The Cognitive Sequalae of COVID-19 and Long COVID - The Inconspicuous Wound of the Pandemic

A Thesis Submitted for the Degree of Doctor of Philosophy

by

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Thesis Abstract

A novel disease named coronavirus disease 2019 (COVID-19) was discovered in the year 2019, and soon after declared a pandemic by the World Health Organization. Coronaviruses are neurotropic in nature and since the emergence of COVID-19 many studies have reported neuropsychological symptoms in infected individuals, including headaches, dizziness, seizures, depression, and also cognitive deficits. These symptoms can persist for many weeks to months and are commonly referred to as long COVID. This thesis, therefore, aimed to examine the neuropsychological impact of COVID-19, more specifically on cognitive function and psychological well-being cross-sectionally in a working-age sample, and in a sub-sample longitudinally. Furthermore, it explored the impact of long COVID on brain structures, again in a working-age sample.

Three empirical studies were conducted, study one was a behavioural study investigating the effects of COVID-19 on cognitive function (processing speed, attention, working memory, executive function, and memory), and the associations of physical and mental health (specifically, depression, anxiety, stress, and sleep) with cognitive function in adults (*N* = 222) from the general population. Study two involved a follow-up of the sample investigated in study one to determine the longitudinal impact of COVID-19 and long-COVID symptoms on cognitive function, mental health, and sleep. Study three used whole brain magnetic resonance imaging to examine the association of persistent COVID-19 symptoms with grey matter, white matter, cerebral spinal fluid and various subcortical brain volumes (accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus), and its association with cognitive function, mental health, and sleep in a working-age, general population sample (*N* = 43) of COVID-19 survivors.

The findings of study one showed significantly larger processing speed intra-individual variability, on average, in the COVID group, relative to the non-COVID group, with no significant difference observed in other cognitive variables. However, participants who required hospitalisation due to their diagnosis of COVID-19, relative to those who did not, showed poorer cognitive function in multiple domains, and total long-COVID symptom load was negatively associated with performance in all cognitive domains. In study two, a trend-

level improvement at the six-month follow-up was observed in processing speed intra-individual variability in the COVID group with no significant change in the non-COVID group. A significant reduction in total long-COVID symptom load occurred at follow-up, and this correlated with an improvement in executive function, especially in the non-hospitalised COVID group. However, cognitive disruption persisted in COVID group participants with a history of hospitalisation and/or long-COVID symptoms. In study three, total persistent COVID-19 symptom load was significantly associated with smaller putamen volume, multiple cognitive domains, mental health, and sleep quality (medium-to-large effect sizes). Smaller putamen volume was also correlated with a disruption in multiple cognitive domains and poorer sleep quality, though only the relationship between lower executive function and persistent COVID-19 symptom load was mediated by smaller putamen volume.

In conclusion, the findings showed a negative impact of COVID-19 on cognitive function, although to a lesser extent in this working-age sample than those reported earlier in older samples, and some improvement was visible after a six-month period. Hospitalisation history and long-COVID symptoms, however, were associated with wide-spread disruption in cognitive function and poor sleep quality. The disruption in cognitive function, in particular executive function, due to persistent COVID-19 symptoms seemed to be mediated by smaller putamen volume. These findings provide further insight into the relationship between COVID-19 and cognitive function, its effect on the brain, and the potential serious impact of hospitalisation history and long COVID on cognitive function and brain health. Overall, our findings suggest a need for longitudinal monitoring as well as remediation and support for those individuals who were hospitalised when acutely ill and/or have a diagnosis of long COVID.

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Dedicated to my Baa, Bapuji, Nanibaa & Nana - my loving grandparents.

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ACE2	Angiotensin Converting Enzyme 2
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BBB	Blood Brain Barrier
BMI	Body Mass Index
CNS	Central Nervous System
CoV/CoVs	Coronavirus/Coronaviruses
COVID-19	Coronavirus Disease 2019
CSF	Cerebral Spinal Fluid
DASS-21	The Depression, Anxiety and Stress Scale-21
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTI	Diffusion Tensor Imaging
EEG	Electroencephalogram
fMRI	Functional Magnetic Resonance Imaging
GM	Grey Matter
HCoV/HCoVs	Human Coronavirus/Human Coronaviruses
ICD-10	International Statistical Classification of Diseases and Related Health Problems - 10th Revision
ICU	Intensive Care Unit
ICV	Intracranial Volume
MCI	Mild Cognitive Impairment
MERS-CoV	Middle East Respiratory Syndrome
MRI	Magnetic Resonance Imaging
ms	Millisecond
MyCognition	MyCQ
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
PASC	Post-Acute Sequelae of COVID-19
PNS	Peripheral Nervous System
PSC	Persistent COVID-19 Symptoms
PSQI	Pittsburgh Sleep Quality Index
RA	Response Accuracy
RNS	Ribonucleic Acid
RT/RTs	Reaction Time/Reaction Times
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SF-36	Short Form Health Survey-36
SPSS	Statistical Package for Social Sciences
UK	United Kingdom
WHO	World Health Organization
WM	White Matter
α	Alpha
β	Beta
γ	Gamma
δ	Delta
η_p^2	Partial Eta Squared

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Chapter One: COVID-19, Its Origins and Clinical Manifestations

1.1 Chapter Aims and Overview

Human biology and behaviour, directly and indirectly, are known to be affected by viruses, and vice-versa (Sankaran & Weiss, 2021). This chapter begins with an overview of coronaviruses (CoVs), the origins and history of CoVs, and the different types of CoVs that can and have infected humans. The chapter then explores the impact and clinical manifestation of the most recent Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) infection, with a particular focus on the central nervous system (CNS) post infection. The final part of this chapter delves into the long-term impact of coronavirus disease 2019 (COVID-19), the long-term symptoms and the potential causes of these symptoms, with an emphasis on neuropsychological symptoms.

1.2 Coronaviruses – Origins and Aetiology

CoVs in animals have been documented since the 1930's, and human coronaviruses (HCoVs) were first identified in the early 1960's. CoVs are positive-sense ribonucleic acid (RNA) viruses with spikes on their surface that resemble crowns, hence aptly named corona- (crown) virus (Kahn & McIntosh, 2005; Singhal, 2020; Ye et al., 2020). CoVs have unique characteristics compared to other RNA viruses and two characteristics in particular that stand out: (1) they have larger genomes, and (2) they can replicate easily (Umakanthan et al., 2020). CoVs come from the Coronaviridae family (Coronavirinae sub-family), and they have 16 non-structural proteins and four structural proteins, namely envelope proteins (E), membrane proteins (M), nucleocapsid proteins (N), and spike proteins (S). It is these very spike proteins which facilitate the entry of the virus into the host cell. The CoVs spike protein includes a key receptor-binding domain, which is pivotal to the entry and infecting process (Hulswit et al., 2016; Li, 2012; Ye et al., 2020).

CoVs are generally categorised into four different genera: Alphacoronavirus (α), Betacoronavirus (β), Deltacoronavirus (δ), and Gammacoronavirus (γ) (Liu et al., 2020; Umakanthan et al., 2020). Although the exact origin of CoVs has been difficult to identify, it

has been noted that a vast majority of α- and β-coronaviruses come from bats and rodents, whereas most γ- and δ-coronaviruses gene sources come from birds (Liu et al., 2020). Moreover, CoVs are zoonotic in nature, this means they can spread from animals to humans. The transmission from animals to humans has been ongoing for numerous years and can happen directly (via contact with animals) and/or indirectly (e.g., food and/or environmental pathogens) (Haider et al., 2020; Hulswit et al., 2016; Ye et al., 2020). Once the virus has sufficiently adapted to the human host, transmission can also occur between humans (Docea et al., 2020). Although CoVs are highly contagious and zoonotic, not all CoVs are known to infect humans.

1.2.1 Human Coronaviruses

Of the four CoV genera, only two CoVs can infect humans (and mammals) and they are, α- and β-coronaviruses, δ- and γ-coronaviruses exclusively infect animals (in particular birds) (Docea et al., 2020; Wertheim et al., 2013). Combining both the α- and β-coronaviruses, a total of seven human CoVs have been known to infect humans, these are: 229E and NL63 from the α-coronavirus and OC43, HKU1, SARS-CoV, (Middle East Respiratory Syndrome) MERS-CoV and the most recently discovered SARS-CoV-2 from the β-coronavirus (Chen et al., 2020). The first four HCoVs (229E, NL63, OC43, and HKU1) are known to only present themselves with mild upper and/or lower respiratory infections, which have a similar symptomology to the common cold. However, over a span of 20 years, two extremely pathogenic and fatal CoVs have crossed from animals to humans, resulting in high levels of morbidity and mortality. These two CoVs are SARS- and MERS-CoV, and they have both resulted in pandemics (Baharoon & Memish, 2019; Chen et al., 2020; Docea et al., 2020; Liu et al., 2020).

1.2.1.1 SARS-CoV Pandemic

The first SARS-CoV pandemic occurred in the year 2002 in China's Guangdong province. It was the next major pandemic seen in the new century after the avian influenza pandemic (Piret & Boivin, 2021). The SARS-CoV virus spread rapidly and by mid-2003 it had spread to 30 different countries, with over 8000 cases and more than 770 deaths reported globally. These numbers

indicate an average fatality rate of 10% (Chen et al., 2020; Umakanthan et al., 2020; Ye et al., 2020). It is thought that the origins of the SARS-CoV pandemic were in the wet markets of China, where animals (wild and exotic) were kept in unsanitary, overcrowded conditions. It is believed this is where the virus jumped from animals, possibly civets, to humans. The spread of the virus has largely been attributed to the lack of knowledge and understanding about CoVs and infection control in general. The spread of the virus was also further facilitated by air travel, as infected individuals could travel without any restrictions (Cheng et al., 2007).

Individuals who were infected with SARS-CoV typically reported shortness of breath, fever, a new cough, muscle aches, and pains. Diarrhoea, sore throat, and runny nose were also symptoms associated with SARS-CoV but not as prevalent as the former symptoms (Peiris et al., 2003). A small minority of individuals also experienced severe and potentially life-threatening symptoms, requiring mechanical intervention and resulting in organ damage and failure (Ye et al., 2020). In addition to these respiratory and bodily symptoms, some people exhibited CNS symptoms. These have been widely documented through case studies, post-mortem analysis, and animal studies. A post-mortem study conducted on 18 patients after the SARS-CoV epidemic revealed that the SARS-CoV genome sequence was detected in the brain of eight patients who had been infected with SARS-CoV, particularly in the hypothalamus (Gu et al., 2005). Moreover, a case study of a 39-year-old male from China described the patient experiencing delirium and dysphoria almost a month after testing positive. Brain scans of the patients also revealed necrosis, swelling of the brain (referred to as edema), and ischemia (Xu et al., 2005).

1.2.1.2 MERS-CoV Epidemic

Nearly a decade later, in 2012, the MERS-CoV outbreak began in the Middle East, Saudi Arabia. Although most of the cases were confined to the Middle East, some cases were also reported in European countries (Ye et al., 2020). Cases of MERS-CoV that have been reported outside of the Middle East have predominantly been put down to air travel (Chen et al., 2020). Unlike the SARS-CoV outbreak which seemingly ended, MERS-CoV is still spreading, although not exponentially. As of April 2024, a total of 2613 confirmed cases of MERS-CoV and 941 deaths associated with the virus have been reported. The fatality rate of MERS-CoV at present

is around 36%, relative to SARS-CoV, this is much higher (World Health Organization [WHO], 2024a). MERS-CoV is also zoonotic, and it is believed to have originated from bats, before infecting the intermediate hosts, the dromedary camels. Although MERS-CoV was only identified in humans in 2012, antibodies to the virus have been spotted in dromedary camels since the early 1990's (Baharoon & Memish, 2019; Umakanthan et al., 2020).

The clinical manifestation of MERS-CoV also includes respiratory difficulties and acute pneumonia, similar to SARS-CoV, but it can also affect other organs and can cause acute renal failure in infected patients (Ye et al., 2020). The less severe but more common symptoms include fever, chills, cough, and shortness of breath. Some patients have also reported gastrointestinal symptoms, such as vomiting, diarrhoea, and abdominal pain. Severe disease could result in multiple organ failure and even mortality, which in comparison to SARS-CoV is much higher in MERS-CoV (Baharoon & Memish, 2019; Ye et al., 2020). Similar to SARS-CoV, neurological symptoms have also been reported in MERS-CoV patients. Case studies conducted in the year 2014 on three patients post infection showed that they all experienced some form of neurological symptom, including confusion, ataxia, and coma (Arabi et al., 2015). To ensure these symptoms were not related to pre-existing conditions and/or other comorbidities, magnetic resonance imaging (MRI) of the brain was conducted on these three patients. The scans showed lesions in multiple areas of the brain, including frontal, parietal and temporal lobes, the cerebellum, the basal ganglia and in the WM. However, whether this could solely be attributed to MERS-CoV was in question as no viral particles were found in the cerebral spinal fluid (CSF) or the brain tissue (Arabi et al., 2015). However, animal studies examining the clinical manifestation of MERS-CoV have shown the virus to cross and damage the blood brain barrier (BBB), in turn causing damage to brain tissue (Jiang et al., 2021).

1.2.1.3 SARS-CoV-2 Pandemic

In 2019, a new disease named COVID-19 was discovered in Wuhan, Hubei province, China. This disease originated from the virus belonging to the second group of β-coronavirus which contains Severe Acute Respiratory Syndrome Coronavirus, and thus named SARS-CoV-2 in full (Ciotti et al., 2020; Lai et al., 2020; Mao & Jin, 2020). As of May 2024, there have been over 775 million reported cases globally, with over seven million reported deaths worldwide. The

United Kingdom (UK) itself has over 24 million reported cases and 232,112 deaths (WHO, 2024b). The number of individuals with a current or past diagnosis of COVID-19 is much higher compared to the last SARS- and MERS-CoV outbreaks. These statistics, however, may not be a true representation of the prevalence and could in fact be an undercount. Due to numerous barriers experienced during the peak of the pandemic (e.g., the lack of testing during the early days) and the fact that many countries have now abolished the requirement for compulsory testing, has naturally resulted in a gap in the knowledge and an inaccuracy in the statistical prevalence (Alvarez et al., 2023). In addition, fatality and mortality rates for COVID-19 have also been difficult to calculate across the world. Factors such as age, sex, ethnicity, medical comorbidities, variants, and vaccines all played a role in the rate of both severity and mortality worldwide (Khunti et al., 2020; Lin et al., 2021; Pareek et al., 2020). Moreover, some countries have found it difficult to estimate the number of excess deaths in their given population, primarily due to a lack of sufficient testing and formal death certificates. With the pandemic still ongoing and the lack of accuracy in confirmed diagnosis and mortality worldwide, it has been difficult to determine the exact fatality and mortality rate for COVID-19 (Taylor, 2022).

Contrary to the first two CoV outbreaks, the origin of SARS-CoV-2 has been under debate for some time. Since its emergence two theories have emerged and divided the world. The more controversial theory suggests a laboratory leak occurred, resulting in the accidental and/or deliberate release of the virus in the community (Looi, 2023a). This theory has been propagated widely through the use of the internet and social media (Frutos et al., 2022), which were not influential tools during the SARS-CoV and MERS-CoV outbreaks. Although this theory has gained a significant amount of traction, the WHO stated the laboratory leak explanation to be “extremely unlikely” after a 12-day investigation in Wuhan. Their conclusion was based on the fact that the viruses held in the Wuhan laboratory were genetically dissimilar to that of the SARS-CoV-2 genetic code (Dyer, 2021). The second, more probable theory, suggests that SARS-CoV-2 also emerged from a wet market in Wuhan, similar to SARS-CoV (Looi, 2023a). During the start of the COVID-19 epidemic in Wuhan, the epicentre was the Huanan market which sells live wild animal stock. Moreover, two of the first documented cases were directly related to the Huanan market (Frutos et al., 2022; Holmes et al., 2021). Although there is still speculation with regards to the exact origin of COVID-19, the consensus

amongst the scientific community remains towards SARS-CoV-2 spreading from an animal to a human, with the most probable origin being from a wet market (Looi, 2023a).

Initial symptoms of COVID-19 have varied since the start of the pandemic, with some individuals remaining completely asymptomatic and others experiencing a range of symptoms varying in severity from mild to severe/fatal (Umakanthan et al., 2020). During the early days of the pandemic, COVID-19 symptoms were reported to be a temperature, a new continuous cough, and a loss of taste and/or smell. However, as the pandemic continued and new variants emerged, the symptoms reported by infected individuals changed gradually. In early 2022, the National Health Service (NHS) along with the UK government amended the symptoms listed from four to 12 (NHS, 2023a), which aligned with the symptoms that were being reported by infected individuals, as seen below in Table 1.1. Moreover, symptom severity, similar to mortality, also depended on numerous factors such as pre-existing medical conditions, co-morbidities, age, sex, ethnicity, the different variants, and vaccine status (Zhang et al., 2022). Similar to the previous HCoV outbreaks, COVID-19 has also demonstrated neurological symptoms in infected patients, both during and post infection. Neurological symptoms exhibited by patients have ranged from impaired consciousness, seizures, headaches, strokes, and other neuropsychiatric and acute cerebrovascular diseases (Heneka et al., 2020; Mao & Jin, 2020). These neurological and neuropsychiatric manifestations in COVID-19 patients raises queries on the neuroinvasive potential of SARS-CoV-2.

