have a prior neurological diagnosis, and were assessed at a single post-acute appointment median (IQR) 384 (155-574) days after admission, including cognitive testing, self-reported measures, neuroimaging and serum sampling. Within the COVID-CNS cohort, the median (IQR) age was 54 (44-63) years, 202 (58%) were male, 271/348 (78%) were of white ethnicity, and 89/311 (29%) had severe SARS-CoV-2 disease symptoms, as per the WHO clinical severity scale (Table 1) (22). 57/294 (19%) had been vaccinated against SARS-CoV-2 prior to COVID-19. 190/351 (54%) had a neurological or psychiatric complication associated with their COVID-19 illness (the NeuroCOVID group with six clinical diagnostic subgroups), and 161/351 (46%) had no neurological complication (the COVID group) (Fig. 1). Compared to the COVID group, the NeuroCOVID group were more likely to have mild COVID-19, were assessed earlier post-hospital admission, and had higher self-rated scores for mental health measures (Table 1).

Cognition

Hypothesis 1: COVID-19 is associated with post-acute objectively measurable cognitive deficits

Patients in all groups were significantly less accurate and slower in their responses than would be expected based upon their demographics compared with subsampled normative data (Fig. 2a). The lowest Global Deviation from Expected (GDfE [IQR]) scores were seen in patients who had had encephalopathy (-1.51 [2.87]) and to a lesser extent those who had had cerebrovascular (-1.20 [1.75]) or inflammatory (-0.98 [1.55]) complications (Fig. 2a). Prior to COVID-19 illness 11/137 (8%) NeuroCOVID and 15/152 (10%) COVID patients were concerned about their memory, increasing to 84/139 (60%) and 66/150 (44%) after COVID-19 illness respectively, of whom 35/82 (43%) and 45/66 (68%), respectively, perceived their memory problems to be progressive. Memory concerns were associated with greater objective deficits in median [IQR] GDfE scores in both NeuroCOVID (-1.26 [1.51] vs -0.76 [1.83], p=0.008) and COVID groups (-1.30 [1.78] vs -0.59 [1.39], p<0.001). The positive predictive value of memory concerns for cognitive impairment was 0.92 in NeuroCOVID and 0.89 in COVID groups.

Hypothesis 2: Certain cognitive domains are more greatly impaired than others

Analysis of individual tasks identified global impairment across all cognitive domains in both accuracy and response time (RT) in all clinical diagnostic groups (Fig. 2b) - and no evidence for domain-specific deficits. In addition, this pattern of generalised cognitive impairment did not vary significantly according to the clinical diagnostic group (Eta2=0.04, p=0.151).

Recovery occurs over months and may be incomplete

Follow-up 1 was completed by 51 NeuroCOVID and 30 COVID patients at median (IQR) 111 (102-163) days after their post-acute appointment. The NeuroCOVID and COVID groups at follow-up were of similar median (IQR) age (57 [46-65] and 53 [48-60] years) and sex (31/51 [61%] and (20/30 [67%] male) respectively, as the cohort as a whole, but both groups had higher median (IQR) GDfE (-0.61 [-1.34 to- 0.16] and -0.60 [1.08-0.075]) at their initial post-acute assessment. In both the NeuroCOVID and COVID groups, there was evidence of recovery in cognitive performance comparing the post-acute assessment to both follow-up 1 and follow-up 2, but not between follow-up 1 and follow-up 2 (Fig. 2c). A total of 48/51 NeuroCOVID and 27/30 COVID patients had prior serum sampling for brain injury markers and 21/51 and 15/30 respectively had prior neuroimaging. In the NeuroCOVID group, when accounting for timing of COVID-19, a multivariate model (R2=0.42, p=0.103) demonstrated a trend towards an association between a raised Tau and reduced recovery. A multivariate model in the COVID group (R2=0.51, p=0.017) demonstrated that patients were less likely to recover if they were infected with COVID-19 earlier in the pandemic and had a higher Ubiquitin Carboxy-Terminal Hydrolase L1 (UCH-L1) (Extended Data Table 1).

Hypotheses 3 and 4: Clinical factors associated with greater deficits

The clinical factors associated with cognitive impairment differed in the NeuroCOVID and COVID groups (Table 2). The multivariate model of the NeuroCOVID group containing only clinical factors did not explain a significant proportion of the variance (R2=0.25, p=0.069). In the multivariate model of the COVID group (R2=0.45, p<0.001), cognitive impairment was associated with symptoms of depression (p<0.001), multimorbidity (p=0.039), COVID-19 illness earlier in the pandemic, particularly during the first wave, and increased COVID-19 severity (Table 2). Treatment with corticosteroids demonstrated a protective effect (p=0.0048).

In univariate analysis of pre-selected variables in the full cohort, GDfE scores were most strongly associated (coefficient [SE]) with a COVID-19 associated history of encephalopathy (-0.83 [0.26], p=0.002), admission date during the period 01/09/2020-01/03/2021 (-0.74 [0.18], p<0.001), post-acute subjective cognitive impairment (-0.64 [0.14], p<0.001), and depression (-0.06 [0.01]/unit, p<0.001). In both NeuroCOVID and COVID groups respectively, correlation matrices revealed high correlation between scores in Patient Health Questionnaire-9 (PHQ-9) and PTSD Checklist for DSM-5 (PCL-5) (0.78, 0.79), Generalised Anxiety Disorder Assessment (GAD-7) (0.71, 0.83), Chalder Fatigue Scale (CFQ) physical (0.54,0.49), mental (0.43 ,0.51) subscales and subjective cognitive impairment (0.42, 0.64). Pre-existing depression or a history of antidepressant use were not significantly associated with post-acute cognitive impairment.

Serum markers: Brain injury markers are raised at one year follow-up

Compared to healthy controls, median [IQR] serum neurofilament light chain (Nfl-L, a marker of axonal injury), and glial fibrillary acidic protein (GFAP; a marker of astrocyte injury) were significantly raised in patients who had had COVID-19 (12.4 pg/mL [9.2-18.0] and 94.3 pg/mL [65.6-128.2], both p<0.001), and further raised in those with neurological complications (15.2 pg/mL [10.5-21.7], p=0.001 and 105.4 pg/mL [79.9-154.8], p=0.047) respectively (Fig. 3a).Tau was raised exclusively in those with neurological complications (1.32 pg/mL [0.57-1.98] vs 0.69 pg/mL [0.40-1.22], p<0.001).

Hypothesis 5: Cognitive deficits are associated with structural volumetric changes on MRI

Participants who underwent neuroimaging in the NeuroCOVID (n=84/190) and COVID (n=73/161) groups were similar to the overall cohort in median (IQR) age (52 [44-60] and 51 [45-57] years) and proportion of males (60/84 [71%] and 45/73 [62%]).

The thickness and volume of regions represented by the composite Image Derived Phenotype (IDP) z-scores did not differ significantly between NeuroCOVID and COVID groups (Fig. 3b, Extended Data Table 2). One-way ANOVA revealed a significant difference in IDP composites between diagnostic subgroups in terms of global thickness composite (F=3.223, p=0.00524) but this did not persist after False Discovery Rate correction (p=0.0734). Post-hoc Tukey group comparisons for this thickness composite found significant differences between the neuropsychiatric subgroup and cerebrovascular (mean difference =0.871, adjusted p=0.0251), encephalopathy/delirium (mean difference 0.936, adjusted p=0.0119), and peripheral subgroups (mean difference 0.769, adjusted p=0.0395).

Pearson's correlations between GDfEs and IDP composites indicated significant correlations between overall cognition and the total brain IDP composite in the NeuroCOVID group (R=0.296, p=0.0444) and the overall cohort (R=0.272, p=0.0041; Extended Data Table 1). Global volume composite had significant correlations with cognitive deficits in the overall cohort (R=0.242, p=0.0022) (Fig. 3C), with a correlation in the NeuroCOVID group (R=0.271, p=0.0127) but not persisting after False Discovery Rate correction.

The bilateral volume of anterior cingulate cortex was significantly and moderately positively correlated with overall cognition in the NeuroCOVID group (R=0.307, p=0.0444), the COVID group (R=0.307, p=0.0280) and the overall cohort (R=0.299, p=0.00195; Fig. 3c).

Cluster analysis: Cognitive deficits, anterior cingulate volume and glial fibrillary acidic protein

An unsupervised cluster analysis, corrected for multiple comparisons, demonstrated that faster RT in memory tasks correlated with parahippocampal gyrus, anterior cingulate cortex and insula volumes (Fig. 4). Insula volume (r=0.15) and orbitofrontal cortex thickness (r=0.14) were correlated with executive function. Symptoms of depression were negatively correlated with immediate memory (r=-0.25), language (r=-0.20) and perceptual-motor function (2D Manipulations r=-0.12) as well as anterior cingulate cortex volume (r=-0.20). Subjective memory impairment was associated with inaccurate (r=-0.24) and slow (r=-0.19) responses on memory tasks and reduced superior temporal

gyrus (r=-0.20) and insula (r=-0.091) volume. Raised Nfl-L in serum was weakly correlated with reduced thickness composite (r=-0.102) and reduced superior temporal gyrus volume (r=-0.033) and thickness (r=-0.048). In a multivariate model of GDfE in the NeuroCOVID group (R2=0.45, p<0.001) (Table 2), cognitive deficits were associated with reduced anterior cingulate cortex volume (p=0.0269) and increased age (p=0.0381). In the COVID group (R2=0.44, p<0.001), cognitive deficits were associated with symptoms of depression (p<0.001), increased multimorbidity (p=0.0103) and a raised GFAP (p=0.0123).

Discussion

This prospective, national, multicentre study of 351 COVID-19 patients who required hospitalisation with and without new neurological complications demonstrated that post-acute cognitive deficits, relative to 2,927 matched controls, were associated with elevated brain injury markers in serum and reduced grey matter volume. In contrast to studies early in the pandemic that identified dysexecutive syndromes predominant in acute infection (8, 11), our study found global, persistent cognitive deficits even in those without clinical neurological complications. When compared to normative age-matched data, these deficits were equivalent in magnitude to ageing from 50 to 70 years of age (1). This study indicated cognitive deficits were associated with the severity of the initial infective insult, post-acute mental health status, and a history of COVID-19 associated encephalopathy, with strong concordance between subjective and objective deficits. Despite some improvement at the first follow-up, by the second there was a plateau in the cognitive recovery trajectory and there was evidence of ongoing neuronal and astrocytic injury one year after acute COVID-19, even in those without neurological complications, with demonstration of underpinning neuroanatomical substrates (23, 24, 25).

The findings are both clinically significant and biologically plausible. Raised brain injury markers have been demonstrated in acute and post-acute COVID-19 and are associated with dysregulated innate and adaptive immune responses (14, 26). The pattern of acute inflammatory proteins can predict post-acute cognitive outcomes (27) and the finding, here, that acute treatment with corticosteroids may be protective for cognition is consistent with previous research (28), and further supports the hypothesis that brain injury in COVID-19 is immune-mediated. We have additionally shown that persistently raised serum GFAP was associated with post-acute cognitive impairment. GFAP is expressed by astrocytes, which participate in neuroimmune interactions within the brain. Its appearance in the plasma typically indicates injury of these cells and has been proposed as a prognostic biomarker for cognitive decline in the general population (29).

Cognitive deficits were global, of significant magnitude, and spanned both accuracy and RT. Deficits were moderately to strongly associated with symptoms of depression, and the anterior cingulate cortex volume, which has functional roles in connecting cognition, attention, and emotion (30). An attentional basis for cognitive impairment with associated difficulties in memory encoding would be consistent with the global nature of the deficits including the immediate memory task. The anterior cingulate cortex is also frequently implicated in studies of depression utilising Positron Emission Tomography targeting translocator protein, which is interpreted as indicating microglial activation or neuroinflammation (31). Longitudinal research using UK Biobank data reported volume loss in the anterior cingulate cortex and other limbic structures following mild SARS-CoV-2 infection (7), but prior literature has also shown that the anterior cingulate cortex has reducing volume in older age (32, 33). In our unsupervised cluster analysis, reduced cortical thickness, particularly in the superior temporal gyrus, was found to be associated with raised Nfl-L, potentially indicating a regional substrate for axonal injury in this population. Some literature has suggested that neuroinflammation and neurodegeneration can mediate structural brain changes and neuropsychiatric sequelae (34), and that serum Nfl-L might be associated with changes to the superior temporal gyrus in these contexts (35). The severe persistent deficits in those with COVID-associated acute encephalopathy, in this cohort who did not have a pre-

COVID history of neurological disease, suggest that a picture of encephalopathy and/or delirium in the context of infection is not just an unmasking of latent cognitive impairment but rather may precede lasting brain dysfunction (6).

Advancing mechanistic understanding of post-COVID cognitive deficits has the potential to provide insight into therapeutic targets. This analysis implicates neurochemical and neuromodulatory mechanisms that both have potential to be targeted. There is growing biochemical evidence that neurological complications in COVID-19, including cognitive impairment, are immune-mediated, which is corroborated here by clinical demonstration of the protective effect of acute treatment with corticosteroids (28). In the post-acute phase, conceptually, if the anterior cingulate cortex were confirmed to be a nexus of late deficits, its dopaminergic neurochemical linkage provides a target for neuromodulatory therapy, with potential for utilising drugs already approved for use in humans, as well as attention training therapies (36).

The strengths of this study included its multimodality such as the use of robust longitudinal cognitive assessment, high quality clinical data, serum biomarkers, and nationally harmonised three Tesla neuroimaging data. Importantly, the GDfE scores reported represent how cognitive performance differs from what would be expected on an individual level based upon age, sex, level of education and first language, using data from a large normative dataset (2). This reduces the risk of confounding due to premorbid state. The inclusion of patients with neurological complications allowed more complete assessment of the heterogeneous impact of COVID-19 on brain dysfunction. The pre-registered statistical analysis plan was conducted with minimal deviation and provides increased confidence in results, which were broadly consistent with documented hypotheses. Limitations included the lack of premorbid assessment or acute biomarkers beyond routine clinical tests, probable age- and severity-selection bias in those completing study assessments particularly computerised cognitive assessment and MRI scanning, and the exclusive use of preselected brain regions for neuroimaging analysis. Additionally, the UK Biobank pipeline utilised does not completely address some potential confounds such as head motion. Although structural scans, as utilised in this study, are not thought to suffer from degradation of image quality as a result of head motion to the same extent as other modalities, it is worth acknowledging that such confounds could increase the risk of false positives (37, 38). However, this study aimed to address this by excluding scans with significant motion artefact (39). Finally, the analysis of recovery trajectories was underpowered which limits interpretation, but there was evidence of a trend towards recovery that continued into the second year.

Taken together, this prospective multicentre longitudinal cohort study found evidence of pervasive global cognitive impairment, associated with persistently raised brain injury markers, depression symptomatology, and reduced anterior cingulate cortex volume. A strong concordance between subjective and objective cognitive deficits, underpinned by neuroanatomical and biochemical changes at almost a year post-infection, indicates that patient experience needs to be acknowledged by clinicians in this context. However, care needs to be taken in both inferring cause and effect, and extrapolating these results to a broader COVID-19 population. Mechanisms underpinning this potentially immune-mediated construct of depression, cognition and brain injury need to be further elucidated, to allow the development of targeted therapeutic interventions.