1.3 COVID-19 and the Nervous System

During the early stages of the pandemic, the primary focus was on the mortality and morbidity of COVID-19. However, as time went on, the focus broadened to understand the neuropsychological manifestation of COVID-19 (Nakamura et al., 2021). Neuropsychological complications have been observed in two ways, firstly alongside a COVID-19 diagnosis, known as para-infection and secondly, through complications and symptoms exhibited post an infection and recovery, referred to as post-infection (Taga & Lauria, 2022). The extent to which SARS-CoV-2 infects the nervous system and results in neurological symptoms will be explored in further sections.

Table 1.1

List of initial and updated COVID-19 symptoms

Initial list of COVID-19 symptoms	Updated list of COVID-19 symptoms
Temperature	High temperature or shivering
New continuous cough	New continuous cough
Loss of taste	Loss or change to sense of taste and/or smell
Loss of smell	Shortness of breath
	Exhaustion/fatigue
	Body aches
	Headache
	Sore throat
	Blocked or runny nose
	Loss of appetite
	Diarrhoea
	Feeling and/or being sick

Note. Updated list is accurate as of March 2023 (NHS, 2023).

1.3.1 Neuroinvasive Potential

Out of the seven HCoVs, only three have previously been identified as neuroinvasive and neurotropic in nature. These are: 229E, OC43, and SARS-CoV (Pezzini & Padovani, 2020). The three CoV outbreaks that have been witnessed in the last century show the pathogenicity and transmissibility of these viruses (Y. Yan et al., 2020). However, prior to the emergence of SARS-CoV, there was limited knowledge on the neuroinvasive potential of CoVs. Many put this down to the fact that the general consensus for many years was that CoVs only resulted in a common cold, and it was believed that CoVs primarily only caused respiratory problems (Li et al., 2020).

Recent literature, however, has demonstrated the neuroinvasive potential of SARS-CoV-2 which can be divided into two categories: (1) peripheral nervous system (PNS) manifestation, which includes symptoms such as changes and/or impairment in taste and smell, nerve pain, myalgia, myopathy, Guillain-Barré Syndrome as well as other sensory problems, and (2) CNS manifestation, which can include but are not limited to symptoms such as headaches, cognitive deficits, depression, anxiety, stroke, and haemorrhages (Andalib et al., 2021; Ellul et al., 2020; Mao et al., 2020; Wildwing & Holt, 2021).

1.3.2 Peripheral Nervous System Manifestations

Since the start of the COVID-19 pandemic, evidence has been accumulating showing the neuroinvasive potential of SARS-CoV-2 in the PNS. The first probable evidence of COVID-19 induced PNS manifestation comes from a retrospective study conducted on 214 hospitalised patients with COVID-19 in China (Mao et al., 2020). Of the 214 patients, 36% of the sample exhibited PNS symptoms. The most prevalent PNS symptoms amongst this group was impaired taste and smell (Mao et al., 2020). Dysfunction in taste and smell was also noted by another European study which measured these functions in 417 patients who had mild-to-moderate COVID-19 symptoms. Over 88% of patients in this study reported a dysfunction in their sense of taste and more than 85% of patients reported either a complete loss or distorted sense of smell (Lechien et al., 2020). It is important to note that the percentage of loss of taste and/or taste reported in this study could be high due to patients subjectively reporting their symptoms. Moreover, no specific clinical examinations took place to quantify the subjective responses.

As noted earlier, severe PNS complications and symptoms, such as, Guillain-Barré Syndrome have also been observed in patients. Guillain-Barré Syndrome is a disorder in which the body's immune system starts attacking the PNS, in turn damaging nerves and muscles (Andalib et al., 2021; Khatoon et al., 2022). The first reported case of Guillain-Barré Syndrome was in Wuhan in January 2020. The patient in question did not exhibit the typical COVID-19 symptoms and only presented with weakness in their limbs (Zhao et al., 2020). From the report of this first case up until date, many potential cases correlating with COVID-19 have been recorded across the world. A large systematic review and meta-analysis (Palaiodimou et al., 2021) on 136,746 COVID-19 patients between December 2019 and December 2020 found a pooled prevalence of 0.15% for Guillain-Barré Syndrome. This percentage is quite small but still above the global incidence rate of 0.02% in the general population (Palaiodimou et al., 2021; Sejvar et al., 2011). A retrospective epidemiological review and cohort study conducted by Keddie et al. (2021) in the UK, however, found that the prevalence of Guillain-Barré Syndrome was lower in the first few months of the pandemic relative to the general incidence rate prior to the pandemic (Keddie et al., 2021). Therefore, further investigations are needed to confirm the link between COVID-19, Guillain-Barré Syndrome and the general PNS manifestation.

Another PNS manifestation reported in the literature after a COVID-19 diagnosis involves neuromuscular difficulties such as myopathy. Myopathy and/or critical illness myopathy is a disorder affecting metabolism and the skeletal muscle structure. Signs and symptoms usually include muscles weakness and pain (Nagy & Veerapaneni, 2021). Many singular case studies have observed a correlation between a positive COVID-19 diagnosis and critical illness myopathy (Bagnato et al., 2020; Dodig et al., 2022; Tankisi et al., 2020). Post-mortem investigations in COVID-19 non-survivors also showed inflammatory signs in skeletal muscles, as well as myositis (Aschman et al., 2021). Nearly all of the patients described in these case studies and post-mortem investigations had severe COVID-19 and needed hospitalisation, and many of them were in the Intensive Care Unit (ICU) and needed intubating. It could, therefore, be argued that the PNS neuromuscular trouble faced by patients could be as a result of hospitalisation and not the virus itself. There is clearly evidence showing a correlation between COVID-19 and critical illness myopathy, but whether this is causal and a direct action of the virus is in question. It seems more likely that critical illness myopathy is an indirect action of COVID-19 and predominately affects severely ill patients (Bagnato et al., 2020).

Overall, PNS symptoms during and following a COVID-19 diagnosis are difficult to identify and reach a formal diagnosis as electrophysiological investigations are needed to ascertain a diagnosis (Frithiof et al., 2021), and at present, many studies lack this very aspect. This may explain why the prevalence rate for PNS symptoms is low as they are generally less frequently reported and investigated.

1.3.3 Central Nervous System Manifestations

CNS symptoms of SARS-CoV-2 infection have also been widely reported. Mao et al. (2020) reported on CNS symptoms as well as PNS symptoms in their research. They found that, out of 78 patients, 25% reported neurological symptoms related to the CNS post a confirmed COVID-19 diagnosis. CNS symptoms that were experienced by patients included dizziness and headaches. Interestingly, some patients exhibited symptoms such as headaches prior to a confirmed diagnosis of COVID-19 (Mao et al., 2020). Many similar studies followed suit around the world, investigating the neurological symptoms exhibited in hospitalised patients post a confirmed COVID-19 diagnosis and many of them found overlapping results with

headaches, dizziness, and impaired consciousness all accompanying a COVID-19 diagnosis (Altunisik et al., 2021; Chou et al., 2021; Romero-Sánchez et al., 2020).

A systematic review (Chen et al., 2021) looking at the neurological symptoms and complications post a COVID-19 diagnosis also supported the above findings. Headaches and dizziness were detected in 64 different studies, including a total of 18,682 COVID-19 patients. Within these studies headache had a prevalence rate of between 2% and 66.1% and dizziness, ranged between 2.5% and 21.4%. In all 64 of these studies, patients who had mild to moderate COVID-19 reported experiencing headaches and dizziness more frequently in comparison to the severely and critically ill. In addition, nine studies consisting in total of 2890 COVID-19 patients reported some form of impaired consciousness, including agitation and confusion. Prevalence rates of impaired consciousness ranged vastly between studies, ranging from 1.4% to 69% (Chen et al., 2021). Although this evidence provides the scientific community with an insight in to the impact of COVID-19 in the CNS, most of these reports are subjective. To counter this, clinical examinations and post-mortem studies have also been conducted to examine the extent to which COVID-19 can impact an individual's neurological functioning in the CNS.

Post-mortem examinations have revealed cerebrovascular abnormalities in the brains of COVID-19 non-survivors, in particular evidence of strokes and haemorrhages (Martin et al., 2022). In addition, Moriguchi et al. (2020) found SARS-CoV-2 RNA in the CSF of an infected patient. This patient was diagnosed with meningitis and convulsive encephalitis. Notably, this patient tested negative for SARS-CoV-2 via the nasal swab, but spinal fluid specimens came back positive. Further examination of this patient revealed inflammation of the hippocampus in the brain (Moriguchi et al., 2020). As serious as these neurological manifestations can be, due consideration should also be given to the fact that it is extremely difficult to attribute these severe neurological manifestations solely to a SARS-CoV-2 infection, when in fact they could simply be a by-product of the infection. The exact mechanism and extent of the neuroinvasive potential of in the CNS remains vague (Reza-Zaldívar et al., 2021).

1.4 COVID-19 and the Central Nervous System Infiltration

Comparing the prevalence of the COVID-19 induced PNS and CNS manifestation, it is clear that the CNS manifestations are reported in a greater frequency relative to PNS related COVID-19 manifestations. Based upon this, it is important to understand how the CNS is infiltrated by SARS-CoV-2. Generally, the CNS has multiple layers of protection. However, some viruses such as CoVs, can penetrate these barriers and infect both glial cells and neurons (Reza-Zaldívar et al., 2021). A virus needs a host cell to infect the body and also reproduce and replicate itself (Ni et al., 2020). A concept which is gaining traction revolves around SARS-CoV-2 particles binding to Angiotensin Converting Enzyme 2 (ACE2) receptors in a greater affinity compared to other HCoVs. This could potentially be due to the structural changes in the spike protein of SARS-CoV-2 (Lima et al., 2020). ACE2 receptors are found in the majority of human organs, vessels and also the CNS, and ACE2 was identified as the receptor cell for the previous SARS-CoV pandemic (Lima et al., 2020; Ni et al., 2020; Verdecchia et al., 2020). Given the similarities between SARS-CoV and SARS-CoV-2, scientists sought out to answer whether ACE2 was also the receptor cell for SARS-CoV-2. In March 2020, research conducted by Lan et al. (2020) revealed the formation of the receptor-binding domain of SARS-CoV-2 spike proteins which had attached to ACE2 receptors. In addition, R. Yan et al. (2020) showed ACE2 receptors with the receptor-binding domain of the SARS-CoV-2 spike protein in full via cryo-electron microscopy imaging. The evidence from both these studies proved to be vital in confirming that ACE2 is the receptor cell for SARS-CoV-2 (Davidson et al., 2020; Lan et al., 2020; R. Yan et al., 2020). However, more than a year on, critiques are now exploring whether co-receptors and alternative receptors, such as NRP1 (neuropilin) or CD147, could be alternate entry receptors for SARS-CoV-2.

There could in fact be multiple pathways which could explain the neuroinvasive potential of COVID-19. These potential pathways are split into direct and indirect. An indirect infection in the brain could occur due to hypoxia, as a result of respiratory failure or the body's immune response (Bougakov et al., 2021). However, the direct pathways which have become increasingly popular in the COVID-19 field and could explain the invasion of the CNS, the neuroinvasive and neurotropic nature of SARS-CoV-2 , are the neuronal retrograde route and the haematogenous route (Bougakov et al., 2021; Pezzini & Padovani, 2020). Previous CoVs have also shown to use either the haematogenous or neuronal retrograde pathways to infect

the CNS. Therefore, it could be argued that SARS-CoV-2 will not be an exception to this (Lima et al., 2020). Moriguchi et al. (2020) provide support to the direct pathway theory, i.e., the neuronal retrograde route and the haematogenous route, as they detected SARS-CoV-2 RNA in the CSF of a COVID-19 patient. Even though their study was able to justify the direct pathway of SARS-CoV-2 in to the CNS, critiques may point out that it did not provide a clear answer as to which of the two routes the virus utilises to infect the CNS.

1.4.1 The Haematogenous Route

The first of the two pathways that a virus can take when directly infecting the CNS is the haematogenous route. The haematogenous route shows how the human circulatory system can be utilised by a virus to access the CNS and infect multiple organs. A virus like SARS-CoV-2 would take advantage of the body's bloodstream to gain access to the brain by crossing the BBB. There are two ways in which a virus could do this: (a) through using endothelial and epithelial cells, and (b) through infecting leukocytes (Nagu et al., 2021; Pezzini & Padovani, 2020; Reza-Zaldívar et al., 2021).

1.4.1.1 Blood Brain Barrier

To gain access and cross the BBB, the virus could either use ACE2 receptors in the endothelial cells or the epithelial cells. These cells would act as intermediate host cells for the virus before it accesses the BBB and attaches itself to the ACE2 receptors of neurons within the CNS (Al-Sarraj et al., 2021; Desforges et al., 2019; Nagu et al., 2021; Pezzini & Padovani, 2020). Evidence for this route comes from past CoVs and present day COVID-19 studies. SARS-CoV-2 viral particles have supposedly been found in the endothelial cells of patients who had a confirmed diagnosis of COVID-19 (Varga et al., 2020). These were found via an electron microscopy conducted during post-mortem analysis of the patients' kidneys (Varga et al., 2020). Although this study (Varga et al., 2020) found infected endothelial cells in the kidneys and not the CNS, it still provides some support to the hematogenous route and the virus's ability to infect endothelial cells and other organs. In addition, two case studies (Patrì et al., 2021) of patients developing severe skin disorders due to their COVID-19 diagnosis suggested that these skin disorders could be induced due to endothelial dysfunction and the virus

infecting these cells (Patrì et al., 2021). Even though there is past and developing evidence of HCoVs making use of the haematogenous route, many critiques are questioning this and its suitability to the function of SARS-CoV-2. Past research has shown that SARS in particular does not infect other cells in the brain and was only found in neurons, raising questions about its neuroinvasive potential via the haematogenous route (Morris & Zohrabian, 2020). Yet, on the other hand, the fact that neurological symptoms such as impaired consciousness are reported widely post a SARS-CoV-2 infection, suggests that SARS-CoV-2 may be different to SARS-CoV and may in fact be able to infiltrate the brain (Bostancıklıoğlu, 2020).

1.4.1.2 Trojan Horse

The second direct pathway that a virus can use to infiltrate the CNS is named the 'Trojan Horse' mechanism. This mechanism involves lymphocytes (a type of white blood cell) and macrophages (cells that identify and destroy harmful organisms) as a vehicle to enter the CNS and hereafter cross the BBB (Reza-Zaldívar et al., 2021). Previous HCoVs have provided evidence to the 'Trojan Horse' mechanism, in particular, 229E and SARS-CoV in which leukocytes have been infected (Nagu et al., 2021; Reza-Zaldívar et al., 2021). Up until recently research exploring whether macrophages were infected in COVID-19 was extremely limited. Yet, what is believed to be one of the first study (Percivalle et al., 2021) exploring the infection of macrophages due to different SARS-CoV-2 variants supports the 'Trojan Horse' mechanism. This study found that for the SARS-CoV-2 virus, monocytes and macrophages were passive vehicles for the virus, therefore transporting the virus to other organs and target cells inside the body (Percivalle et al., 2021).

Even though both haematogenous routes explored above could explain the CNS infiltration, further evidence is required to confirm the assumption that SARS-CoV-2 is neuroinvasive due to the utilisation of the haematogenous pathway.

1.4.2 The Neuronal Retrograde Route

The second pathway that SARS-CoV-2 could take to infect the CNS is the neuronal retrograde route. Some viruses can use the neuronal retrograde route to infect the peripheral nerve

endings and the neurons within them. Viruses would travel in a retrograde manner to the CNS utilising the neuronal transport proteins, such as, kinesins and dynein found in the PNS (Lima et al., 2020). Autonomic neurons, sensory neurons, and motor neurons are most generally infected and used by viruses within the PNS. However, it has been suggested that the olfactory nerve, housing the olfactory neurons, is probably the strongest route for SARS-CoV-2 dissemination within the CNS. This is said to be due to the particularly high affinity of ACE2 receptors found in the olfactory cells (Lima et al., 2020; Reza-Zaldívar et al., 2021). It has been hypothesised that SARS-CoV-2 particles could gain access through the olfactory nerve, which leads to the olfactory bulb, and the virus would then spread to various structures in the CNS from here, i.e., the piriform cortex, thalamus, and the brain stem (Pezzini & Padovani, 2020; Tassorelli et al., 2020). This theory could explain why individuals infected with SARS-CoV-2 report losing their sense of taste and/or smell. An interesting finding by St-Jean et al. (2004) showed that the removal of the olfactory bulb in mice restricted the spread of the HCoV-OC43. Mice who had been inoculated with the HCoV appeared to show the virus solely in the olfactory bulb (St-Jean et al., 2004). This is significant as SARS-CoV-2 is reported to be very similar to SARS-CoV but also to HCoV-OC43 (Iroegbu et al., 2020). On the other hand, early reports investigating the direct invasion of the CNS via the neuronal retrograde route is disputed by some critiques. Supposedly, ACE2 receptors are not expressed in the olfactory sensory neurons, but are in the olfactory epithelium. This finding would then refute claims of SARS-CoV-2 being able to directly infect the CNS via this route and may give support to the haematogenous route instead (Pezzini & Padovani, 2020). Although understanding the neuronal retrograde pathway is still in its elementary stages for SARS-CoV-2, virus dissemination in the CNS can result in detrimental effects at all stages of infection.