Methods

Study population

Patients 16 years were recruited over 19 months (March 2021–Oct 2022) from 17 UK sites through the COVID-CNS, a case-control study within the National Institute of Health Research (NIHR) COVID-19 BioResource (REC reference 17/EE/0025; 22/EE/0230 (East of England—Cambridge Central Research Ethics Committee)). COVID-CNS included

hospitalised patients with COVID-19 without a prior relevant neurological diagnosis, who have had a new acute neurological or psychiatric complication (NeuroCOVID) alongside COVID-19 controls without these diagnoses (COVID), matched on a group level by age, sex, ethnicity, clinical frailty status, COVID-19 severity, and epoch of admission during the pandemic (40, 41). Some neurological or psychiatric complications required secondary care input without hospitalisation, partially related to pandemic pressures and risk assessments, and a proportion of the COVID group were therefore recruited who attended the emergency department but were not admitted. This analysis contains a patient subset that completed cognitive testing. Case ascertainment varied by study site but patient identification was most frequently via inpatient and outpatient attendance, neurology referrals, and SARS-CoV-2 positive laboratory reports. Participants were assessed at a single post-acute appointment which took place 1-26 months post-discharge, including a computerised cognitive assessment (Cognitron), patient-reported measures, blood sampling via venepuncture, 3T MRI and a clinical examination. Self-reported measures included PCL-5, GAD-7, PHQ-9 and CFQ. Multimorbidity, defined as ≥2 comorbidities, and Anticholinergic Burden score (a measure of how many medications taken might cumulatively contribute to an anticholinergic effect) were collected from past medical history and medications (42). To create a normative community comparator group, we sampled ≥8 individuals for each COVID-CNS participant matched for age, sex, first language, and level of education who completed the same cognitive assessment from a large normative dataset (1, 2). The research team completed a Case Record Form to collect harmonised clinical data across sites regarding acute admission and neurological complications.

Eligibility criteria

Patients with significant pre-existing neurological or psychiatric disorders managed in secondary care or pre-existing cognitive impairment were excluded. In the case of doubt about eligibility, this was discussed on a case-by-case basis at a national multi-disciplinary case evaluation panel (full criteria, see Supplementary Table 1).

Cognitive outcome

The cognitive assessment included seven tasks from the Cognitron assessment battery completed once under supervised conditions and twice online during follow-up (Supplementary Information 2). We included patients within the COVID-CNS cohort who had completed at least the first supervised assessment. Cognitron is sensitive, specific, and valid in the general population and disease cohorts (1, 2, 43, 44). Cognitive tasks were selected to sample across five domains defined by the DSM-5 classification (45) - Executive Function; Learning and Memory; Complex Attention; Perceptual-Motor Control and Language. Accuracy and median RTs were extracted by task, comprising 13 measures. These data were transformed into Deviation from Expected (DfE) scores using established linear models trained on a large normative dataset (>400,000 individuals) designed to predict performance based upon demographics. In this analysis, GDfE, DfE accuracy and DfE RT represent how an individual performs compared to what would be expected based upon their age, sex, first language and level of education. Any cognitive impairment was defined as GDfE less than expected (<0). A technical correction was applied excluding those responding unfeasibly fast or slow based upon normative data. Follow-up 1 and 2 were completed three and six months following the post-acute assessment. Recovery of cognitive performance was calculated as GDfE at Follow-up 1 minus GDfE at post-acute appointment.

Brain injury marker measurement

Brain injury markers were measured in serum using a Quanterix Simoa kit run on an SR-X Analyser (Quanterix, Billerica, MA, USA, Neurology 4-Plex A Advantage Kit, cat#102153). We assessed Nfl-L, UCH-L1, Tau, and GFAP. Normative

values were taken from n=60 healthy controls recruited to the NIHR BioResource, reflecting the median (IQR, range) age distribution of the cohort as a whole (50 [32-62, 20-79] years) (46).

Neuroimaging

3T MRI protocols were harmonised and the published standardised protocol was consistent across sites (39). Specific brain regions were selected based on extant literature *a priori* to analysis; the parahippocampal gyrus, entorhinal cortex, orbitofrontal cortex, anterior cingulate cortex, insula and superior temporal gyrus (7, 47, 48, 49, 50, 51). MRI data were processed with FSL and Freesurfer, using the established UK Biobank pipeline, (37, 39, 52) modified for COVID-CNS, in order to produce biologically relevant metrics of brain structure and function - IDPs. IDPs from T1 and T2-FLAIR weighted MRI were obtained for global brain regions and for cortical regions as defined by Desikan-Killiany parcellation. IDPs represent grey matter thickness, volume and surface area. Fifty-four of these IDPs were selected as representative of general brain structure and the a priori selected brain regions. Volume and surface IDPs were found to be collinear (Variance Inflation Factor >10) and so 38 IDPs representing volume and thickness were included in subsequent analysis (for a full list, see Supplementary Table 2). Individual IDPs were compared to the COVID-CNS population means and standard deviations in order to calculate z-scores such that IDPs from disparate regions could be analysed in unison. Z-scores were combined into 14 composite z-scores, representative of volume and thickness of a priori regions of interest.

Model development

Candidate variables for linear models were pre-defined clinically important variables; age, sex, COVID-19 severity, clinical diagnostic group, level of education, frailty, mental health (PHQ9, GAD7 and PCL5), Chalder fatigue scale (53), vaccination against COVID-19, acute treatment with steroids, acute serum inflammatory markers (C-reactive protein (CRP) and white cell count (WCC)), subjective cognitive impairment, and time since COVID-19. The four brain injury markers and fourteen neuroimaging composites were additional candidate variables. Collinearity was assessed using correlation matrices. Variables were selected for the final model based on explanation of variance, biological plausibility, and missingness (<20% missingness). Date of admission and days since admission were included in all models. Final models represent complete case analysis. Within the pre-registration, three sample size calculations were undertaken to determine adequate power (95%) at the 0.05 significance level for the cross-sectional analysis.

Statistical analysis

The full analysis plan was pre-registered prior to data access and is openly available via Open Science Framework (21). In summary, the primary outcome measure was GDfE on computerised cognitive assessment. DfE effect sizes are calculated comparing COVID-CNS participants to matched community controls. We used standard two-sided $p<.05$ criteria for determining statistical significance, with false discovery rate correction where applicable. There were minor deviations from the analysis plan: there were seven individuals in the overall COVID-CNS cohort who had non-COVID respiratory illness who were excluded from this analysis due to small numbers. Additionally, the community normative group was not stratified by COVID-19 status due to lack of data. We report multiple regression models for GDfE rather than accuracy and RT separately to improve clarity. We based models on complete case analysis rather than multiple imputation as existing data was deemed sufficient (<20% missingness). For MRI analysis, we report the analyses of a priori defined regions. Cortical volume and surface area were co-linear and therefore cortical volume only was included (Variance Inflation Factor >10). The statistical analysis plan was otherwise conducted as documented. Statistical analyses were performed in R (The R Foundation©, version 3.6.1 or later). Potential confounders were included as

candidate variables in all multiple regression models. These variables were premorbid state including pre-existing cognitive impairment, age, education, fatigue, subjective cognitive impairment and mental health. The GDfE score represents performance compared to what would be expected by age, sex, level of education and first language and therefore reduces the risk of confounding from these variables. GDfE is based on linear models trained on normative data from >400,000 individuals. Fatigue, subjective cognitive impairment and mental health measures were found to be collinear and PHQ-9 score explained the most variance in GDfE. PHQ-9 was therefore included in both final multiple linear regression models in Table 2.

Patient and public involvement

The COVID-CNS Patient and Public Involvement and Engagement panel represents patients across the brain-mind spectrum and through its bimonthly meetings has influenced the study throughout. Specifically, to support this analysis, the panel trialled and provided feedback on the cognitive testing prior to use, supported actioning of participant feedback, and guided presentation of findings.