1.5 COVID-19 Symptom Categorisation

SARS-CoV-2 shares many similarities with its predecessors, in particular, SARS-CoV and MERS-CoV. Both of these previous CoVs have also resulted in persistent, long-term symptoms and health problems (Chippa et al., 2023). Moreover, it can strongly be suggested from the evidence above that the SARS-CoV-2 virus can impact the human nervous system and manifest in various ailments and symptoms during infection and shortly after. Moreover, the understanding of SARS-CoV-2 has broadened from being seen as a sole respiratory virus to

now a systemic illness impacting multiple organs at all stages of infection and recovery (Chippa et al., 2023; Guzman-Esquivel et al., 2023). It is due to this, that after careful consideration and a vast amount of research, the National Institute for Health and Care Excellence (NICE) issued guidelines on COVID-19 symptom categorisation (NICE, 2022), and they are:

- Acute COVID-19,
- Ongoing COVID-19,
- Post COVID-19.

1.5.1 Acute COVID-19

Acute COVID-19 refers to the presentation of symptoms between day zero and four weeks (Datta et al., 2020; NICE, 2022). Symptoms during the acute phase of COVID-19 arise due to the initial illness caused by the SARS-CoV-2 virus and the replication of the virus within the host body (Datta et al., 2020), potential explanations have been explored above. Symptoms experienced at this stage vary in severity and traditionally were limited to a temperature, a new continuous cough, and the loss of taste/smell. The list of symptoms evolved over time in line with the emergence of new variants, and expanded to include symptoms mentioned in Table 1.1 (Looi, 2023b; NHS, 2023a). Generally, most infected patients experience a short-term illness, with symptoms waning 12-14 days after testing positive (Guzman-Esquivel et al., 2023). Moreover, in comparison to early variants, newer variants such as Omicron result in a less severe acute presentation of symptoms, which could also partly be explained by the introduction and uptake of vaccinations and an increasing immunity to the ever-evolving SARS-CoV-2 strains (Looi, 2023b).

1.5.2 Ongoing COVID-19 and Post COVID-19

Ongoing COVID-19 symptoms refer to individuals experiencing symptoms between four and 12 weeks post a diagnosis. Post COVID-19 syndrome refers to individuals experiencing symptoms lasting ≥ 12 weeks and/or they develop during the ongoing COVID-19 stage, with no alternative explanation/diagnosis (NICE, 2022). Although there is a differentiation between the ongoing and post COVID-19 timescales, the wider population tends to refer to

this period as ‘long COVID’. The term ‘long COVID’ was coined by patients who were experiencing symptoms and/or developed symptoms many weeks after a confirmed diagnosis and in essence, did not recover from the infection (Alwan & Johnson, 2021; Michelen et al., 2021). These symptoms can include, but are not limited to, the symptoms experienced during the acute stage of infection. In fact, there is no single list of symptoms that would define long COVID. According to the NHS there are 26 common long-COVID symptoms whereas the Office for National Statistics (ONS) has a list of 34 self-reported symptoms (NHS, 2023b; ONS, 2023a). The most commonly reported symptoms based on a review of 27 studies (19 studies on ongoing symptoms and eight studies on post COVID symptoms) include: fatigue (47%), shortness of breath (32%), and muscle pain (25%) (Aiyegbusi et al., 2021). Interestingly, these top three prevalent symptoms remained the most common even after a year, based on a different review conducted by Han et al. (2022). Many patients also reported neuropsychological symptoms post an infection, in particular, ‘brain fog’ (Kubota et al., 2023; Nouraeinejad, 2023). Brain fog, similar to long COVID, is a term coined by patients themselves and refers to a form of cognitive disruption, in particular difficulty concentrating, fatigue, and forgetfulness and has been widely reported in the literature (Badenoch et al., 2022; Kubota et al., 2023; McWhirter et al., 2023; Smith et al., 2022).

The most common symptoms listed both by the NHS and ONS are depicted in Figure 1.1. They have been categorised under the headings of either neurological, psychiatric, pulmonary, dermatological, musculoskeletal, ophthalmological, otolaryngological (ear, nose, and throat [ENT]), cardiac, gastrointestinal, and general health based on the predominant symptom that is exhibited. However, it is important to understand that this is not exhaustive list of long-COVID symptoms. The vast number of symptoms exhibited during the ongoing and post COVID-19 phase which results in long COVID or post-COVID syndrome could be attributed to a multitude of reasons, including risk factors such as female sex, increased inflammation, autoantibodies, and even micro blood clots, to name a few (Davis et al., 2023; Jarrott et al., 2022; Low et al., 2023; Phetsouphanh et al., 2022).

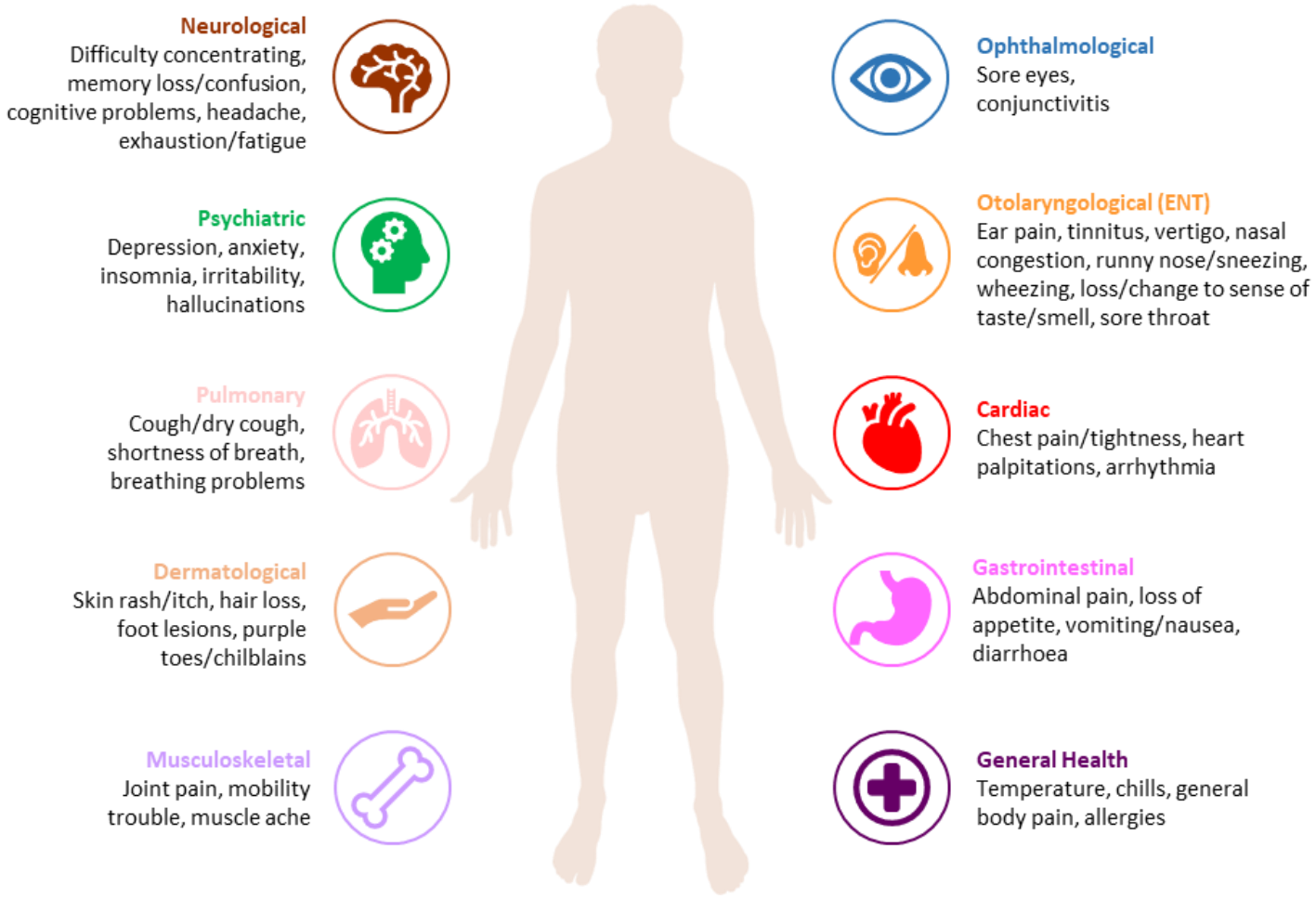
1.5.2.1 Long COVID Prevalence and Potential Mechanisms

Given the multitude of various symptoms and the complications around testing, the prevalence of long COVID has been difficult to measure accurately, and reported estimates vary significantly (Hastie et al., 2023). The WHO states an estimated 10-20% of COVID-19 survivors are living with long COVID (WHO, 2023), a vast contrast to the UK ONS who have estimated 2.9% of the population (1.9 million people) were reporting ongoing COVID-19 symptoms as of March 2023 (Hastie et al., 2023; ONS, 2023b; O'Mahoney et al., 2023). A meta-analysis conducted by O'Mahoney et al. (2023) analysing 194 studies, across the world, totalling over 735,000 participants, deduced that 45% of COVID-19 survivors experienced an unresolved symptom on average 126 days post infection (Hastie et al., 2023; O'Mahoney et al., 2023). This number is far beyond the estimates of the WHO and the ONS, and could be attributed to the lack of objective markers or testing for long COVID.

It is clear from the evidence that long COVID is fairly prominent and debilitating, but the underlying pathophysiology of long COVID is still fairly unknown (Castanares-Zapatero et al., 2022; Navis, 2023). Potential explanations of long COVID currently in the literature include: autoimmunity, reactivation of latent SARS-CoV-2 particles, immune dysregulation resulting in inflammation, and viral persistence (Batiha et al., 2022; Castanares-Zapatero et al., 2022; Iwasaki & Putrino, 2023; Kenny et al., 2023; Liew et al., 2023; Tziolos et al., 2023). Further research is required to ascertain the exact pathophysiology and the underlying mechanisms that are at play in long COVID.

Figure 1.1

Common long-COVID symptoms



1.6 Chapter Summary

This chapter has summarised the origins of COVID-19 and its impact both in the survivors and non-survivors. It has highlighted that SARS-CoV-2 is in fact quite similar to its predecessors and can also have a neurological manifestation. This chapter has briefly explained the effect of COVID-19 on both the PNS and CNS through various diseases and symptomologies, followed by the route the virus could take to infiltrate the CNS. Although the pandemic has come to an organic end with all restrictions being lifted and life returning to 'normal', the physical, psychological, and cognitive manifestations reported post a diagnosis are significantly life-changing and need to be investigated continuously. The next chapter will focus on the short and long-term impact of COVID-19 on neuropsychological functions and behaviour, with a particular focus on cognitive function and psychological well-being.

Chapter Two: Cognitive and Mental Health Impact of COVID-19 and Long COVID

2.1 Chapter Aims and Overview

Since its emergence, COVID-19 has shown its ability to clearly infiltrate the CNS. Due to this, many individuals have experienced detrimental effects, both physical and psychological (Shanbehzadeh et al., 2021). In the previous chapter, PNS and CNS manifestations and some of the symptoms that are experienced by COVID-19 and long-COVID patients were briefly touched upon. This chapter will consider in more detail the neuropsychological effects of COVID-19 and long COVID, with a particular focus on cognitive function and psychological well-being. It will first cover the importance of both intact cognitive function and psychological well-being for adults in everyday life, and then focus on the impact of COVID-19 and long COVID on various cognitive domains and psychological well-being.

2.2 Importance of Cognitive and Psychological Well-being

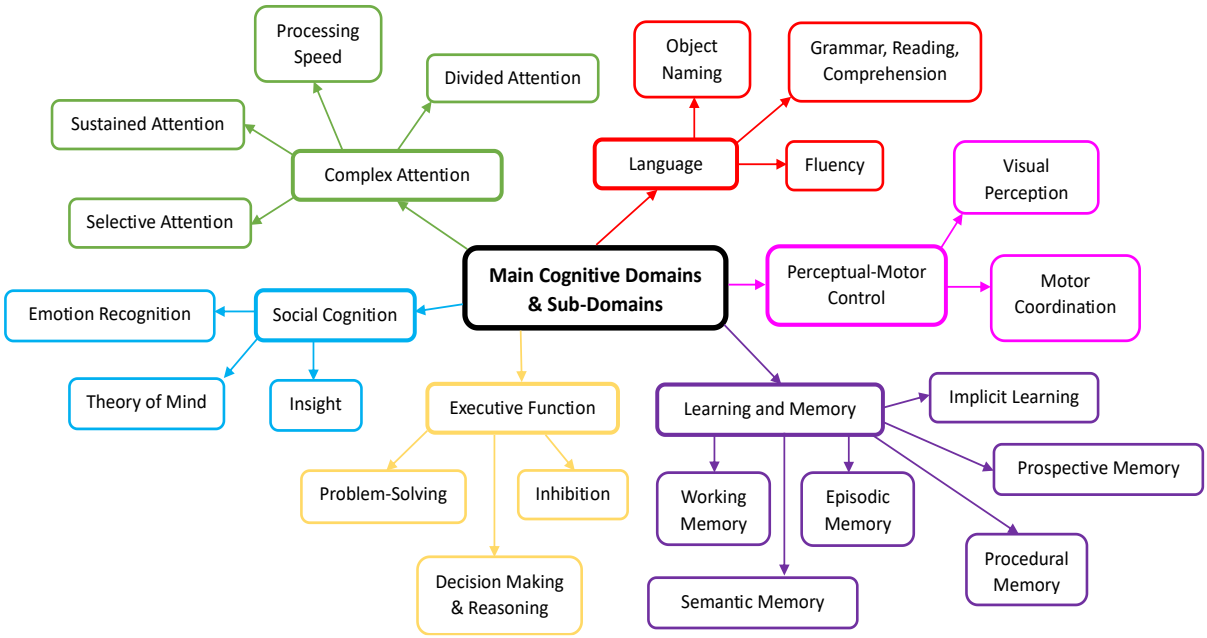
2.2.1 Cognitive Function

Healthy cognitive function, which encompasses the mental ability for acquiring information, problem solving, learning, reasoning, manipulating, and storing information, is crucial for normal health and ageing (Kiely, 2014; Morley et al., 2015). Cognitive function is conceptualised into multiple hierarchical domains, with numerous sub-domains within, that are mutually intertwined and typically dependent upon one another (Harvey, 2019; Kiely, 2014). The main overarching domains according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) include social cognition, complex attention, learning and memory, perceptual motor-control, language, and executive function (Sachdev et al., 2014) (Figure 2.1). A reduction in normal functioning of any of these domains, yet remaining independent in daily living, can constitute a diagnosis of mild cognitive impairment (MCI). MCI is the grey area between normal and/or changes in cognitive functioning associated with ageing and a more severe diagnosis of dementia (Gauthier et al., 2006; Geda, 2012; Petersen

et al., 2014). Yet, not all cases of MCI progress to a diagnosis of dementia and, moreover, MCI may be reversible in some cases (Richardson et al., 2019).

Figure 2.1

Main overarching cognitive domains and sub-domains (DSM-V)



Numerous conditions can affect cognitive functioning, most of which are age-related. A large longitudinal study (*N* = 10,626 at baseline; *n* = 5512 at wave five) investigating the cognitive trajectory in adults over eight years in England (UK) found increasing age to be correlated with all cognitive domains (Zaninotto et al., 2018). Moreover, lifestyle (e.g., healthy diet and exercise), and environmental factors also play a part in the maintenance of normative cognitive function (Motohiro et al., 2021; Wang et al., 2021; Zaninotto et al., 2018). In addition to the factors mentioned above, neurotropic viruses, for example, herpes simplex virus-1 and non-neurotropic viruses, such as, influenza, are known to negatively influence cognitive function (Jurgens et al., 2012; Thomas et al., 2013; Watson et al., 2013). Based upon this, it would be plausible to expect that SARS-CoV-2 could also affect cognitive function in some shape or form.

2.2.2 Psychological Well-being

Psychological well-being is equally of the utmost importance. Psychological well-being does not have a straightforward definition and is often quantified as the self-reported levels of enjoyment, pleasure, fulfilment, meaning, and happiness in everyday life. It may also include resilience and coping mechanisms (e.g., emotion regulation) (Huppert, 2009; Tang et al., 2019). It must be noted that sustainable psychological well-being does not revolve around feeling happy at all times. Healthy psychological well-being also acknowledges the negative emotions (e.g., grief, disappointment) and the ability to regulate these. If these negative emotions do however persist long-term and affect everyday life, psychological well-being is impacted (Huppert, 2009).

There are numerous factors that can impact psychological well-being, including lifestyle factors such as alcohol consumption, smoking habits, nutrition, physical and social activities (Sapranaviciute-Zabazlajeva et al., 2022), financial status (Oskrochi et al., 2018), and even an individual's neurobiology (King, 2019), to name a few. Interestingly, both psychological well-being and cognitive function can impact each other and form a cycle. Greater psychological well-being can aid in the maintenance of intact cognitive function, which in turn further improves psychological well-being (Huppert, 2009). Therefore, it could be argued that if either psychological well-being or cognitive function are impaired due to COVID-19, the other could possibly automatically be affected.

2.3 COVID-19 and Long COVID: The Impact on Cognitive Function

From the onset of the pandemic, understanding the neuropsychological impact of COVID-19 has been a priority, as even a small change in normal neuropsychological functioning can impact everyday living (Aretouli & Brandt, 2010). A vast amount of literature has been accumulated since the start of the COVID-19 pandemic showing the effects of COVID-19 on cognitive function (Table 2.1). Many reviews (Ceban et al., 2022; Crivelli et al., 2022; Houben & Bonnechère, 2022; Sobrino-Relaño et al., 2023; Tavares-Júnior et al., 2022) have reported a prevalence rate of post COVID-19 cognitive impairment to be between 2.6% and 81%. These impairments have been reported in multiple cognitive domains, and the most prominent of these will be explored in further detail, below.

Table 2.1

A detailed description of studies examining the impact of COVID-19 on cognitive function

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
Albu et al., 2022 (Spain)	Multidisciplinary outpatient rehabilitation of physical and neurological sequelae and persistent symptoms of covid-19: a prospective, observational cohort study	Prospective, observational cohort (less than 3 months post initial symptoms) June 2020 – December 2020	DGS, RAVLT	43 (44%)	52 ± 11.4	/	/	- 37.5% reported subjective cognitive impairments at baseline. - 72.2% of participants scored lower than expected when compared against age and education in at least one cognitive domain. - Cognitive impairments included: altered verbal learning (58.1%); long-term verbal memory (51.6%); verbal recognition (19.4%); executive control (19.7%), working memory (9.7%); attention (9.7%) and orientation in space (3.2%). - After an 8 week intervention, improvements were observed in verbal learning, long-term verbal memory and executive control.
Alemanno et al., 2021 (Italy)	COVID-19 cognitive deficits after respiratory assistance in the subacute phase: a COVID-rehabilitation unit experience	Observational, Longitudinal (5-20 days after onset of symptoms and 1 month follow-up) March 2020 – June 2020	MMSE, MoCA	87 (28.7%) (at baseline)	67.23 ± 12.89 (at baseline)	/	/	- 80% had neuropsychological deficits as shown in the MoCA and MMSE, broken down into the groups below: Group 1 (Orotracheal intubation) MoCA: *M* = 21.6 ± 5.2; MMSE: *M* = 26.7 ± 2.7 Group 2 (Non-invasive ventilation) MoCA: *M* = 16.8 ± 7.1; MMSE: *M* = 22.7 ± 5.8 Group 3 (Venturi masks) MoCA: *M* = 15.9 ± 6.9; MMSE: *M* = 22.2 ± 6.2 Group 4 (No oxygen therapy) MoCA: *M* = 19.1 ± 6.8; MMSE: *M* = 22.8 ± 6.9
Almeria et al., 2020 (Spain)	Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment	Observational (between 10 and 35 days post-discharge)	TAVEC, WMS-IV, DGS forward and Backward, Letter and Numbers, TMT-A, TMT-B, SDMT, SCWT, Phonemic	35 (54%)	47.6 ± 8.9	/	/	- Impaired scores were observed in the TAVEC, DST backwards, TMT-A, TMT-B, SDMT, Stroop colour, Stroop interference, semantic fluency, phonemic fluency, WMS-IV: VR, BNT for patients. - Patients who presented with headache, anosmia, dysgeusia, diarrhoea and those who required oxygen

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
		April 2020 – June 2020	and Semantic fluency, BNT					therapy had lower scores in memory, attention and executive function subtests as compared to asymptomatic patients. - Neuropsychological deficits related to COVID-19 infection were seen in attention, memory and executive function domains.
Amalakanti et al., 2021 (India)	Cognitive assessment in asymptomatic COVID-19 subjects	Cross-Sectional (acute stage of COVID-19 diagnosis) June 2020 – July 2020	MoCA	93 (52.3%)	36.2 ± 11.7	102 (54.7%)	35.6 ± 9.8	- Asymptomatic COVID-19 participants scored lower in certain domains of the MoCA in comparison with the healthy controls (HCs), in particular, Fluency: Cases: 0.9 ± 0.6 vs HC: 1.6 ± 0.7; p <.001; Visuo-perception: Cases: 2.4 ± 0.7 vs HC: 2.8 ± 0.7; p = .03; Naming: Cases: 3.6 ± 0.5 vs HC: 3.9 ± 0.2; p = .02 - No significant difference between cases and controls in MoCA, executive function, orientation, calculation, abstraction, delayed recall, and attention. - Older COVID positive participants scored lower on the MoCA compared to their younger counterparts.
Arbula et al., 2024 (Italy)	Insights into attention and memory difficulties in post-COVID syndrome using standardized neuropsychological tests and experimental cognitive tasks	Cross-Sectional (on average 8.3 months after onset of first COVID-19 related symptom) January 2021 – March 2022	MoCA, SDMT	33 (75.8%)	54.1 ± 6.9	27 (63%)	57 ± 6.1	- Significant attention deficits in post-COVID patients across both neuropsychological measurements and experimental cognitive tasks. Significant group differences present for attention and memory related tasks. - Mild executive function and naming impairments also emerged from the neuropsychological assessment. - Notably, 61% of patients reported significant prospective memory failures in daily life.
Beaud et al., 2021 (Switzerland)	Pattern of cognitive deficits in severe COVID-19	Observational (5.5 ± 2.4 days post ICU discharge) Uns.	MoCA, FAB	13 (23%)	64.8 ± 7.6	/	/	- Lower executive functions for patients with normal MoCA scores and more extensive cognitive impairment in executive, memory, attentional and visuospatial functions, with relatively preserved orientation and language, for patients with mild to severe MoCA deficits (MoCA: M = 19.7 ± 7.5).

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
								- In the FAB, the most affected was lexical fluency, impaired in all patients except in one (FAB: *M* = 10.9 ± 5.5).
Becker et al., 2021 (USA)	Assessment of cognitive function in patients after COVID-19 infection	Observational (on average 7.6 months post infection) April 2020 – May 2021	DGS forwards and backwards, TMT-A, TMT-B, HVLT-R, Phonemic and category fluency	740 (63%)	49 ± 14.2	/	/	- Most prominent deficit in processing speed (*n* = 133), followed by executive functioning (*n* = 118), phonemic fluency (*n* = 111) and category fluency (*n* = 148), memory encoding (*n* = 178), and memory recall (*n* = 170). - Hospitalized patients more likely to have impairments in attention (OR: 2.8; 95% CI: [1.3-5.9]), executive functioning (OR: 1.8; 95% CI: [1.0-3.4]), category fluency (OR: 3.0; 95% CI: [1.7-5.2]), memory encoding (OR: 3.0; 95% CI: [1.7-5.2]), and memory recall (OR: 2.2; 95% CI: [1.3-3.8]). - Patients treated in the ED more likely to have impaired category fluency (OR: 1.8; 95% CI: [1.1-3.1]) and memory encoding (OR: 1.7; 95% CI: [1.0-3.0]) than outpatient group.
Becker et al., 2023 (USA)	Greater executive dysfunction in patients post-COVID-19 compared to those not infected	Observational (on average 8 months from diagnosis) Uns.	DGS, TMT-A, TMT-B, HVLT-R, phonemic and category fluency	417 (61%)	49.0 ± 14.3	151 (68%)	50.4 ± 13.5	- Participants who were COVID positive were significantly more likely than controls to have an impairment in executive functioning, more so if the COVID participant was hospitalised.
Blazhenets et al., 2021 (Germany)	Slow but evident recovery from neocortical dysfunction and cognitive impairment in a series of chronic COVID-19 patients	Longitudinal (6 months post symptom onset). Uns.	MoCA	8 (25%)	66 ± 14.2	/	/	- MoCA scores improved between the first (19.1 ± 4.5) and second assessments (23.4 ± 3.6). Although they are still below the cut-off score for normal cognitive function (26/30).
Bonizzato et al., 2022 (Italy)	Cognitive, behavioral, and psychological manifestations of	Observational, Longitudinal (follow-up 3	MoCA, MMSE	12 (42%)	71.3 ± 10.1	/	/	- At baseline, seven patients (58.3%) had performance below cut-off at the MMSE and six (50%) at MoCA. - At discharge, four patients (33.3%) obtained scores below cut-off at the MMSE, and six (50%) at the MoCA.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
	COVID-19 in post-acute rehabilitation setting: preliminary data of an observational study	month post-discharge)						- Among the eight patients tested at the follow-up, two (25%) had a poor performance at the MMSE, four (50%) at the MoCA.
Cecchetti et al., 2022 (Italy)	Cognitive, EEG, and MRI features of COVID-19 survivors: a 10-month study	Longitudinal (2 months and 10 months post hospital discharge) April 2020 – May 2020	MMSE, FAB, SDMT, TMT-A, TMT-B, RAVLT, DGS	49 (26.5%)	60.8 ± 12.6	36 (44%)	56.9 ± 13.6	- 53% of participants at baseline exhibited a cognitive impairment. - Executive function impairment correlated with respiratory distress. - Immediate recall and delayed recall significantly different between controls and COVID group with COVID group performing worse. - Improvement observed at follow-up.
Cian et al., 2022 (Italy)	Cognitive and neuropsychiatric features of COVID-19 patients after hospital dismission: an Italian Sample	Prospective, observational January 2021 – May 2021	MMSE, RAVLT, CPM47, CDT, Phonemic/semantic and alternative fluency test, DGS forward and backwards	29 (41%)	58.4 ± 10.0	29 (Uns.)	Uns.	- Among COVID positive, 62% had at least one pathological test (vs. 13% in COVID negative; p = .000) and significantly worst performances than COVID negative in RAVLT learning (42.55 ± 10.44 vs. 47.9 ± 8.29, p = .04), RAVLT recall (8.79 ± 3.13 vs. 10.38 ± 2.19, p = .03), and recognition (13.69 ± 1.47 vs. 14.52 ± 0.63, p = .07). - Chi-square on dichotomous values (normal/pathological) showed a significant difference between groups in Digit backward test (pathological 7/29 COVID+ vs. 0/29 COVID−; p = .005). - COVID positive patient assessed by tele-neuropsychology showed a vulnerability in some memory and executive functions (working memory, learning, delayed recall, and recognition).
Crivelli et al., 2022 (Argentina)	Cognitive consequences of COVID-19: results of a cohort study from South America	Cross-Sectional (5 months post-diagnosis) Uns.	MoCA, TMT, DGS Forwards, Digit-Symbol Coding, Craft Story, RAVLT, Benson Figure, WISC, SCWT, MINT, phonological	45 (49%)	57 ± Uns.	45 (44%)	50 ± Uns.	- Significant differences between groups were found in cognitive variables of memory (p = .016, d = 0.73), attention (p <.001, d = 1.2), executive functions (p <.001, d = 1.4), and language (p = .002, d = 0.87).