Declarations

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Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interests

RB holds equity and serves as a director for Centile Bioscience Inc. PJH holds equity and serves as director for H2 Cognitive Designs LTD. RU was speaker at promotional educational event Otuska; Consultancy Vitaris and Springer Healthcare in the last 3 years. TP reports consultancy for Arialys Therapeutics Inc., speaker honoraria from Janssen. AC is President FND Society, Associate editor JNNP, gives independent testimony in Court on a range of neuropsychiatric topics. EB consults for GSK, SR One, Boehringer Ingelheim, Sosei Heptares. TS is Director of The Pandemic Institute which has received funding from Innova and CSL Seqirus and Aviva and DAM Health. TS was an advisor to the GSK Ebola Vaccine programme and the Siemens Diagnostic Programme. TS Chaired the Siemens Healthineers Clinical Advisory Board. TS Co-Chaired the WHO Neuro-COVID task force and sat on the UK Government Advisory Committee on Dangerous Pathogens, and the Medicines and Healthcare Products Regulatory Agency (MHRA) Expert Working Group on Covid-19 vaccines. TS Advised to the UK COVID-19 Therapeutics Advisory Panel (UK-TAP). TS was a Member of COVID-19 Vaccines Benefit Risk Expert Working Group for the Commission on Human Medicines (CHM) committee of the Medicines and Healthcare products Regulatory Agency (MHRA). TS has been a member of the Encephalitis Society since 1998 and President of the Encephalitis Society since 2019.

Data availability statement

Data and samples from the COVID-Clinical Neuroscience Study are available for collaborative research by application through the NIHR BioResource Data Access Committee https://bioresource.nihr.ac.uk/using-our-bioresource/apply-for-bioresource-data-access/. The Committee decide on academic applications, with escalation to the NIHR BioResource Steering Committee for contentious applications, and/or applications from industry. Participants in the NIHR BioResource have all consented to the sharing of de-identified data with bona fide researchers worldwide, for research in the public interest. There are limits to these consents both by expectation and legal - some datasets may not be shared beyond a safe setting in the UK.

Code availability

Code will be made publicly available via https://github.com/tnggroup/covidcns

References

1. Hampshire A, Chatfield DA, MPhil AM, Jolly A, Trender W, Hellyer PJ, et al. Multivariate profile and acute-phase correlates of cognitive deficits in a COVID-19 hospitalised cohort. eClinicalMedicine. 2022;47:101417.
2. Hampshire A, Trender W, Chamberlain SR, Jolly AE, Grant JE, Patrick F, et al. Cognitive deficits in people who have recovered from COVID-19. EClinicalMedicine. 2021;39:101044.
3. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res Ther. 2020;12(1):69.
4. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. The Lancet Psychiatry. 2021;8(5):416–27.
5. Otani K, Fukushima H, Matsuishi K. COVID-19 delirium and encephalopathy: Pathophysiology assumed in the first 3 years of the ongoing pandemic. Brain Disorders. 2023;10:100074.1.

6. Michael BD, Walton D, Westenberg E, García-Azorín D, Singh B, Tamborska AA, et al. Consensus Clinical Guidance for Diagnosis and Management of Adult COVID-19 Encephalopathy Patients. J Neuropsychiatry Clin Neurosci. 2023;35(1):12–27.
7. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022;604(7907):697–707.
8. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med. 2020;382(23):2268–70.
9. Perrottelli A, Sansone N, Giordano GM, Caporusso E, Giuliani L, Melillo A, et al. Cognitive Impairment after Post-Acute COVID-19 Infection: A Systematic Review of the Literature. J Pers Med. 2022;12(12):2070.
10. Meinhardt J, Streit S, Dittmayer C, Manitius RV, Radbruch H, Heppner FL. The neurobiology of SARS-CoV-2 infection. Nat Rev Neurosci. 2023;
11. Tavares-Júnior JWL, de Souza ACC, Borges JWP, Oliveira DN, Siqueira-Neto JI, Sobreira-Neto MA, et al. COVID-19 associated cognitive impairment: A systematic review. Cortex. 2022;152:77–97.
12. Quan M, Wang X, Gong M, Wang Q, Li Y, Jia J. Post-COVID cognitive dysfunction: current status and research recommendations for high risk population. The Lancet Regional Health - Western Pacific. 2023;38:100836.
13. Dunai C, Collie C, Michael BD. Immune-Mediated Mechanisms of COVID-19 Neuropathology. Front Neurol. 2022;13:882905.
14. Needham EJ, Ren AL, Digby RJ, Norton EJ, Ebrahimi S, Outtrim JG, et al. Brain injury in COVID-19 is associated with dysregulated innate and adaptive immune responses. Brain. 2022;145(11):4097–107.
15. Klein RS, Garber C, Howard N. Infectious immunity in the central nervous system and brain function. Nat Immunol. 2017;18(2):132–41.
16. Reis PA, Castro-Faria-Neto HC. Systemic Response to Infection Induces Long-Term Cognitive Decline: Neuroinflammation and Oxidative Stress as Therapeutical Targets. Front Neurosci. 2021;15:742158.
17. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306–16.
18. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023;21(3):133–46.1.
19. Tabacof L, Tosto-Mancuso J, Wood J, Cortes M, Kontorovich A, McCarthy D, et al. Post-acute COVID-19 Syndrome Negatively Impacts Physical Function, Cognitive Function, Health-Related Quality of Life, and Participation. Am J Phys Med Rehabil. 2022;101(1):48–52.
20. Becker JH, Vannorsdall TD, Weisenbach SL. Evaluation of Post–COVID-19 Cognitive Dysfunction: Recommendations for Researchers. JAMA Psychiatry. 2023;80(11):1085–6.
21. Wood GK. COVID-19 Clinical Neuroscience Study: Cognition Analysis. 2022 May 9 [cited 2023 Dec 7]; Available from: https://osf.io/fgyhb
22. 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):e192–7.
23. Gaetani L, Blennow K, Calabresi P, Filippo MD, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry. 2019;90(8):870–81.
24. Zwirner J, Lier J, Franke H, Hammer N, Matschke J, Trautz F, et al. GFAP positivity in neurons following traumatic brain injuries. Int J Legal Med. 2021;135(6):2323–33.
25. Kanberg N, Ashton NJ, Andersson LM, Yilmaz A, Lindh M, Nilsson S, et al. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. Neurology. 2020;95(12):e1754–9.

26. Dunai C, Michael BD, Needham EJ, Tharmaratnam K, Williams R, Huang Y, et al. Para-infectious brain injury in COVID-19 persists at follow-up despite attenuated cytokine and autoantibody responses. Nat Commun. 2023;14(1):8487.
27. Taquet M, Skorniewska Z, Hampshire A, Chalmers JD, Ho LP, Horsley A, et al. Acute blood biomarker profiles predict cognitive deficits 6 and 12 months after COVID-19 hospitalization. Nat Med. 2023;29(10):2498–508.
28. Grundmann A, Wu C, Hardwick M, Baillie JK, Openshaw PJM, Semple MG, et al. Fewer COVID-19 Neurological Complications with Dexamethasone and Remdesivir. Ann Neurol. 2023;93(1):88–102.
29. Verberk IMW, Laarhuis MB, Bosch KA van den, Ebenau JL, Leeuwenstijn M van, Prins ND, et al. Serum markers glial fibrillary acidic protein and neurofilament light for prognosis and monitoring in cognitively normal older people: a prospective memory clinic-based cohort study. The Lancet Healthy Longevity. 2021;2(2):e87–95.
30. Rolls ET. The cingulate cortex and limbic systems for emotion, action, and memory. Brain Struct Funct. 2019;224(9):3001–18.
31. Holmes SE, Hinz R, Conen S, Gregory CJ, Matthews JC, Anton-Rodriguez JM, et al. Elevated Translocator Protein in Anterior Cingulate in Major Depression and a Role for Inflammation in Suicidal Thinking: A Positron Emission Tomography Study. Biological Psychiatry. 2018;83(1):61–9.
32. Bergfield KL, Hanson KD, Chen K, Teipel SJ, Hampel H, Rapoport SI, et al. Age-related networks of regional covariance in MRI gray matter: reproducible multivariate patterns in healthy aging. Neuroimage. 2010;49(2):1750–9.
33. Salat D, Lee S, van der Kouwe A, Greve D, Fischl B, Rosas H. Age-Associated Alterations in Cortical Gray and White Matter Signal Intensity and Gray to White Matter Contrast. Neuroimage. 2009;48(1):21–8.
34. Krogseth M, Davis D, Jackson TA, Zetterberg H, Watne LO, Lindberg M, et al. Delirium, neurofilament light chain, and progressive cognitive impairment: analysis of a prospective Norwegian population-based cohort. The Lancet Healthy Longevity. 2023;4(8):e399–408.
35. Cruz-Gomez ÁJ, Forero L, Lozano-Soto E, Cano-Cano F, Sanmartino F, Rashid-López R, et al. Cortical Thickness and Serum NfL Explain Cognitive Dysfunction in Newly Diagnosed Patients With Multiple Sclerosis. Neurol Neuroimmunol Neuroinflamm. 2021;8(6):e1074.
36. Jahn N, Sinke C, Kayali Ö, Krug S, Leichter E, Peschel S, et al. Neural correlates of the attention training technique as used in metacognitive therapy - A randomized sham-controlled fMRI study in healthy volunteers. Front Psychol. 2023;14:1084022.
37. Alfaro-Almagro F, Jenkinson M, Bangerter NK, Andersson JLR, Griffanti L, Douaud G, et al. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage. 2018;166:400–24.
38. Alfaro-Almagro F, McCarthy P, Afyouni S, Andersson JLR, Bastiani M, Miller KL, et al. Confound modelling in UK Biobank brain imaging. Neuroimage. 2021;224:117002.
39. Duff E, Zelaya F, Almagro FA, Miller KL, Martin N, Nichols TE, et al. Reliability of multi-site UK Biobank MRI brain phenotypes for the assessment of neuropsychiatric complications of SARS-CoV-2 infection: The COVID-CNS travelling heads study. PLoS One. 2022;17(9):e0273704.
40. Marshall JC, Murthy S, Diaz J, Adhikari NK, Angus DC, Arabi YM, et al. A minimal common outcome measure set for COVID-19 clinical research. The Lancet Infectious Diseases. 2020;20(8):e192–7.
41. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95.
42. Lisibach A, Benelli V, Ceppi MG, Waldner-Knogler K, Csajka C, Lutters M. Quality of anticholinergic burden scales and their impact on clinical outcomes: a systematic review. Eur J Clin Pharmacol. 2021;77(2):147–62.

43. Cheetham NJ, Penfold R, Giunchiglia V, Bowyer V, Sudre CH, Canas LS, et al. The effects of COVID-19 on cognitive performance in a community-based cohort: a COVID symptom study biobank prospective cohort study. eClinicalMedicine. 2023;62:102086.
44. Del Giovane M, Trender WR, Bălăeţ M, Mallas EJ, Jolly AE, Bourke NJ, et al. Computerised cognitive assessment in patients with traumatic brain injury: an observational study of feasibility and sensitivity relative to established clinical scales. eClinicalMedicine. 2023;59:101980.
45. Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, et al. Classifying neurocognitive disorders: the DSM-5 approach. Nat Rev Neurol. 2014;10(11):634–42.
46. Michael BD, Dunai C, Needham EJ, Tharmaratnam K, Williams R, Huang Y, et al. Para-infectious brain injury in COVID-19 persists at follow-up despite attenuated cytokine and autoantibody responses. Nat Commun. 2023;14(1):8487.
47. Aminoff EM, Kveraga K, Bar M. The role of the parahippocampal cortex in cognition. Trends Cogn Sci. 2013;17(8):379–90.
48. Kas A, Soret M, Pyatigoskaya N, Habert MO, Hesters A, Le Guennec L, et al. The cerebral network of COVID-19-related encephalopathy: a longitudinal voxel-based 18F-FDG-PET study. Eur J Nucl Med Mol Imaging. 2021;48(8):2543–57.
49. Jobson DD, Hase Y, Clarkson AN, Kalaria RN. The role of the medial prefrontal cortex in cognition, ageing and dementia. Brain Commun. 2021;3(3):fcab125.
50. Cameron S. Carter, Matthew M. Botvinick, Jonathan D. Cohen. The Contribution of the Anterior Cingulate Cortex to Executive Processes in Cognition. Reviews in the Neurosciences. 1999;10(1):49–58.
51. Hosp JA, Dressing A, Blazhenets G, Bormann T, Rau A, Schwabenland M, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. Brain. 2021;awab009.
52. Elliott LT, Sharp K, Alfaro-Almagro F, Shi S, Miller KL, Douaud G, et al. Genome-wide association studies of brain imaging phenotypes in UK Biobank. Nature. 2018;562(7726):210–6.
53. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. Journal of Psychosomatic Research. 1993;37(2):147–53.
54. Xia M, Wang J, He Y. BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics. PLoS One. 2013;8(7):e68910.

Tables

Table 1: Demographics of cohort, comparing NeuroCOVID and COVID groups.

Characteristic	Overall, N = 351[1]	NeuroCOVID, N = 190[1]	COVID, N = 161[1]	p-value[2]
Age (years)	54 (44, 63)	54 (43, 63)	54 (44, 62)	>0.9
Sex				0.061
Female	149 (42%)	72 (38%)	77 (48%)	
Male	202 (58%)	118 (62%)	84 (52%)	
First language				0.4
English	307 (87%)	169 (89%)	138 (86%)	
Other	44 (13%)	21 (11%)	23 (14%)	
Level of education				0.022
Degree	166 (47%)	83 (44%)	83 (52%)	
School, vocational	158 (45%)	97 (51%)	61 (38%)	
None of the above	27 (7.7%)	10 (5.3%)	17 (11%)	
Pre-morbid Clinical Frailty Scale				0.013
Managing well (1-3)	261 (91%)	137 (87%)	124 (96%)	
Mild (4-5)	23 (8.0%)	18 (11%)	5 (3.9%)	
Moderate-severe (6-8)	3 (1.0%)	3 (1.9%)	0 (0%)	
Unknown	64	32	32	
WHO COVID-19 Severity				<0.001
Ambulatory mild disease	84 (27%)	61 (39%)	23 (15%)	
Hospitalised: moderate	138 (44%)	47 (30%)	91 (59%)	
Hospitalised: severe	89 (29%)	49 (31%)	40 (26%)	
Unknown	40	33	7	
Days since admission	384 (155, 574)	341 (179, 463)	473 (138, 728)	0.005
Unknown	41	32	9	
Admission date				0.026
01/03/2020 – 01/09/2020	93 (29%)	49 (28%)	44 (30%)	
01/09/2020 – 01/03/2021	107 (33%)	64 (37%)	43 (29%)	
01/03/2021 – 01/09/2021	42 (13%)	28 (16%)	14 (9.5%)	
01/09/2021 – 01/03/2022	61 (19%)	23 (13%)	38 (26%)	
01/03/2022 - 01/09/2022	17 (5.3%)	8 (4.7%)	9 (6.1%)	
Unknown	31	18	13	
Prior COVID-19 vaccination	57 (19%)	31 (20%)	26 (18%)	0.7
Unknown	57	37	20	

Acute steroid treatment	148 (48%)	72 (45%)	76 (52%)	0.2
Unknown	45	29	16	
Memory concerns	164 (47%)	98 (52%)	66 (41%)	0.048
Unknown	2	1	1	
PHQ-9 score	5.0 (2.0, 10.0)	6.0 (2.0, 10.0)	4.0 (1.0, 9.5)	0.042
Unknown	36	18	18	
GAD-7 score	3.0 (0.0, 8.0)	3.0 (0.5, 8.0)	2.5 (0.0, 6.0)	0.13
Unknown	30	15	15	
PCL-5 score	10 (2, 22)	12 (4, 24)	6 (1, 19)	0.002
Unknown	99	49	50	
Cognitron Global Score	-0.92 (-1.83, -0.26)	-1.11 (-2.00, -0.35)	-0.83 (-1.70, -0.19)	0.063
Cognitron Accuracy	-0.89 (-1.58, -0.21)	-1.04 (-1.67, -0.29)	-0.75 (-1.53, -0.09)	0.050
Cognitron RT	0.61 (-0.05, 1.54)	0.70 (-0.04, 1.78)	0.50 (-0.06, 1.39)	0.11
[1] Median (IQR); n (%)				
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test				

Table 2: Univariate associations, clinical linear regression model and complete linear regression models for Global DfE (GDfE) Score in NeuroCOVID and COVID groups. All regression models include interaction terms for Admission date:Days since admission and COVID-19 vaccination:Age.* p < 0.05, **p < 0.01, ***p < 0.001. +GDfE represents how an individual performs compared to what would be expected based upon their age, sex, first language and level of education.++model contains additional interaction term Steroid treatment:Admission date.