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
			fluency					
Darley et al., 2021 (Australia)	Persistent symptoms up to four months after community and hospital-managed SARS-CoV-2 infection	Prospective cohort study (4 months post diagnosis). May 2020 – July 2020	CogState Cognitive Test Battery	78 (34.6%)	47 ± 16	/	/	- Out of 78 participants, cognitive impairment was evident in eight patients (10%); five participants had mild and three had moderate cognitive impairments. - Psychomotor speed was the most impaired in the participants.
De Lorenzo et al., 2020 (Italy)	Residual clinical damage after COVID-19: A retrospective and prospective observational cohort study	Observational (on average 23 days post discharge) April 2020 – May 2020	MoCA	185 (34%)	57 ± Uns.	/	/	- MoCA scores of <24 were observed in 25.4% of patients
Del Brutto et al., 2021 (Ecuador)	Cognitive decline among individuals with history of mild symptomatic SARS-CoV-2 infection: A longitudinal prospective study nested to a population cohort	Observational, longitudinal (pre-COVID-19 cognitive data available. 6 months post start of pandemic.) May 2020 – June 2020	MoCA	52 (62%)	59.4 ± 10.6	41 (66%)	66.6 ± 10.6	- Cognitive decline was observed in 11 (21%) individuals who had tested positive for SARS-CoV-2 on the MoCA. - The mean post-pandemic MoCA score was significantly lower among SARS-CoV-2 individuals (21.7 ± 4 vs. 19.6 ± 4.2; p = .010) but not in their seronegative counterparts (21.5 ± 5 vs. 21 ± 4; p = .618).
Delgado-Alonso et al., 2022 (Spain)	Cognitive dysfunction associated with COVID-19: A comprehensive neuropsychological study	Cross-sectional (9 months post infection) April 2020 – May 2021	DGS Forwards and Backwards, Corsi, SDMT, BNT, JLO, ROCF, FCSRT, verbal fluency, SCWT, VOSP, computerized neuropsychological battery Vienna Test System	50 (75%)	51.06 ± 11.65	50 (Uns.)	Uns.	- COVID-19 patients showed a diminished performance on several tests (processing speed, divided attention, selective attention, visual vigilance, intrinsic alertness, working memory, and inhibition; episodic memory; and visuospatial processing). - Patients with COVID-19 reporting cognitive symptoms showed a reduced cognitive performance, especially in the attention-concentration and executive functioning, episodic memory, and visuospatial processing domains.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
Diana et al., 2023 (Italy)	Monitoring cognitive and psychological alterations in COVID-19 patients: a longitudinal neuropsychological study	Longitudinal assessments at 6 (T0), 16 (T1) and 22 months (T2) post recovery April 2020 – March 2021	T0: MMSE; Attentional Matrices; TMT; DGS forward and backward; RVLT; BSRT; FAB; verbal fluency by letter and category; Weigl's Sorting Task; Raven's Matrices T1, T2: Same as above and OORT; SDMT; CDT; the Modified Five Point Test for non-verbal fluency, and the alternate verbal fluency.	T0: 21 (29%) T1: 19 (26%) T2: 16 (25%)	T0: 57 ± 15 T1: 57 ± 15 T2: 59 ± 15	/	/	- Around 50% of COVID-19 patients presented with cognitive deficits at T0. The most affected domain was verbal memory. Pathological scores diminished over time, but a high rate of borderline scores was still observable. Longitudinal analyses highlighted improvements in verbal and non-verbal long term memory, as well as attention, and executive functioning. - Depression and PTSD-related symptoms were present in 30% of patients. The latter decreased over time and were associated to attentional-executive performance.
Douaud et al., 2022 (UK)	SARS-CoV-2 is associated with changes in brain structure in UK Biobank	Cross-sectional and longitudinal (on average, 4.7 months post diagnosis. Pre-COVID-19 cognitive data also available) April 2020 – May 2021	TMT-A, TMT-B, SDMT, Reaction Time Test, Fluid Intelligence, Numeric Memory, Pairs Matching Test	401 (57.1%) (at scan one)	58.9 ± 7 (at scan one)	384 (57.3%)	60.2 ± 7.4 (at scan one)	- Participants who were infected with SARS-CoV-2 showed, on average, a greater cognitive decline between the two time points (pre- vs post-COVID-19 infection). - A significantly greater increase in the time taken to complete Trail Making A (7.8%, P_{uncorr} = .0002, P_{FWE} = .005) & B (12.2%, P_{uncorr} = .00007, P_{FWE} = .002) between COVID+ and COVID- group.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
Dressing et al., 2021 (Germany)	Neuropsychologic profiles and cerebral glucose metabolism in neurocognitive long COVID Syndrome	Observational (3 months post-acute diagnosis) June 2020 – January 2021	MoCA, HVLT, DST, BVMT-R, TMT, FWIT, SDMT, fluency	31 (64.5%)	53.6 ± 12.0	/	/	- The most frequently impaired domain was visual memory (7/31 [23%] patients; other domains ≤ 2/31 [≤ 7%]). - Impaired individual tests on single-subjects level were most frequently observed for verbal and visual memory tests. - Almost half of the patients (*n* = 15, 49%) were completely unimpaired in the neurocognitive test battery. - Mild impairment was detected through the MoCA in nine patients (29%; range 23-25 points).
Ermis et al., 2021 (Germany)	Neurological symptoms in COVID-19: a cross-sectional monocentric study of hospitalized patients	Observational (during acute-phase of COVID-19 infection) March 2020 – September 2020	MoCA	53 (39.6%)	63 ± Uns.	/	/	- Impairment was noticed primarily in executive function, attention, language and delayed recall.
Ferrando et al., 2022 (USA)	Neuropsychological, medical, and psychiatric findings after recovery from acute COVID-19: a cross-sectional study	Observational (Uns.) Uns.	RBANS	60 (68%)	41.4 ± 13.5	/	/	- The clinical group with cognitive complaints scored lower than age-adjusted participants in attention, processing speed, memory, and executive function tests. - Impairment predicted by acute COVID-19 symptoms, current depression score, number of medical comorbidities, and subjective cognitive complaints in the areas of memory, language, and executive functions.
Ferrucci et al., 2021 (Italy)	Long-lasting cognitive abnormalities after COVID-19	Observational (between 4-5 post hospital discharge) February 2020 – April 2020	BRB-NT includes the SRT[1], SPART, SDMT, PASAT, WLG	38 (28.9%)	53.45 ± 12.64	/	/	- Of all participants, 42.1% had processing speed deficits. - Moreover, 26.3% showed delayed verbal recall deficits. - 18.4% showed impairment in visual long-term memory. - 15.8% showed impairment in visual short-term memory. - 10.5 % showed deficits in immediate verbal recall. - Twenty-one percent presented with deficits in both processing speed and verbal memory.
Ferrucci et al., 2022 (Italy)	One-year cognitive follow-up of COVID-	Observational and longitudinal (5 and 12 month follow-up	BRB-NT includes the SRT[1], SPART, SDMT, PASAT, WLG	76 (26.3%)	56.24 ± 12.08	/	/	- At 5 months, more than half (63.2%) of patients had deficits in at least one test, 40.8% in at least two tests and 23.7% in three or more tests.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
	19 hospitalized patients	post hospitalisation) February 2020 – April 2020						- The most affected domain at 5 months was processing speed (SDMT, 40.8% of patients reporting), followed by long-term verbal memory (SRT[1]-D, 26.3%; SRT[1]-LTS, 17.1%; SRT[1]-CLTR, 19.7%) and long-term visuospatial memory (SPART-D, 18.2%). - At 12 months, 49.1% still showed deficits in at least one cognitive test, 32.1% showed deficits in at least two tests and 13.2% showed deficits in three or more tests. - Processing speed remained the most frequently affected domain at 12 months (SDMT, 28.3%), followed by long-term visuospatial (SPART-D, 18.9%) and verbal (SRT[1]-D, 15.1%) memory. - Compared to T1 (5 months), a significant improvement in cognitive performance was observed for all tests of verbal memory (SRT[1]-LTS, p = .005; SRT[1]-CLTR, p = .028; SRT[1]-D, p = .047) and attention/processing speed (SDMT, p <.001; PASAT-3, p = .005; PASAT-2, p = .024). - No significant improvements for tests of visuospatial learning (SPART, p = .565), visuospatial delayed recall (SPART-D, p = .520) and verbal fluency (WLG, p = .329) were observed.
Galderisi et al., 2024 (Italy)	Cognitive impairment after recovery from COVID-19: Frequency, profile, and relationships with clinical and laboratory indices	Cross-Sectional March 2021 – September 2022	MoCA, MCCB	259 (36.7%)	53.95 ± 9.1	477 (48%)	46.2 ± 13.4	- More than one third of the screened COVID-19 positive participants presented a cognitive impairment, relative to the COVID-19 negative group. - The MCCB showed that 45% of the subjects had a cognitive impairment involving attention, working memory, verbal learning, visual learning, and reasoning and problem solving.
Graham et al., 2021 (USA)	Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized	Cross-Sectional May 2020 – November 2020	PROMIS, NIH Toolbox	50 (66%)	43.7 ± 11.8	50 (74%)	42.6 ± 10.8	- SARS-CoV-2 positive participants performed worse in attention and working memory cognitive tasks compared to a demographic-matched US population control group.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
	Covid-19 "long haulers"							
Groiss et al., 2020 (Germany)	Prolonged neuropsychological deficits, central nervous system involvement, and brain stem affection after COVID-19 - a case series	Case-Series (3 weeks post hospital discharge) Uns.	MoCA, MMSE, SDMT	4 (/)	59.5 ± 17.6	/	/	- All patients showed clinically relevant impairment of cognition. - MoCA: Patient 1 Impaired (21) & Patient 2 impaired (16) - MMSE: Patient 1 Impaired (−18.81), Patient 2 Impaired (−4.29) & Patient 3 Impaired (14).
Guo et al., 2022 (Numerous)	COVCOG 2: cognitive and memory deficits in long COVID: a second publication from the COVID and cognition study	Cross-Sectional and longitudinal	Word List Recognitive Memory Test, Pictorial Associate Memory Test, CFT, Mental Rotation, WCST, Number Counting Test, Relational Reasoning Test	181 (71.8%)	Uns.	185 (63.8%)	Uns.	- Significant negative influence of COVID-19 on memory, post controlling for age, sex, country, and education level [$F(1,304) = 10.903$, $p = .001$]. - Significant difference between groups on the Category Fluency [$F(1,307) = 6.297$, $p = .013$, $\eta_p^2 = .02$], but this disappeared when controlling for demographic variables. - Individuals who had a COVID-19 history had significantly lower performance ($U = 3.29$, $p < .001$) and slower reaction time ($U = 3.53$, $p < .001$) relative to the non-COVID group on the Word List Recognition Memory Test. - A weaker trend was seen in the Pictorial Associative Memory Test, suggesting a reduced performance in the COVID group ($t = 1.91$, $p = .056$) and no impact on reaction time ($p = .671$). - Category Fluency, COVID group repeated more words ($U = 2.35$, $p = .019$), but they gave fewer incorrect (related) words ($U = 2.23$, $p = .026$) compared to the non-COVID group. However, these effects disappeared after factoring out age, sex, country, and education level. - No significant differences between the groups in Executive Function, there was a significant group difference in Executive Function Reaction Time [$t(311) = 2.610$, $p = .009$],

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
								but this dropped below significance once demographics were accounted for. - There were no significant differences between groups on performance on the 2D Mental Rotation Test.
Hampshire et al., 2021 (UK)	Cognitive deficits in people who have recovered from COVID-19	Cross-Sectional (Uns.) January 2020 – December 2020	Great British Intelligence Test (nine tests)	81,337 (55%)	46.7 ± 15.7	Uns.	Uns.	- Recovered COVID-19 patients exhibited significant cognitive deficits in comparison to controls. - Impairments were higher for people who had been hospitalized. - Deficit most pronounced in paradigms on reasoning, problem solving, spatial planning and target detection. - Recovery from COVID-19 may be associated with problems in executive function.
Hellgren et al., 2021 (USA)	Brain MRI and neuropsychological findings at long-term follow-up after COVID-19 hospitalisation: an observational cohort study	Observational (5 months post infection) March 2020 – May 2020	RBANS	35 (20%)	59 ± 6.4	/	/	- Out of 35 patients, 16 (46%) showed cognitive impairments; 6 of these (17%) showed mildly/moderately impaired cognition, and 10 patients (29%) had severely impaired cognition. - Immediate Memory and Delayed Memory were the variables where the most impairment was noticed.
Hellmuth et al., 2021 (USA)	Persistent COVID-19-associated neurocognitive symptoms in non-hospitalized patients	Case-Series (14 days post infection) Uns.	MoCA, CVLT, MMSE, WAIS-IV, D-KEFS fluency, TMT-A, TMT-B, ROCF, SCWT, NAB	2 (100%)	44.5 ± 11.5	/	/	- Commonly used cognitive screens were normal, while more detailed testing revealed working memory and executive functioning deficits
Henneghan et al., 2022 (USA)	Cognitive impairment in non-critical, mild-to-moderate COVID-19 survivors	Observational (3.8 months post diagnosis) January 2021 - April 2021	BrainCheck – FDA Approved online test TMT-A, TNT-B, DSST, SCWT, List Learning Test	72 (74%)	36 ± 12	/	/	- 40% of participants demonstrated objective cognitive impairment and 15% endorsed subject cognitive impairment. - The largest number of participants showed impairment on the Stroop test (24%), a measure of executive functioning. - On attention and processing speed males were more impaired ($X^2 = 5.86$, $p = .02$).

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
Herrera et al., 2023 (Spain)	Cognitive impairment in young adults with post COVID-19 syndrome	Observational (at least 4 months post diagnosis) Uns.	BTA; DGS forward and backward; TAVEC; ROCF; SCWT; WAIS-IV; fluency tasks	214 (85%)	47.5 ± 7.4	/	/	- < 85% of the participants showed alterations in at least one neuropsychological test performance, including attention which showed the greatest deficit and processing speed. - Younger age correlated with worse performance in processing speed, verbal memory and executive function tasks. - No differences in any of the tests between hospitalized and non-hospitalized patients.
Hosp et al., 2021 (UK)	Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19	Observational (1 month after onset of symptoms) April 2020 – May 2020	MoCA, HVLT-R, TMT, SCWT, DGS forward and backward, SDMT, Fluency tasks	29 (38%)	65.2 ± 14.4	/	/	- Of patients performing below the cut-off in the MoCA test, 14 (54%) were mild to moderately impaired (MoCA 18–25) and four (15%) were severely impaired (MoCA 10–17).
Jaywant et al., 2021 (USA)	Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19	Cross-Sectional (43.2 days post hospital admission). April 2020 – July 2020	BMET	57 (25%)	64.5 ± 13.9	/	/	- Forty-six patients (81%) reported cognitive impairment, ranging from mild to severe, with mild impairment being the most common. Deficits were common in working memory (55%), set-shifting (47%), divided attention (46%), and processing speed (40%)
Krishnan et al., 2022 (USA)	Neurocognitive profiles in patients with persisting cognitive symptoms associated with COVID-19	Observational (5.5 months post onset) September 2020 - April 2021	WMS-IV, Logical Memory, RAVLT, BVMT-R. WRAT-4, BNT, lexical and semantic verbal fluencies, JLO, DGS, Matrix Reasoning, WAIS-IV, DKEFS, SCWT, TMT-A, TMT-B,	20 (90%)	44.75 ± 10.8	/	/	- The two most commonly reported persistent symptoms included cognitive symptoms, specifically memory deficits (95%) and lack of concentration/brain fog (85%). - Mild cognitive deficits were seen on tests involving attention and processing speed and executive function. Patients showed impairment on the following tests: Trail Making Test A (20%), Continuous Performance Test (Hit RT (21%), Hit RT ISI Change (36%), and Hit RT Block Change (21%)), Wisconsin Card Sorting Test Trials to First

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
			WCST, Conners CPT 3, SDMT					Category (53%), and Brief Visuospatial Memory Test Revised Recognition Discrimination (20%). - 50% of patients who did not require hospitalization (*n* = 12) and 63% of hospitalized patients (*n* = 8) demonstrated cognitive impairments (1.5 *SD* below the mean) on four or more cognitive measures.
Lamontagne et al., 2021 (USA & Canada)	Post-acute sequelae of COVID-19: Evidence of mood & cognitive impairment	Cross-Sectional (Uns.) January 2020 – March 2021	ACS, ANT	50 (29%)	30.8 ± 7.8	50 (35%)	29.1 ± 9.9	- Selective impairment in attention was observed in the post-COVID group, marked by deficits in executive functioning while alerting and orienting abilities remained intact. Effects were most pronounced among individuals diagnosed 1–4 months prior to assessment. - A significant main effect of Group [$F(3,77) = 2.07$, $p < .05$], such that accuracy in the control group ($M = 96.0\%$, $SE = 2.3$) was significantly higher than both the acute COVID-19 ($M = 83.2\%$, $SE = 5.9$) and Post-Acute Sequalae COVID group ($M = 88.1\%$, $SE = 4.1$) groups, $p < .05$.
Liu et al., 2022 (China)	One-Year Trajectory of cognitive changes in Older survivors of COVID-19 in Wuhan, China: a longitudinal cohort study	Cross-Sectional, longitudinal (6 and 12 months follow-up) February 2020 - April 2020	Chinese version of the TICS-40, Chinese version of the short form of the IQCODE	1438 (51.95%)	69 ± Uns.	438 (49.32%)	67 ± Uns.	- The incidence of cognitive impairment in survivors 12 months after discharge was 12.45%. Individuals with severe cases had lower Telephone Interview of Cognitive Status-40 scores than those with non-severe cases and control individuals at 12 months (median [IQR]: severe, 22.50 [16.00-28.00]; non-severe, 30.00 [26.00-33.00]; control, 31.00 [26.00-33.00]). Severe COVID-19 was associated with a higher risk of early-onset cognitive decline (odds ratio [OR], 4.87; 95% CI, 3.30-7.20), late-onset cognitive decline (OR, 7.58; 95% CI, 3.58-16.03), and progressive cognitive decline (OR, 19.00; 95% CI, 9.14-39.51), while non-severe COVID-19 was associated with a higher risk of early-onset cognitive decline (OR, 1.71; 95% CI, 1.30-2.27) when adjusting for age, sex, education level, BMI, and comorbidities.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
Manera et al., 2021 (Italy)	Clinical features and cognitive sequelae in COVID-19: a retrospective study on N = 152 patients	Observational (3 months post infection) May 2020 – May 2021	MMSE	152 (33.6%)	67 ± 13.2	/	/	- Overall prevalence of cognitive deficits as assessed via the MMSE was 12.5%. - Impaired MMSE performance was more frequently observed in mild to moderate cases (26.3%).
Mattioli et al., 2021 (Italy)	Neurological and cognitive sequelae of Covid-19: a four month follow-up	Cross-Sectional (4 months post-acute infection) February 2020.	COWA, CVLT, TOL, MMSE	120 (75%)	47.86 ± Uns.	30 (73.3%)	45.73 ± Uns.	- No significant differences were observed between COVID-19 patients and controls in any cognitive assessment.
Mazza et al., 2021 (Italy)	Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up	Observational (3 months after hospital discharge)	BACS	226 (34.1%)	58.5 ± 12.79	/	/	- A high rate of cognitive deficits was observed in COVID-19 survivors at three months, with only 22% of the participants showing a good performance in all the cognitive domains. - - Executive functions and psychomotor coordination were the most impacted cognitive domain in 50% and 57% of the participants respectively. - Information processing, verbal fluency, and working memory were impaired in around 30% of the sample.
Méndez et al., 2021 (Spain)	Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors	Observational (2 months post discharge) March 2020 – April 2020	SCIP, COWAT, WAIS-III	179 (41.3%)	57 ± Uns.	/	/	- 105 (58.7%) patients met criteria for moderate neurocognitive impairment and 33 (18.4%) for severe neurocognitive impairment. - 38% of patients presented moderate impairment and 11.2% severe impairment in immediate verbal memory. In relation to delayed memory, 11.8% of survivors had moderate impairment and 2.8% had severe impairment. In semantic verbal fluency, 34.6% of patients had moderate deficits and 8.4% severe deficits. Lastly, working memory was moderately impaired in 6.1% and severely impaired in 1.1% of survivors.
Miskowiak et al., 2021 (Denmark)	Cognitive impairments four months after	Observational (3-4 months post discharge)	SCIP-D, TMT-B, CFQ	29 (41%)	56.2 ± 10.6	100 (59%)	56 ± 6.9	- The percentage of patients with clinically significant cognitive impairment ranged from 59% to 65% depending on the applied cut-off for clinical relevance of cognitive

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
	COVID-19 hospital discharge: Pattern, severity and association with illness variables	March 2020 - June 2020						impairment, with verbal learning and executive functions being most affected. - Patients displayed global cognitive impairments with a moderate to large effect size (SCIP total: $t = -2.78$, $df = 35.3$, $p = .01$; $d = -0.70$), and moderate impairments in verbal learning and working memory (VLT-I: $t = -3.06$, $df = 127$, $p = .003$, $d = -0.62$; WMT: $t = -2.11$, $df = 34.0$, $p = .04$, $d = -0.44$). Again, patients' delayed memory performance was unimpaired (VLT-D: $p = .17$), whereas there was only a non-significant trend toward verbal fluency and psychomotor speed impairments in patients compared with HC (VFT: $p = .08$; PMT: $p = .09$).
Miskowiak et al., 2022 (Denmark)	Cerebral metabolic rate of glucose and cognitive tests in long COVID patients	Cross-Sectional June 2020 – December 2021	SCIP-D, TMT-B	8 (63%)	54 ± 15	6 (50%)	56 ± 13	- Significantly impairment working memory and executive function in the impaired versus the intact groups.
Miskowiak et al., 2023 (Denmark)	Cognitive impairments among patients in a long-COVID clinic: Prevalence, pattern and relation to illness severity, work function and quality of life	Cross-Sectional June 2020 – December 2021	SCIP-D, TMT-B, CFQ	194 (56%)	50.8 ± 15.4	150 (56%)	50.9 ± 9.0	- Moderate to large impairments were seen in global cognition and in working memory and executive function, while mild to moderate impairments occurred in verbal fluency, verbal learning and memory. - Hospitalised and non-hospitalised patients showed similar degree of cognitive impairments when adjusted for age and time since illness. - Patients in the cognitively impaired group were older, female, more often hospitalised, had a higher BMI and more frequent asthma.
Monti et al., 2021 (Italy)	Two-months quality of life of COVID-19 invasively ventilated survivors; an Italian single-center study	Prospective cohort study (On average 61 days [51-71] post discharge from ICU). Uns.	MMSE (telephone version)	39 (10%)	56 ± 10.5	/	/	- Only 1 patient had cognitive impairment on the MMSE (telephone version) scale.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
Negrini et al., 2021 (Italy)	Neuropsychological features of severe hospitalized coronavirus disease 2019 patients at clinical stability and clues for postacute rehabilitation	Observational, case series (1 month post hospitalisation) Uns.	MMSE, FAB	9 (33%)	60.4 ± 16.3	/	/	- General cognitive decline was observed in 33.3% who had a pathologic MMSE score (*M* = 26.5 ± 2.9). All of these patients had low scores in the domain of attention and calculation, short-term memory, constructional praxia, and written language. - Only 1 patient demonstrated a decay of executive frontal functioning via the Frontal Assessment Battery (*M* = 15.4 ± 2.3), with deficits in conceptualization, lexical fluency, and motor programming.
Nogueira et al., 2022 (Portugal)	Effects of restraining measures due to COVID-19: Pre- and post-lockdown cognitive status and mental health	Observational, longitudinal (pre-COVID-19 cognitive data available with an approximate gap of 1.5 years between the assessments) June 2020 - Nov 2020	MMSE, MoCA, TMT-A, TMT-B, WAIS-III, DGS, Fluencies Protocol	150 (74.7%)	69.02 ± 7.95	/	/	- Significant differences were found in the MoCA total score, with an increase in performance in the second assessment (p = .020). - Performance of the TMT significantly differed between pre- to post-COVID-19 evaluations, with participants taking longer to finish the tasks in the 2nd assessment (TMT-A: p = .002; TMT-B: p = .000). - The same pattern was found for another measure of speed processing, with a significant decrease of the mean standardized score being observed (p = .002)
Ortelli et al., 2021 (Italy)	Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom	Cross-Sectional (Uns.) April 2020 – May 2020	MoCA, FAB, VT, SCWT, NT	12 (16.67%)	67 ± 9.6	12 (33.33%)	64.3 ± 10.5	- Significantly poorer global MoCA and FAB scores as compared to HCs. MoCA: Cases; 17.8 ± 5.3 vs HC: 26.8 ± 3.1; p <.001. FAB: Cases: 12.3 ± 2.3 vs HC: 16.7 ± 1.2; p < .001 - In regards to vigilance and executive attention, patients had significantly longer RTs in two out of three computerized tasks, while the error percentage was significantly higher in all three tasks compared to HCs.
Patel et al., 2021	Cognitive impairment and	Observational (Uns.)	MoCA	77 (36%)	61 ± 16.6	/	/	- 80.5% of patients exhibited cognitive impairment on admission.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
(USA)	functional change in COVID-19 patients undergoing inpatient rehabilitation	March 2020 – August 2020						- 45 patients with retest data, there were significant improvements in MoCA thus suggesting that cognitive impairment is frequent among COVID-19 patients, but improves over time and is associated with functional gain during inpatient rehabilitation.
Poletti et al., 2022 (Italy)	Long-term consequences of COVID-19 on cognitive functioning up to 6 months after discharge: role of depression and impact on quality of life	Cross-Sectional, Longitudinal (follow-up 1-3 and 6 months later) May 2020 – February 2021	BACS	312 (62%)	52.6 ± 8.8	165 (44%)	50.5 ± 9.2	- 79% of patients at 1 month and 75% at 3- and 6-month follow-up showed cognitive impairment in at least one cognitive function with no significant difference in cognitive performances between 1-, 3-, and 6 months. - COVID-19 survivors scored lower than controls in psychomotor coordination and attention and speed of information processing, performed worse than controls and similar to major depressive disorder patients in verbal fluency and executive functions, but did not differ from HC in working memory and verbal memory.
Puchner et al., 2021 (Austria)	Beneficial effects of multi-disciplinary rehabilitation in post-acute COVID-19: an observational cohort study	Observational (Uns.) April 2020 – July 2020	WMSIV, VVM, TAP	23 (30%)	57 ± 10	/	/	- Only 14 out of the 23 participants underwent a cognitive assessment. - Cognitive deficits of concentration, memory, and/or executive functions were found in 29% of the tested participants.
Raman et al., 2021 (UK)	Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge	Cross-Sectional (1.6 months after discharge) March 2020 – May 2020	MoCA	58 (41.4%)	55.4 ± 13.2	30 (40%)	53.9 ± 12.3	- 28% of participants had a total MoCA-score under cut-off (<26) compared to 17% of HCs but no significant difference between cases and controls was observed in the MoCA. - Impaired executive/visuospatial function was observed in patients compared to HCs.
Rousseau et al., 2021 (Belgium)	Post-intensive care syndrome after a critical COVID-19: cohort study from a	Observational, Longitudinal (follow-up 3 months later)	MoCA	32 (28%)	62 ± Uns.	/	/	- The effect of COVID-19 at the 3 month follow-up was evident in the MoCA scores as only 6.2% of patients fully recovered and had scores within the normal range at this timepoint.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
	Belgian follow-up clinic	March 2020 – July 2020						
Serrano del Pueblo et al., 2024 (Spain)	Brain and cognitive changes in patients with long COVID compared with infection-recovered control subjects	Single-Centre, Cross-Sectional March 2020 – April 2020	ACE III, WAIS III, BNT, Buschke Selective Reminding Test, ROCF, RMBT	83 (71%)	50.5 ± 2.59	22 (36%)	50.8 ± 1.03	- The mean global cognitive function of patients with Long COVID assessed by ACE III was significantly below the infection-recovered-controls. - We observed that 48% of patients with Long COVID had episodic memory deficit, with 27% also impaired overall cognitive function, especially attention, working memory, processing speed and verbal fluency.
Solaro et al., 2021 (Italy)	Cognitive impairment in young COVID-19 patients: the tip of the iceberg?	Cross-Sectional November 2020 – March 2021	MoCA	32 (41%)	53.7 ± 4.8	/	/	- 36.67% of patients scored below the threshold of the MoCA and therefore were depicting cognitive impairment.
Soldati et al., 2021 (Brazil)	Telephone screening of cognitive status (TICS) in severe COVID-19 patients: utility in the era of social isolation	Observational (on average 3.2 months post hospital discharge) March 2020 – May 2020	TICS	23 (21.73%)	53.6 ± 11.7	/	/	- 39% of participants scored less than 33 points on the TICS: *M* = 31.9 ± 1.2
van der Borst et al., 2021 (the Netherlands)	Comprehensive health assessment 3 months after recovery from acute coronavirus disease 2019 (COVID-19)	Observational (3 months post recovery) April 2020 – July 2020	TICS, CFQ	124 (40%)	59 ± 14	/	/	- Abnormal TICS scores were observed in 15% of patients (scored <34).
Vannorsdall et al., 2022 (USA)	Cognitive dysfunction, psychiatric distress, and functional decline after COVID-19	Observational (4 months post-acute diagnosis)	RAVLT, TMT, DST, fluency	82 (58.5%)	54.5 ± 14.6	/	/	- Out of 82 patients, 67% demonstrated ≥1 abnormally low cognitive score, Processing speed (35%), verbal fluency (26%–32%), learning (27%), and memory (27%) were most commonly impaired.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
		July 2020 – January 2021						- Patients requiring ICU stays displayed more severe and heterogenous impairment than those requiring less intensive treatment.
Whiteside et al., 2021 (USA)	Neurocognitive deficits in severe COVID-19 infection: Case series and proposed model	Case-Series (Uns.) Uns.	WAIS-IV, RDS, HVLT-R, RBANS, BDAE, TMT, TSAT, GDS	3 (33.3%)	70 ± 7	/	/	- Neurocognitive deficits after severe COVID-19 infection, particularly in encoding and verbal fluency.
Woo et al., 2020 (Germany)	Frequent neurocognitive deficits after recovery from mild COVID-19	Cross-Sectional (20-105 days post recovery) Uns.	TICS	18 (57.9%)	42.11 ± 14.3	10 (40%)	38.4 ± 14.4	- COVID-19 patients scored significantly lower in the TICS-M (*M* = 38.83) compared to healthy controls (*M* = 45.8), especially in short-term memory (*p* = .004), attention (*p* = .029) and concentration/language tasks (*p* = .009).
Yesilkaya et al., 2021 (Turkey)	COVID-19-related cognitive dysfunction may be associated with transient disruption in the DLPFC glutamatergic pathway	Case-Study (3 months post initial diagnosis). Uns.	FAB, GDS, TMT-A, TMT-B, CVLT	1 (0%)	29	/	/	- The patient's FAB score was 13 and GDS stage was 3. A number of errors were detected in both A and B parts of TMT and the scores were 2 and 4, respectively. The patient repeated 7 words in his first trial of CVLT. Overall, the results suggested impairment in varying spheres of cognition including memory, executive functioning, motor programming, attention and concentration.
Zhao et al., 2022 (UK)	Rapid vigilance and episodic memory decrements in COVID-19 survivors	Longitudinal May 2021	Sequence of 11 cognitive tasks	53 (43.4%) 36 (Uns.)	28.0 ± 8.6	83 (37.3%) 44 (Uns.)	29.0 ± 10.3	- COVID group displayed mild episodic memory impairment, relative to age-matched controls. - COVID-19 survivors had 30.6% false-positive responses which drove the impairment witnessed between the two groups. This finding may suggest that the deficit may be due impairments in binding information. - Older participants, relative to younger, had significantly larger memory deficits. In addition, there was no difference between elderly participants and COVID+ participants, suggesting COVID-19 survivors perform as if they're older. - Impairment in episodic memory resolved over time.

Author (s) (Country)	Study Title	Recruitment Strategy & Evaluation Period	Cognitive Tests	Patients		Controls		Results
				N (% F)	Age (*M* ± *SD*)	*N* (% F)	Age (*M* ± *SD*)	
Zhao et al., 2024 (UK & Germany)	Long COVID is associated with severe cognitive slowing: a multicentre cross-sectional study	Cross-Sectional May 2021 – July 2023	SRT^2, NVT	194 (74.2%)	48.8 ± 10.1	No-PCC 63 (57.1%) No-COVID 113 (46%)	No-PCC 48.7 ± 10.5 No-COVID 48.3 ± 11.5	- Pronounced cognitive slowing in patients with PCC, relative to age-matched healthy individuals who previously had symptomatic COVID-19 but not PCC. - Cognitive slowing was evident on a 30-s task measuring SRT^2, with patients with PCC responding to stimuli ∼3 standard deviations slower than HCs. - This finding was replicated across two clinic samples in Germany and the UK. - Comorbidities such as fatigue, depression, anxiety, sleep disturbance, and post-traumatic stress disorder did not account for the cognitive slowing in patients with PCC.
Zhou et al., 2020 (China)	The landscape of cognitive function in recovered COVID-19 patients	Cross-Sectional (2-3 weeks post COVID-19 infection) Uns.	TMT-A, TMT-B, SCT, CPT, DGS	29 (38%)	47 ± 10.5	29 (59%)	42.48 ± 6.94	- COVID participants had lower correct number CPT 2 (9.83 ± 1.93) and CPT 3 (8.21 ± 1.90) relative to the controls (p = .002). There was a trend of significant difference in the reaction time of CPT 1 and CPT 2 and correct number of CPT 2. - However, there was no significant difference between the two groups in TMT, SCT, or DST.

Note: Not applicable = /; Unspecified = Uns.

Abbreviations

ACE III = Addenbrooke's Cognitive Examination III
ACS = Attentional Control Scale
ANT = Attention Network Test
BACS = Brief Assessment of Cognition in Schizophrenia
BDAE = Boston Diagnostic Aphasia Examination
BNT = Boston Naming Test,
BMET = Brief Memory and Executive Test
BRB-NT = Brief Repeatable Battery of Neuropsychological Tests
BSRT = Babcock Story Recall Test
BTA = Brief Test of Attention
BVMT-R = Brief Visuospatial Memory Test-Revised
CDT = Clock Drawing Test
CFQ = Cognitive Failures Questionnaire
CFT = Category Fluency Test
Conners CPT 3 = Conners Continuous Performance Test-3
Corsi = Corsi block tapping test
CPM47 = Coloured Progressive Matrices 47
CPT = Continuous Performance Test
CVAT = Computer Visual Attention Test
CVLT = California Verbal Learning Test
DGS – Digit Span
D-KEFS = Delis-Kaplan Executive Function System
DSST = Digit Symbol Substitution Test
FAB = Frontal Assessment Battery
FCSRT = Free and Cued Selective Reminding Test
GDS = Global Deterioration Scale
HCs = Healthy controls
HVLT-R = Hopkins Verbal Learning Test Revised
IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly
JLO = Judgment Line Orientation
MCCB = The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)
MMSE = Mini-Mental State Examination
MoCA = Montreal Cognitive Assessment
NAB = Neuropsychological Assessment Battery
NIH = National Institute of Health
NT = Navon Task
NVT = Number Vigilance Test
PASAT = The Paced Serial Additions Test
PROMIS = Patient Reported Outcome Measurement Information System
RAVLT = Rey Auditory Verbal Learning Test
RVLT = Rey Verbal Learning Test
RBANS = The Repeatable Battery for the Assessment of Neuropsychological Status
RDS = Reliable Digit Span
RMBT = Rivermead Behavioural Memory Test
ROCF = Rey-Osterrieth Complex Figure
SCIP-D = Screen for Cognitive Impairment in Psychiatry Danish Version
SCT = Sign Coding Test
SCWT = The Stroop Colour and Word Test
SDMT = Symbol Digit Modalities Test
SPART = Spatial Recall Test
SRT^1 = Serial Recall Test
SRT^2 = Simple Reaction Time
TAP = Test of Attentional Performance
TAVEC = Test de Aprendizaje Verbal España-Complutense
TICS = Telephone Interview of Cognitive Status
TMT = Trail Making Test
TMT-A = Trail making A
TMT-B = Trail making B
TSAT = Test of Sustained Attention
OORT = Open-source Open-access Reaction Time
VOSP = Visual Object and Space Perception Battery
VT = Vigilance Task
VVM = Verbal and Visual Memory Test
WAIS = Wechsler Adult Intelligence Scale
WCST = Wisconsin Card Sorting Test
WLG = Word List Generation
WMS-IV = Wechsler Memory Scale- IV
WRAT-4 = Wide Range Achievement Test-IV
WMSIV = Logical Memory I & II of Wechsler Memory Scale-IV

2.3.1 Processing Speed

Processing speed as a cognitive domain refers to the ability of processing information rapidly (Ebaid et al., 2017). The speed of processing information increases through childhood and adolescence and reaches a peak in adulthood, and then a steady decline occurs(Kail & Salthouse, 1994). Processing speed impairment has been found in numerous studies exploring the impact of COVID-19 on cognitive function (Becker et al., 2021; Darley et al., 2021; Delgado-Alonso et al., 2022; Douaud et al., 2022; Ferrando et al., 2022; Ferrucci et al., 2021, 2022; Henneghan et al., 2022; Herrera et al., 2023; Jaywant et al., 2021; Krishnan et al., 2022; Martin et al., 2024; Nogueira et al., 2022; Poletti et al., 2022; Vannorsdall et al., 2022; Zhao et al., 2024). The mean age of participants in the above-mentioned studies was 53 years, ranging between 36 years (Henneghan et al., 2022) and 69 years (Nogueira et al., 2022). Not all of these studies have specified a specific prevalence rate, with the general prevalence of processing speed impairment reported to be between 18% (Becker et al., 2021) and 42% (Ferrucci et al., 2021).

Most of the aforementioned studies in fact reported a cognitive slowing, i.e., taking longer to complete the task which assessed processing speed (Delgado-Alonso et al., 2022; Douaud et al., 2022; Nogueira et al., 2022; Zhao et al., 2024). Many different factors were also mentioned which supposedly played a role in the apparent impairment in processing speed, with some suggesting the impairment is most observed in male sex (Henneghan et al., 2022), and others associating the impairment with COVID-19 severity and hospitalisation status (Becker et al., 2021; Henneghan et al., 2022; Vannorsdall et al., 2022). Only one study (Herrera et al., 2023) suggested that processing speed impairment was associated with younger age. Furthermore, an improvement in processing speed impairment was reported by Ferruci et al. (2022) from the five- to the 12-month follow-up assessment but another study also found no significant change in cognitive scores between the one-, three-, and six-month follow-up assessments (Poletti et al., 2022). More recently, a study solely focused on examining cognitive slowing in individuals with long COVID, compared to two different control groups [(i) individuals who had a previously been diagnosed with COVID-19 but not long COVID, and (ii) individuals with no history of COVID-19], found that long-COVID patients responded significantly more slowly relative to both control groups (Zhao et al., 2024). Slower reaction times (RTs) were also observed in another longitudinal study (Martin et al., 2024) investigating processing speed in

long-COVID patients, compared to healthy controls, with the cognitive slowing still present at the six-month follow-up (Martin et al., 2024). It is therefore clear from the current literature that a processing speed impairment is present in COVID-19 survivors, both with and without a long COVID diagnosis, with a potential improvement observed at follow-up assessments, yet whether this improvement is observed in long-COVID patients requires further research.