Variable	NeuroCOVID			COVID		
	Univariate+	Clinical model	Clinical, imaging and biomarkers	Univariate+	Clinical model	Clinical, imaging and biomarkers++
	Coefficient (SE)	Multivariate estimate (SE) n= 108	Multivariate estimate (SE) n= 72	Coefficient (SE)	Multivariate estimate (SE) n= 96	Multivariate estimate (SE) n= 94
CLINICAL PARAMETERS						
Age (years)	-0.0038 (0.0072)	-0.014 (0.012)	-0.025 (0.012)*	-0.012 (0.0074)	0.013 (0.012)	0.019 (0.013)
Level of education						
Degree	0.76 (0.47)			0.75 (0.31)*	0.21 (0.44)	
School, vocational	0.36 (0.46)			0.11 (0.32)	-0.53 (0.40)	
None of above (ref)						
Clinical Frailty Scale						
Mild (4-5)	-0.24 (0.34)			-0.18 (0.56)		
Moderate-severe (6-8)	1.043 (0.79)			- - -		
Admission date						
01/03/2020-01/09/2020	-0.017 (0.52)	1.14 (1.29)	2.01 (1.16)	-0.07 (0.43)	-1.73 (1.32)	-0.49 (0.76)
01/09/2020-01/03/2021	-0.91(0.51)	-0.24 (0.93)	1.50 (1.01)	-0.62 (0.44)	-1.04 (0.74)	-1.12 (0.49)*
01/03/2021-01/09/2021	-0.57 (0.55)	-1.38 (0.93)	-2.21 (1.10)*	-0.29 (0.51)	0.03 (0.73)	0.054 (0.54)
01/09/2021-01/03/2022 (ref)	-0.37 (0.56)	0.53 (1.72)	0.97 (1.40)	-0.18 (0.44)	-1.34 (1.02)	0.38 (0.66)
01/03/2022-01/09/2022						
Days since COVID-19	0.0011 (0.0022)	-0.00030 (0.0020)	0.00085 (0.0017)	0.0017 (0.0026)	0.0018 (0.0016)	-0.00066 (0.0012)
WHO COVID-19 Severity						
Moderate	-0.16 (0.28)			-0.81(0.28)	-0.89(0.45)	-1.04 (0.43)*
Severe	-0.26 (0.27)			-0.85(0.32)	-0.89(0.48)	-0.93 (0.48)
Mild (ref)						

COVID-19 vaccination	-0.21 (0.30)	0.094 (1.58)		0.24 (0.26)	2.05(1.23)	1.18 (1.26)
Diagnostic group				-		
Cerebrovascular	-0.39 (0.32)	-0.32 (0.48)				
Encephalopathy	-0.84 (0.35)*	-0.59 (0.51)				
Inflammatory	-0.48 (0.38)	-0.35 (0.50)				
Neuropsychiatric	-0.057 (-0.057)	0.066 (0.44)				
Other	-0.31 (0.33)	-0.46 (0.47)				
Peripheral (ref)						
Pre-existing depression	-0.11 (0.29)			-0.064 (0.27)		
PHQ-9 score (/unit)	-0.054 (0.017) **	-0.056(0.023)*		-0.065 (0.017)***	-0.089(0.023) ***	-0.082 (0.024)***
GAD-7 (/unit)	-0.041 (0.021)			-0.073 (0.019)***		
PCL-5 (/unit)	-0.013 (0.0066)			-0.031 (0.0074) ***		
CFQ mental subscale	-0.047 (0.050)			-0.045 (0.053)		
CFQ physical subscale	-0.062 (0.022) **			-0.031 (0.024)		
Anticholinergic Burden Score	-0.22 (0.11) *	-0.24(0.14)	-0.27 (0.20)	-0.30 (0.17)		
Multimorbidity	-0.051 (0.073)			-0.16 (0.058)**	-0.17(0.082) *	-0.22 (0.084)*
Raised CRP	0.0026 (0.0021)			-0.00071 (0.0020)		
Raised WCC	-0.053 (0.032)			-0.0061 (0.034)		
Steroid treatment	-0.25 (0.22)			0.028 (0.20)	0.77(0.27) **	0.62 (0.45)
Subjective cognitive impairment	-0.47 (0.20)*			-0.78 (0.19) ***		
BRAIN INJURY MARKERS (pg/mL)						
Nfl-L	0.00063 (0.0012)			-0.0014 (0.0035)		
GFAP	0.00048 (0.00088)			-0.00041 (0.0015)		-0.0087 (0.0034)*

Tau	0.14 (0.09)		-0.11 (0.14)
UCH-L1	-0.0018 (0.0019)		-0.00029 (0.00031)
NEUROIMAGING			
Composite volume (Z score)	0.40 (0.15)*		0.25 (0.15)
Composite cortical thickness (Z score)	0.31 (0.19)		0.044 (0.19)
Anterior cingulate cortex volume	0.23 (0.078)**	0.17 (0.073)*	0.32 (0.10)**
Superior temporal gyrus volume	0.033 (0.016)*		0.0041 (0.012)
Insula volume	0.011 (0.0046)*		0.00086 (0.0034)
Superior temporal gyrus thickness	0.0023 (0.0068)		0.030 (0.018)
Orbitofrontal cortex thickness	0.22 (0.096)*		0.038 (0.070)