2.3.2 Attention

Attention as a cognitive domain is complex and does not have a set definition. It is broadly defined as a multi-level system in which individuals can source information and select the relevant course of action through various processes of mental prioritisation, which align with the relevant goal, action and/or intention (Narhi-Martinez et al., 2023; Rueda et al., 2023). Attention deficits following an infection of SARS-CoV-2 have widely been reported in the literature (Albu et al., 2022; Almeria et al., 2020; Becker et al., 2021; Crivelli et al., 2022; Delgado-Alonso et al., 2022; Diana et al., 2023; Ermis et al., 2021; Ferrando et al., 2022; Ferrucci et al., 2022; Galderisi et al., 2024; Henneghan et al., 2022; Herrera et al., 2023; Jaywant et al., 2021; Krishnan et al., 2022; Lamontagne et al., 2021; Negrini et al., 2021; Ortelli et al., 2021; Poletti et al., 2022; Serrano del Pueblo et al., 2024; Woo et al., 2020; Yesilkaya et al., 2021). The mean age of participants in the studies mentioned above was 51 years, ranging between 29 years (Yesilkaya et al., 2021) and 67 (Ortelli et al., 2021). The prevalence of attention impairment in COVID-19 survivors, based upon these studies, ranged from 100% (Diana et al., 2023) to 17% (Henneghan et al., 2022).

The main impairment in the attention domain in COVID-19 survivors related to either lower accuracy and/or slower RTs, relative to control groups (Crivelli et al., 2022; Lamontagne et al., 2021; Ortelli et al., 2021; Poletti et al., 2022; Woo et al., 2020). Moreover, many studies utilised a participant pool which included both hospitalised and non-hospitalised COVID-19 survivors. Interestingly, when it comes to attention deficits following a COVID-19 diagnosis, both mild cases that did not require hospitalisation (Delgado-Alonso et al., 2022; Krishnan et al., 2022) and severe cases which did require hospitalisation (Almeria et al., 2020; Becker et al., 2021; Jaywant et al., 2021; Poletti et al., 2022) are reported to show an impairment. Following on from this, Almeria et al. (2020) observed a reduction in attentional scores in

COVID-19 survivors who required oxygen therapy, whereas Jaywant et al. (2021) stated that intubation length or time since extubation was not significantly associated with attentional impairments post a COVID-19 diagnosis. Generally, it has been acknowledged that hospitalisation due to COVID-19 has impeded recovery on many fronts, including worsening cognitive functioning (Prescott, 2021). Other factors which have been associated with deficits in the attention domain post a COVID-19 diagnosis include male sex (Henneghan et al., 2022) and neurological symptoms, such as headaches during the COVID-19 infection (Almeria et al., 2020). In addition, deficits in the attention domain were not age dependent according to Herrera et al. (2023) as more than 25% of participants in each age group [(i) 26-39 years; (ii) 40-40 years; (iii) 50-64 years] exhibited a deficit in the attention task. Similar to processing speed, an improvement in attention deficits has been reported in COVID-19 survivors over time. An improvement of 12.5% and 7% on two separate tasks measuring attention was reported by Ferrucci et al. (2022) between the two time points. In addition, Diana et al. (2023) reported an improvement of 47% in attention scores between the six- and 16-month assessments. An impairment in attention has also been observed in long-COVID patients. Recent research has found significant differences between individuals with long COVID, relative to control groups, with the long COVID group performing worse on attention-related tasks, as well as other cognitive domains (Arbula et al., 2024; Serrano del Pueblo et al., 2024). Arbula et al. (2024) also reported that long-COVID participants scores were in fact not considered as impaired when compared to a normative sample. This clearly highlights the need for further research. It could be argued that other factors may be at play resulting in differences being present between long COVID and COVID-19 survivors, for example, sleep quality (Krishnan et al., 2022).

2.3.3 Working Memory

Working memory when referred to as a cognitive domain is defined as a system which stores and manipulates small amounts of information, which in turn allows for the completion of complex, cognitively demanding tasks (Chai et al., 2018; Cowan, 2014). Similar to the first two domains which have been explored in this chapter, working memory deficits following a SARS-CoV-2 infection have been observed in the literature (Albu et al., 2022; Almeria et al., 2020; Cian et al., 2022; Delgado-Alonso et al., 2022; Galderisi et al., 2024; Graham et al., 2021;

Hellmuth et al., 2021; Jaywant et al., 2021; Mazza et al., 2021; Méndez et al., 2021; Miskowiak et al., 2021; Miskowiak et al., 2022; Miskowiak et al., 2023), although to a lesser extent, relative to processing speed and attention. The mean age of participants in the studies that have mentioned an impairment in working memory was above 53 years, ranging between 44 years (Graham et al., 2021) and 65 years (Jaywant et al., 2021). Relative to the previous two cognitive domains, only a few studies explicitly specified the prevalence of working memory impairment in COVID-19 survivors. Two separate studies (Jaywant et al., 2021; Mazza et al., 2021) found approximately 30% of the participants to exhibit an impairment in working memory, whereas another study (Méndez et al., 2021) reported a moderate working memory deficit in only 6.1% of the participants. A systematic review (Cui et al., 2024) including 16 studies, totalling 4207 COVID-19 patients and 4026 controls, stated the prevalence of working memory impairment to be between 22.5% and 55% in the acute stage of COVID-19 survivors (Cui et al., 2024).

The majority of studies mentioned in this section observed significantly lower scores in COVID-19 survivors for working memory, relative to control groups (Cian et al., 2022; Delgado-Alonso et al., 2022; Galderisi et al., 2024; Graham et al., 2021; Miskowiak et al., 2021; Miskowiak et al., 2022; Miskowiak et al., 2023). The remainder of the studies also found lower scores for working memory but were either observational studies (Almeria et al., 2020; Jaywant et al., 2021; Mazza et al., 2021; Méndez et al., 2021) or a case study (Hellmuth et al., 2021). Although, a working memory impairment was observed in these studies, it was not the most impacted domain, and in a few studies it was actually the least impaired (Mazza et al., 2021; Méndez et al., 2021). In addition, there is no consensus with regards to the magnitude of a working memory impairment, as some studies report small effect sizes (Delgado-Alonso et al., 2022) and others large (Miskowiak et al., 2023). Some factors which have been noted in the literature that are associated with an impairment in working memory include neurological symptoms, such as, headaches and anosmia (Almeria et al., 2020), hospitalisation status (Almeria et al., 2020), elevated lactate dehydrogenase levels which indicate tissue damage (Galderisi et al., 2024), and metabolic changes in the cerebellum (Miskowiak et al., 2022). Although many studies have indicated a disruption in working memory post a COVID-19 infection, none of the above-mentioned studies are longitudinal, therefore it is difficult to make an assumption on the trajectory of this disruption and whether

an improvement is witnessed in survivors. Working memory disruption in long-COVID patients with a confirmed diagnosis has been studied less frequently than COVID-19 survivors in the acute and chronic stage. However, a few studies have observed a working memory impairment in long-COVID patients, relative to healthy controls (Espinar-Herranz et al., 2023; Miskowiak et al., 2023). Another interesting study compared long-COVID patients with an existing cognitive impairment ("impaired group") to long-COVID patients without an existing cognitive impairment ("intact group"), and a significant impairment in working memory was observed between the "impaired group" and the "intact group" (Miskowiak et al., 2022). This study clearly highlights the need for pre- versus post-COVID research design as it could be argued that pre-existing cognitive complaints may worsen post-COVID-19 cognitive disruption.

2.3.4 Executive Function

Executive function is another extremely important cognitive domain and it is the primary construct which allows humans to control and regulate emotion, make decisions, problem solve, plan, and also control impulsive behaviour (Blair, 2016). Executive function houses multiple skills which we as humans use every day, and it is traditionally defined as a top-down process which is implemented to allow for independent thinking, as well as deciding the best course of decision and action, with the evolutionary purpose of survival in mind (Blair, 2016; Diamond, 2013; Koziol & Lutz, 2013). Given the importance of this domain, executive function impairments have been highly studied in the COVID-19 field (Albu et al., 2022; Almeria et al., 2020; Arbula et al., 2024; Beaud et al., 2021; Becker et al., 2021; Becker et al., 2023; Cecchetti et al., 2022; Cian et al., 2022; Crivelli et al., 2022; Delgado-Alonso et al., 2022; Douaud et al., 2022; Ermis et al., 2021; Ferrando et al., 2022; Guo et al., 2022; Hellmuth et al., 2021; Henneghan et al., 2022; Herrera et al., 2023; Krishnan et al., 2022; Lamontagne et al., 2021; Mazza et al., 2021; Miskowiak et al., 2021; K. W. Miskowiak et al., 2022, 2023; Puchner et al., 2021; Raman et al., 2021; Yesilkaya et al., 2021). The studies which reported an impairment in executive function had a mean age of 52, ranging between 29 years (Yesilkaya et al., 2021) and 65 years (Beaud et al., 2021). Although executive function is widely studied and reported in the literature, only a select few studies provided a clear prevalence of executive function

dysfunction in COVID-19 survivors, ranging between 5% (Krishnan et al., 2022) and 62% (Beaud et al., 2021).

Many of the studies which observed an impairment in executive function stated that this domain was one of the most impacted domains after a diagnosis of COVID-19 (Beaud et al., 2021; Becker et al., 2021; Crivelli et al., 2022; Ermis et al., 2021; Henneghan et al., 2022; Herrera et al., 2023; Miskowiak et al., 2021; Miskowiak et al., 2022; Miskowiak et al., 2023; Puchner et al., 2021; Raman et al., 2021), with large effect sizes, a finding which is dissimilar to a systematic review of six studies that reported small-to-medium effect sizes (Velichkovsky et al., 2023). Most of these studies found lower scores for executive function in COVID-19 survivors, especially when compared against healthy controls (Arbula et al., 2024; Crivelli et al., 2022; Delgado-Alonso et al., 2022), however one study specifically observed a difference in RT, rather than the overall score for executive function (Guo et al., 2022), and another in completion time (Douaud et al., 2022). Furthermore, this study actually found little to no direct impact of COVID-19 on executive function (Guo et al., 2022), a finding which has also been echoed in other studies that reported only certain aspects of executive function were impaired (Arbula et al., 2024; Cian et al., 2022; Krishnan et al., 2022). Interestingly, the mean age of studies that reported a severe impairment for executive function was slightly lower than the ones that reported a minimal impact of COVID-19 on executive function, however this cannot be said with certainty as Guo et al. (2022) failed to report the mean age of their participants. A few risk factors have also been associated with an impairment in executive function following a COVID-19 diagnosis; these include, but are not limited to, neurological symptoms during infection (Almeria et al., 2020), hospitalisation status (Almeria et al., 2020; Becker et al., 2021; Becker et al., 2023), respiratory distress (Cecchetti et al., 2022), existing cognitive impairment (Miskowiak et al., 2022), and/or psychopathology (Mazza et al., 2021). Research has indicated that executive function impairment is also present in individuals with a diagnosis of long COVID (Ariza et al., 2023; K. W. Miskowiak et al., 2022, 2023; Pallanti et al., 2023), and this impairment is correlated with long-COVID symptoms, such as, respiratory problems, fatigue, and headaches (Ariza et al., 2023), and even increased cytokine levels, in particular interleukin-6 and ferritin (Ferrando et al., 2022; Pallanti et al., 2023).

2.3.5 Memory (Episodic)

Episodic memory refers to the ability to store, learn and retrieve conscious memories relating to past events and/or experiences, for example, dates, times, and locations of events (Dickerson & Eichenbaum, 2010; Ghetti & Bunge, 2012; Tulving, 2002). Episodic memory itself can be divided into immediate recall (commonly referred to as short-term memory), delayed recall, and recognition (Huo et al., 2018). Episodic memory deficits post a COVID-19 diagnosis have also been reported in the literature (Albu et al., 2022; Becker et al., 2021; Cecchetti et al., 2022; Cian et al., 2022; Delgado-Alonso et al., 2022; Diana et al., 2023; Ermis et al., 2021; Ferrando et al., 2022; Ferrucci et al., 2021; Serrano del Pueblo et al., 2024; Zhao et al., 2022, 2023), although relative to the other four domains that have been explored, literature on this particular domain is fairly limited. Studies which have observed an impairment in episodic memory post a COVID-19 diagnosis have a mean age of approximately 51 years, ranging between 29 years (Zhao et al., 2022) and 63 years (Ermis et al., 2021). The prevalence for episodic memory impairment is sparsely reported, with a wide range, and variance between immediate versus delayed recall. Two separate studies have reported a prevalence of between 14% and 26% (Diana et al., 2023; Ferrucci et al., 2021), whereas another has observed episodic memory impaired in 48% of COVID-19 survivors (Serrano del Pueblo et al., 2024).

All the studies mentioned happen to find an impairment in recall, with some finding an impairment in both immediate and delayed recall (Albu et al., 2022; Cecchetti et al., 2022; Diana et al., 2023), and others in specific aspects of episodic memory, such as delayed recall and immediate recall, respectively (Ermis et al., 2021; Ferrucci et al., 2021). Similar to all the other cognitive domains that have been explored, episodic memory was also impacted the most in COVID-19 survivors, relative to controls, and more so in those individuals that had been hospitalised due to their diagnosis (Becker et al., 2023; Cecchetti et al., 2022; Cian et al., 2022; Delgado-Alonso et al., 2022; Serrano del Pueblo et al., 2024; Zhao et al., 2022). Apart from hospitalisation status, symptoms experienced during the acute stage of COVID-19 and medical comorbidities were also mentioned as risk factors (Ferrando et al., 2022). Nonetheless, an improvement in episodic memory was observed by many longitudinal studies (Cecchetti et al., 2022; Diana et al., 2023; Zhao et al., 2022). An impairment in episodic memory is also observed in long-COVID patients (Serrano del Pueblo et al., 2024; Zhao et al.,

2022), with pre-existing cognitive impairment reported as a risk factor (Zhao et al., 2022). An improvement in episodic memory was also observed in long-COVID patients, yet it is important to note that the impairment witnessed in this group was mild to begin with (Zhao et al., 2022).

2.4 COVID-19 and Long COVID: The Impact on Psychological Well-being and Sleep

In addition to understanding the impact of COVID-19 on cognitive function, scientists and researchers alike have sought to understand the impact of COVID-19 and long COVID on psychological well-being and sleep. It is widely acknowledged that even a small change in psychological well-being and sleep can impact day-to-day life (Ho et al., 2018). Multiple systematic reviews and meta-analyses (Anteneh et al., 2023; Badenoch et al., 2022; De Kock et al., 2021; Schou et al., 2021; Seighali et al., 2024; Singh et al., 2021; Vanderlind et al., 2021; Vindegaard & Benros, 2020; Xiong et al., 2020; Zeng et al., 2023) have taken place to synthesise the vast amount of literature covering the impact of COVID-19 on psychological well-being and sleep. Whilst this is not an exhaustive list, these systematic reviews provide a clear insight into the impact of COVID-19 on psychological well-being and sleep.

The systematic reviews mentioned in this section that have collated research on the psychological impact of COVID-19 vary in size, some were extremely large and analysed 151 different studies, including a total of 1,285,407 participants (Zeng et al., 2023), whereas others were small with eight studies reviewed, totalling 3,489 participants (Anteneh et al., 2023). All these reviews commented on multiple aspects of psychological well-being, including PTSD, depression, anxiety, stress, insomnia. For the purpose of this chapter, the focus will be on depression, anxiety, stress, and sleep. Studies exploring depression as a neuropsychiatric symptom post COVID-19 were mentioned in all the systematic reviews, and the prevalence ranged between 0% (Schou et al., 2021) and 68.5% (Vanderlind et al., 2021). The pooled prevalence ranged between 12.9% (Badenoch et al., 2022) to 43.49% (Anteneh et al., 2023). Anxiety was the second most mentioned, with a prevalence ranging between 5% and 55.2% (Vanderlind et al., 2021), and the pooled prevalence for anxiety ranged between 16.2% (Zeng et al., 2023) and 46.27% (Anteneh et al., 2023). Stress was the least mentioned neuropsychiatric symptom in the various systematic reviews, with only one study mentioning

a range of 8.1% to 81.9% in COVID-19 survivors (Xiong et al., 2020). The pooled prevalence for stress in two different systematic reviews was 31.43% (Anteneh et al., 2023) and 60.7% (Singh et al., 2021). Sleep disturbances following a COVID-19 diagnosis were documented less frequently compared to depression and anxiety. Nonetheless, Vanderlind et al. (2021) reported that approximately 20% to 52.2% of COVID-19 survivors reported some form of sleep disturbance. Many other systematic reviews also observed a similar pooled prevalence, ranging between 13.5% (Zeng et al., 2023) and 34% (De Kock et al., 2021). A large systematic review, including a total of 9,923,461 long-COVID patients reported a pooled prevalence rate of 23% for depression and anxiety, and 45% for sleep disturbances (Seighali et al., 2024). This recent review highlights a potential reduction in depression and anxiety prevalence rates, as also noted by Zeng et al. (2023) who saw a reduction between six and 12 months post a COVID-19 diagnosis. On the contrary, prevalence rates for sleep disturbances appear to have increased.