Figures

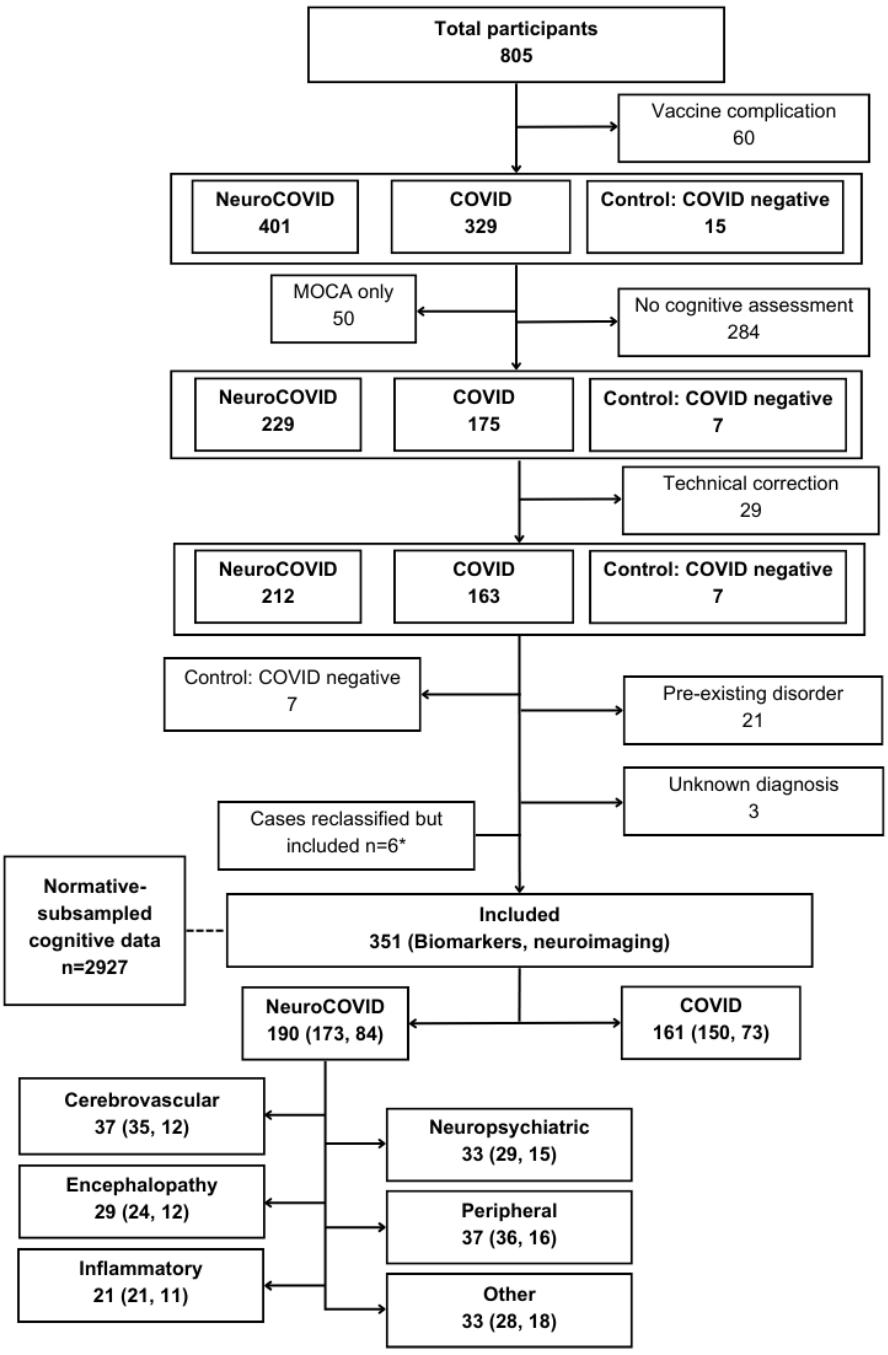

Figure 1

Flow diagram of patients included from the COVID-19 Clinical Neuroscience Study. Nationally at least 16,279 patients were screened of whom at least 2712 were eligible. Matched community data collected separately and held in a large normative database. 'Other' includes autonomic dysfunction (3), cerebral hypoxic injury (2), headache (6), headache and fatigue (2), hyperkinetic movement disorder (2), Parkinsonian movement disorder (2), seizures (7) and speech and sensory (1). MOCA: Montreal Cognitive Assessment.*Six patients with 'anosmia/ageusia' reclassified as COVID from NeuroCOVID.

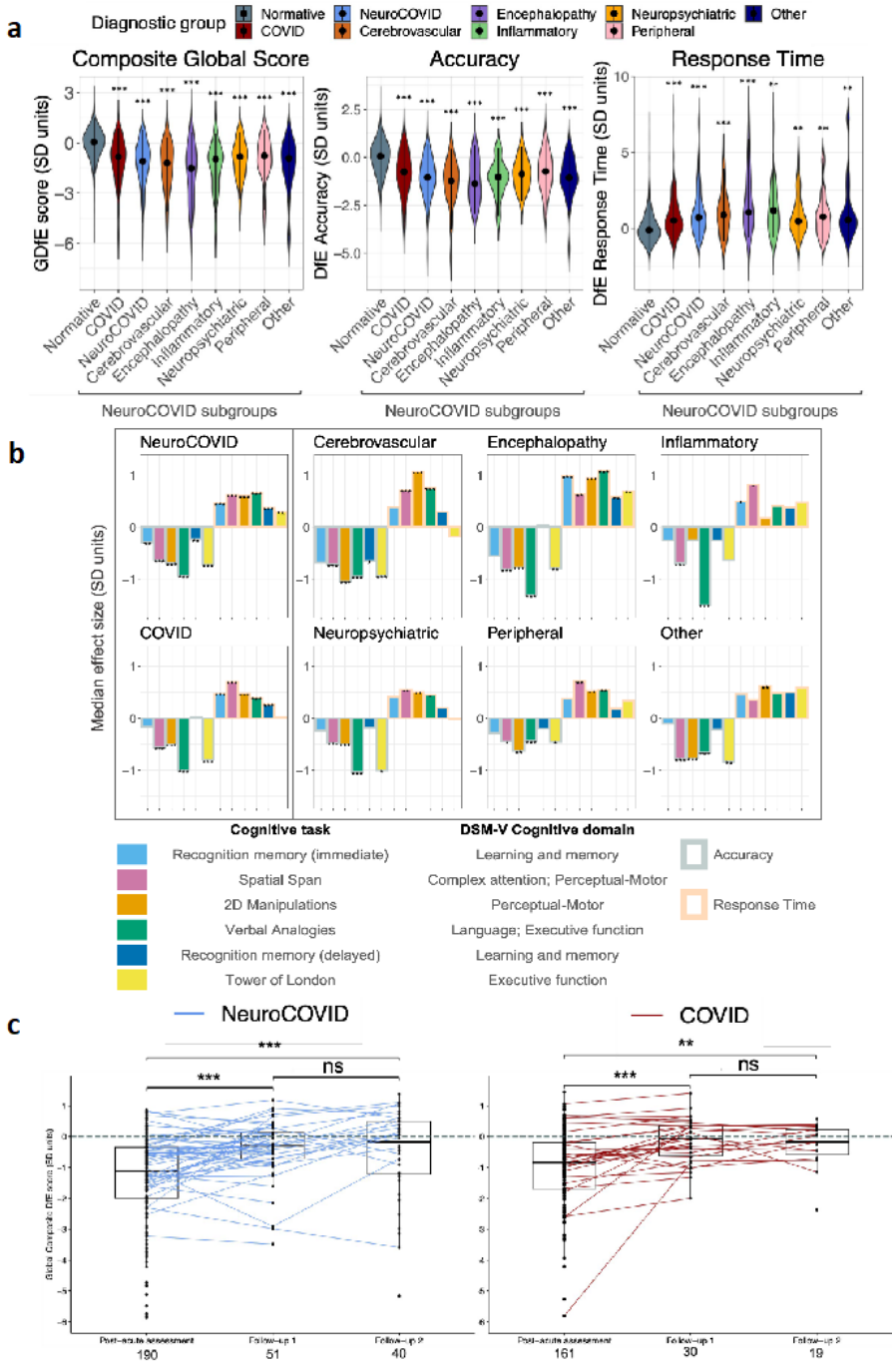

Figure 2

a: Violin plot of Deviation from Expected (DfE) Cognitron scores by diagnostic group including median (IQR)(black). b: Pattern of deficits by median Deviation from Expected accuracy and responsive time compared to matched community controls across six cognitive tasks. c: Recovery trajectories in NeuroCOVID and COVID patients following post-acute assessment. Black dot = single observation, lines connect paired observations.* $p < 0.05$, **$p < 0.01$, ***$p < 0.001$ two sided Mann Whitney U, adjusted for multiple comparisons based on false discovery rate approach in 2a and 2b. ns= non-significant.

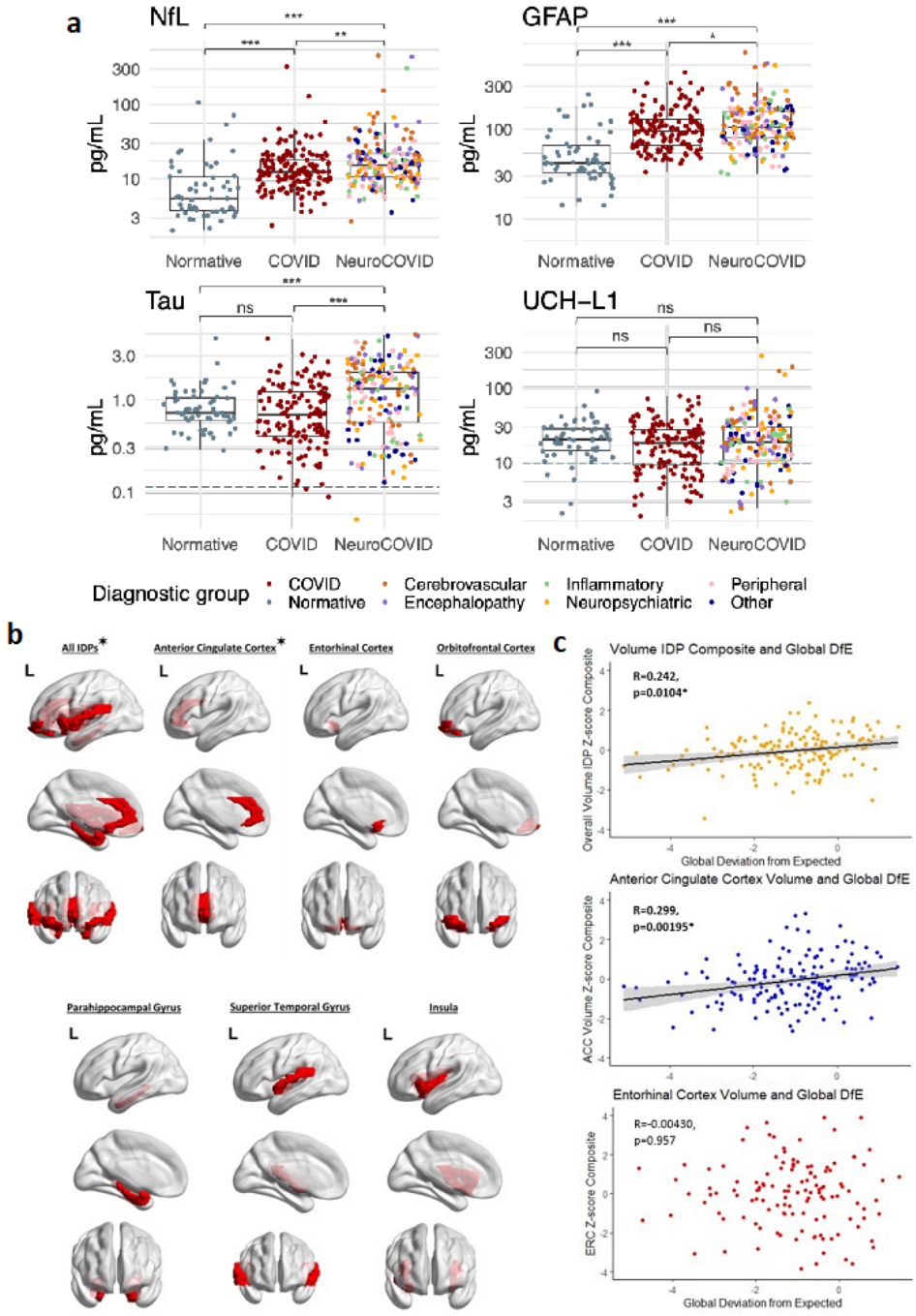

Figure 3

a: Brain injury markers in pg/mL by diagnostic group. Lower limit of quantification (LLOQ marked (dashed)) if included in scale. Normative values from n=60 healthy controls. * p < 0.05, **p < 0.01, ***p < 0.001, ns= non-significant. b: Brain regions represented by the image derived phenotypes (IDPs) utilised in analyses. These regions are parcellated as per the Desikan-Killiani cortical atlas. For each region and regions combined, IDP composites for thickness and volume were utilised. = IDP composites that have significant correlations with overall cognition (Supplementary Table 3). Created using Matlab and BrainNet Viewer (54). c: Scatter plots for IDP composite z-scores against global deviation from expected in the overall cohort, with trend line in black and 95% confidence interval in grey. Significance persisting after False Discovery Rate correction for multiple comparisons

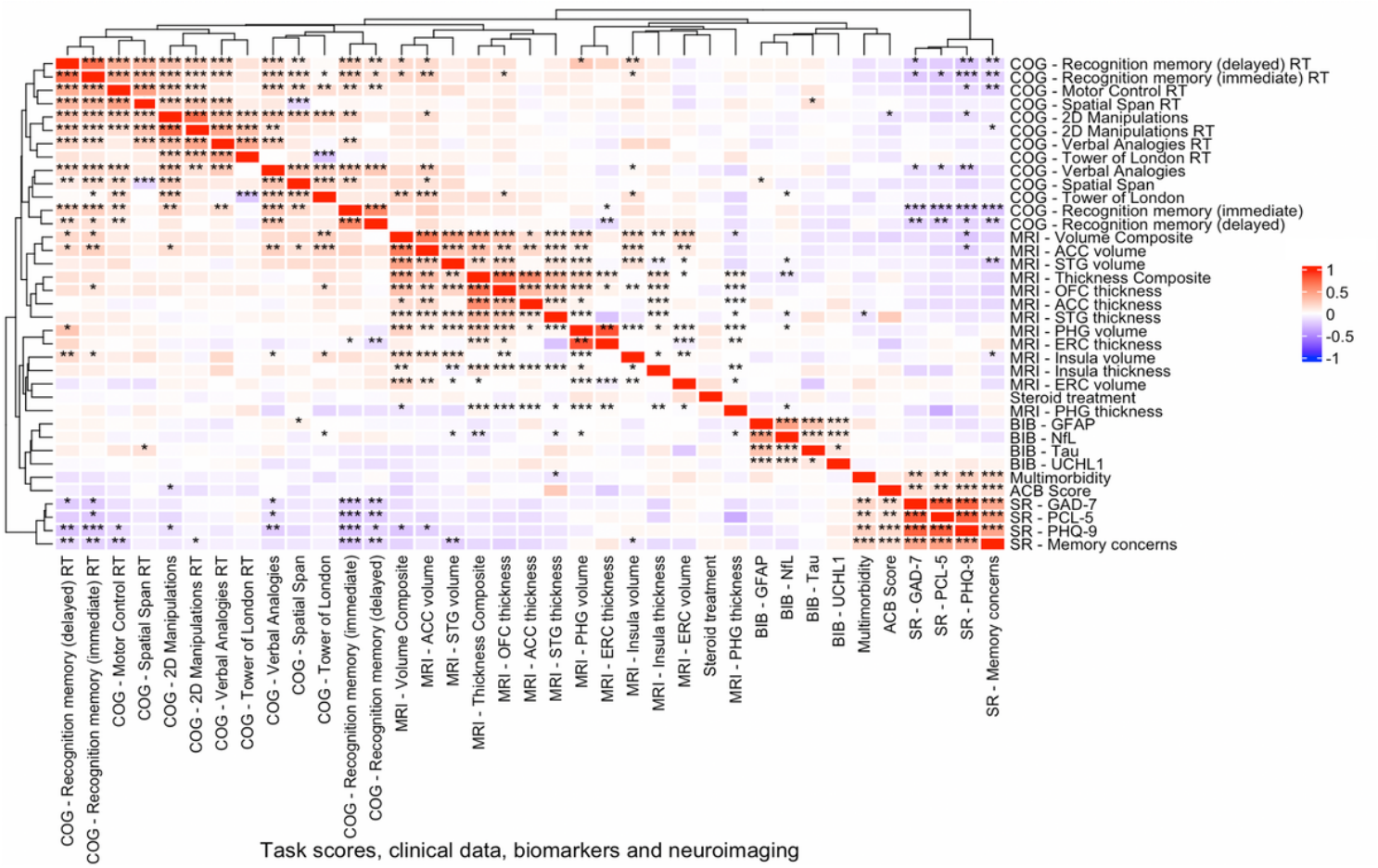

Figure 4

Heatmap and unsupervised cluster analysis in full cohort (n=351) of cognitive tasks shaded by correlation (Spearman), including cognition (accuracy and inverse RT), clinical variables, biomarkers and neuroimaging. * p < 0.05, **p < 0.01, ***p < 0.001 adjusted for multiple comparisons using false discovery rate approach. ACB= Anticholinergic burden, ACC = Anterior cingulate cortex, BIB = Brain injury marker, COG = Cognitive task, ERC = entorhinal cortex, MRI= Magnetic Resonance Imaging, OFC = orbitofrontal cortex, PHG = parahippocampal gyrus, RT= response time, SR = Self-report, STG = Superior temporal gyrus.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- COVIDCNSMembers21Dec2023.pdf
- Supplementarycovidcog.docx
- Extendeddata.docx