Multiple risk factors have been noted in the literature that have been associated with distress in psychological well-being and sleep quality. The vast majority of the reviews reported female sex, pre-existing psychological illnesses, socio-economic factors, such as, employment status and education level (Anteneh et al., 2023; De Kock et al., 2021; Schou et al., 2021; Vanderlind et al., 2021; Vindegaard & Benros, 2020; Xiong et al., 2020), and frontline workers, such as healthcare workers, to be the most impacted (De Kock et al., 2021; Dubey et al., 2020; Singh et al., 2021; Vindegaard & Benros, 2020). More specifically, a lack of personal protective equipment, fear of spreading the virus, and burnout contributed to the higher prevalence seen in frontline workers (De Kock et al., 2021; Dubey et al., 2020). Given the vast impact of COVID-19 and long COVID on psychological well-being and sleep, it is imperative that further research, in particular longitudinal studies, are conducted to understand the trajectory of this impairment.

2.5 Overview of the Findings

As explored above, there is evidence of both a cognitive and psychological well-being disruption post a SARS-CoV-2 infection. There is however a general lack of consensus as to the degree and prevalence of these impairments. Some studies have observed an overlap and

suggest that all aspects of cognitive function and psychological well-being are impacted. On the other hand, some studies only found deficits in specific cognitive domains and psychological well-being. It is also important to consider the effect sizes of these findings. Many studies have reported vastly different effect sizes for the same cognitive domain or a different level of impact on the same psychological well-being aspect. There could be numerous factors which lead to such varying results. Firstly, studies investigating the impact of COVID-19 on neuropsychological function utilised varying assessment tools. This can have benefits, such as, providing a clear picture of the possible impairment but also it can make it difficult to compare results directly. Secondly, studies exploring the impact of COVID-19 on both cognitive function and psychological well-being have predominately utilised hospitalised and/or elderly participants. Some studies which have found a minimal disruption to cognitive function and psychological well-being post a COVID-19 diagnosis and/or no difference between individuals with a confirmed COVID-19 diagnosis and controls have either utilised a younger sample group and/or individuals who experienced a milder infection. Study design also plays a crucial part, as many studies lacked the ability to compare to a control group, limiting the potential to fully understand any possible cognitive and/or psychological impairment.

Given that both cognitive and psychological well-being can be impaired post a COVID-19 diagnosis, it is important to understand the extent to which this impairment is present cross-sectionally and longitudinally. This could potentially aid in a path towards normality and recovery for those individuals that are impacted post COVID-19.

2.6 Chapter Summary

Cognitive function and psychological well-being are important aspects of everyday life and an impairment in either of these can impede daily functioning. This chapter therefore reviewed the impact of COVID-19 on both cognitive function and psychological well-being. The array of literature has highlighted that most cognitive domains, namely, processing speed, attention, working memory, executive function, and memory can all be impacted post a COVID-19 diagnosis. Furthermore, depression, anxiety, stress, and sleep are also disrupted in COVID-19 survivors. Various risk factors that may have potentially contributed to the worsening of

cognitive function and psychological well-being were also explored, with a general consensus suggesting female sex, hospitalisation status, and pre-existing cognitive and/or psychological impairment as being the most prominent risk factors. Although significant impairments appear to be present in cognitive function and psychological well-being in COVID-19 survivors, this chapter has emphasised the need for further longitudinal and cross-sectional research. Many studies solely focused on severely ill, hospitalised and/or elderly individuals. The next chapters will try and address this through empirical investigations that began well before many of the reviewed studies were published.

Chapter Three: Thesis Aims and Objectives

3.1 Introduction

The novel COVID-19 disease which was declared a pandemic by the WHO in early 2020 has caused a large number of infections as well as deaths. As already described in Chapters One and Two, COVID-19 itself appears very similar to its predecessors on multiple fronts, including its ability to infiltrate the CNS. During the start of the pandemic, only a handful of symptoms were thought to be associated with COVID-19 but, as time went on and different variants made their appearance, this list of symptoms grew exponentially. These symptoms include CNS symptoms, some of which were fatal. However, what was concerning was the sheer number of infected individuals reporting both cognitive and psychological complaints, acutely as well as chronically.

Even prior to the pandemic, research had highlighted the importance of intact cognitive functioning and psychological well-being for everyday life (Chapter Two, Section 2.2) and this led to many doctors, scientists, and researchers from around the world turning their attention to the impact of COVID-19 on neuropsychological function. Although the literature in general suggests a correlation between a COVID-19 diagnosis and impaired neuropsychological function, it is difficult to ascertain this impairment without being able to compare results to pre-pandemic data. Moreover, many studies have utilised severely ill, hospitalised, elderly participant groups, findings for whom cannot be generalised to the general population, especially to younger individuals.

This PhD project therefore aimed to examine the impact of COVID-19 on cognitive function, psychological well-being, and multiple brain structures longitudinally, utilising a working-age sample, including a sub-sample for whom pre-COVID-19 data were available.

3.2 Aims and Objectives

The specific aims of the empirical investigations reported in this thesis were as follows:

1. a) To examine the impact of COVID-19 on cognitive function and mental health, as well as the relationship between cognitive function and mental health, in working-age UK

residents using a cross-sectional (between-groups) design, and b) investigate changes in cognitive function from pre-to post-COVID-19 diagnosis in a sub-sample using a within-subjects design (Chapter Four);

2. To examine possible recovery of cognitive function six months after the initial assessment in the sample investigated earlier (Chapter Five);
3. To examine, using whole brain MRI, brain structure and cognitive function in association with persistent COVID-19 related symptoms in working-age adults (Chapter Six)

In order to examine these aims, all participants from the general population provided demographic information, including information related to their COVID-19 diagnosis, if applicable, followed by being assessed on five cognitive domains (processing speed, attention, working memory, executive function, and memory) through the MyCognition PRO mobile application and completing three psychometric tests assessing general health, depression, anxiety and stress and finally, sleep quality. For the final aim, a different set of participants from the general population were required to take part in a single MRI assessment, followed by the MyCognition PRO cognitive assessment and the three psychometric tests.

3.2.1 Plan of Investigation

This thesis contains results from three empirical studies, each corresponding to one of the aims mentioned earlier:

1. A behavioural study investigating the effects of COVID-19 on cognitive function and the associations of psychological well-being on cognitive function (Chapter Four);
2. A follow-up behavioural study investigating the longitudinal impact of COVID-19 and long COVID on cognitive function, mental health, and sleep (Chapter Five);
3. A neuroimaging study investigating the impact of long COVID on brain structures and its association with cognitive function, mental health, and sleep (Chapter Six).

Chapter Four: The Cognitive Impact of COVID-19 – An Empirical Study

This chapter has been published as (Appendix K):

Vakani, K., Ratto, M., Sandford-James, A., Antonova, E., & Kumari, V. (2023). COVID-19 and cognitive function: Evidence for increased processing speed variability in COVID-19 survivors and multifaceted impairment with long-COVID symptoms. *European Psychiatry, 66*(1), e43. https://doi.org/10.1192/j.eurpsy.2023.25

4.1 Chapter Aims and Overview

Existing literature, explored in Chapter Two highlights the negative impact of COVID-19 on cognitive function and psychological well-being. Yet, there is a gap in the literature as not many studies have been able to explore the impact of COVID-19 longitudinally, utilising pre-COVID-19 data. Furthermore, many studies included only participants that had experienced a severe infection and were hospitalised and/or were elderly. The study presented in this chapter therefore focuses on understanding the relationship between a confirmed COVID-19 diagnosis, cognitive function and mental health in a working-age sample from the general population, relative to a control group with no known history of COVID-19, as well as exploring changes from pre- to post-COVID-19 in sub-sample.

4.2 Introduction

A growing body of evidence indicates widespread brain and cognitive changes in people with a history of COVID-19, including those who did not show severe symptoms and did not require hospitalisation (Hampshire et al., 2021; Najt et al., 2021). According to a systematic review (Vanderlind et al., 2021), approximately 15 to 40% of COVID-19 survivors, compared to people without a history of COVID-19, show abnormal performance in one or more cognitive domain(s). More recent cross-sectional studies also indicate attention concentration (Delgado-Alonso et al., 2022; Henneghan et al., 2022), processing speed (Henneghan et al., 2022), memory (Guo et al., 2022), visuospatial processing (Delgado-Alonso et al., 2022), executive function (Delgado-Alonso et al., 2022; Guo et al., 2022; Henneghan et al., 2022), and general cognitive ability (Hampshire et al., 2021) to be negatively impacted by COVID-19. Crivelli et al. (2022) in their review of 27 studies observed impaired attention, executive functions, and memory in adults who had been assessed at some point, ranging from the acute phase to seven months after the COVID-19 infection. Most of the existing studies with an objective assessment of cognitive function, however, have utilised cross-sectional designs and focused on adults in late adulthood [mean age across 27 studies = 56.05 years, (Crivelli et al., 2022)] who may be particularly vulnerable to negative impacts of COVID-19 (Matsui et al., 2023). Furthermore, poor cognitive function itself has been linked to greater COVID-19 infection severity and mortality (Batty et al., 2021), raising the possibility that some of the COVID-19-related cognitive effects may be explained by pre-COVID-19 differences between COVID-19 and non-COVID groups. The only study published to date (*n* = 785, age range: 51–81 years, Biobank cohort data, UK) (Douaud et al., 2022) to use objective measures of cognitive function both pre- and post-COVID-19 reported a slight impairment in processing speed and executive function (as assessed by the Trail Making Test Trails A and B completion time, respectively) at 141 days, on average, from the COVID-19 diagnosis. There was no significant impact of COVID-19 history on eight other cognitive indices derived from six cognitive tests. Furthermore, many COVID-19 survivors report anxiety, depression, sleep difficulties, and PTSD (Dai et al., 2020; Guo et al., 2020; Vanderlind et al., 2021) which could cause or exacerbate cognitive difficulties reported by COVID-19 survivors. For many people, COVID-19 also has lasting effects, commonly referred to as long COVID (Mahase, 2020). In the UK, an estimated 1.9 million people have self-reported long-COVID symptoms at four weeks

post-infection (ONS, 2023). A large study (*N* = 236,379) reported neuropsychiatric diagnosis in 33.62% of patients six-months post-infection, and this prevalence rate rose to 46.2% for patients who had received intensive care (Taquet et al., 2021). Although some of these consequences may be due to pre-existing medical and/or psychiatric conditions (Levine et al., 2020), it seems likely that COVID-19 itself results in short- and long-term neuropsychological symptoms for some people (Butler et al., 2020), and cognitive disruption may be more salient in association with long-COVID symptoms.

The main aims of the present study, therefore, were to examine: (i) the effects of COVID-19 history on cognitive function in the UK residents of working-age (18–69 years); and (ii) the associations of long-COVID symptoms as well as physical and psychological well-being with cognitive function post COVID-19 diagnosis. To achieve these aims, we conducted a cross-sectional investigation of cognitive function and health in individuals with a confirmed COVID-19 diagnosis compared to those with no COVID-19 history (COVID and non-COVID groups, respectively) followed by a longitudinal investigation of participants in the COVID and non-COVID groups for whom pre-COVID-19 pandemic cognitive function data were available through an existing database. Based on the findings of previous reviews (Crivelli et al., 2022; Vanderlind et al., 2021), we expected multifaceted cognitive impairment, with the same cognitive indices being impacted by COVID-19 history in both the cross-sectional and longitudinal investigations. We further expected reduced physical and mental well-being in the COVID compared to the non-COVID group, and explored whether cognitive profiles associated with COVID-19 are explained, at least in part, by poor health and well-being. Lastly, we expected long-COVID symptoms to be associated with reduced cognitive function and poor well-being.

4.3 Methods

4.3.1 Participants and Design

The cross-sectional investigation involved 222 adults (mean age = 38.70, *SD* = 12.08, range: 18–69): 129 with a COVID-19 diagnosis (COVID group) and 93 with no known/confirmed COVID-19 diagnosis (non-COVID group) (see Table 4.1 for the demographic characteristics).

Table 4.1

Sample characteristics

		Cross-Sectional Sample		Longitudinal Sub-sample	
		COVID Group *N* = 129 (23 M, 106 F)	Non-COVID Group *N* = 93 (32 M, 61 F)	COVID Group *N* = 30 (4 M, 26 F)	Non-COVID Group *N* = 33 (7 M, 26 F)
		n (% of *N*)	*n* (% of *N*)	*n* (% of *N*)	*n* (% of *N*)
Ethnicity	White British	107 (82.9%)	41 (44.1%)	24 (80.0%)	28 (84.9%)
	South Asian	13 (10.1%)	42 (45.2%)	2 (6.7%)	2 (6.1%)
	Other Asian	1 (0.8%)	4 (4.3%)	0	1 (3.0%)
	Black British	1 (0.8%)	2 (2.2%)	0	1 (3.0%)
	Mixed Race	6 (4.7%)	3 (3.3%)	3 (10.0%)	0
	Other	1 (0.8%)	1 (1.1%)	1 (3.3%)	1 (3.0%)
Educational Background	High School	7 (5.4%)	5 (5.4%)	2 (6.7%)	4 (12.1%)
	College/6th Form	20 (15.5%)	11 (11.8%)	5 (16.7%)	3 (9.1%)
	Vocational Qualification	16 (12.4%)	7 (7.5%)	4 (13.3.%)	6 (18.2%)
	Bachelor's Degree	50 (38.8%)	33 (35.5%)	12 (40%)	11 (33.3%)
	Master's Degree	26 (20.2%)	31 (33.3%)	6 (20%)	7 (21.2%)
	PhD or Higher	7 (5.4%)	6 (6.5%)	0	2 (6.1%)
	Prefer not to say	3 (2.3%)	0	1 (3.3%)	0
Employment Status	Employed Full-time	61 (47.3%)	54 (58.1%)	15 (50.0%)	13 (39.4%)
	Employed Part-time	26 (20.2%)	12 (12.9%)	5 (16.7%)	5 (15.2%)
	Student Full-time	9 (7.0%)	10 (10.8%)	3 (10.0%)	3 (9.1%)
	Student Part-time	1 (0.8%)	2 (2.2%)	1 (3.3%)	1 (3.0%)
	Unemployed	1 (0.8%)	1 (1.1%)	1 (3.3%)	1 (3.0%)
	Retired	2 (1.6%)	2 (2.2%)	1 (3.3%)	2 (6.1%)
	Semi-retired	3 (2.3%)	3 (3.2%)	1 (3.3%)	1 (3.0%)
	Homemaker	2 (1.6%)	1 (1.1%)	0	1 (3.0%)
	Unable to Work	12 (9.3%)	2 (2.2%)	0	2 (6.1%)
	Other	8 (6.2%)	5 (5.4%)	0	3 (9.1%)
	Prefer not to say	4 (3.1%)	1 (1.1%)	3 (10.0%)	1 (3.0%)
Physical Health Conditions	Cancer	5 (3.9%)	0	3 (10.0%)	0
	Diabetes	10 (7.8%)	5 (5.4%)	2 (6.7%)	1 (3.0%)
	Heart Condition	8 (6.2%)	2 (2.2%)	2 (6.7%)	2 (6.1%)
	Immunosuppressed	8 (6.2%)	2 (2.2%)	1 (3.3%)	1 (3.0%)
	Kidney Disease	1 (0.8%)	0	0	0
	Liver Disease	2 (1.6%)	1 (1.1%)	2 (6.7%)	1 (3.0%)
	Lung Condition	28 (21.7%)	7 (7.5%)	4 (13.3%)	3 (9.1%)
	Neurological Condition	7 (5.4%)	1 (1.1%)	4 (13.3%)	1 (3.0%)
	Obesity	18 (14.0%)	7 (7.5%)	2 (6.7%)	2 (6.1%)
	Organ Transplantation	1 (0.8%)	0	0	0
Mental Health Conditions	Anorexia Nervosa	2 (1.6%)	2 (2.2%)	0	2 (6.1%)
	Anxiety	56 (43.4%)	39 (41.9%)	15 (50.0%)	23 (69.7%)
	ADHD	3 (2.3%)	3 (3.2%)	2 (6.7%)	1 (3.0%)
	Depression	48 (37.2%)	27 (29%)	12 (40.0%)	18 (54.5%)
	Eating Disorder(s)	8 (6.2%)	4 (4.3%)	2 (6.7%)	3 (9.1%)
	Insomnia	29 (22.5%)	13 (14%)	4 (13.3%)	9 (27.3%)

OCD	7 (5.4%)	5 (5.4%)	2 (6.7%)	3 (9.1%)
Panic Disorder	10 (7.8%)	7 (7.5%)	3 (10.0%)	7 (21.2%)
Personality Disorder	4 (3.1%)	1 (1.1%)	1 (3.3%)	1 (3.0%)
Phobias	9 (7.0%)	7 (7.5%)	3 (10.0%)	4 (12.1%)
PTSD	18 (14.0%)	6 (6.5%)	5 (16.7%)	6 (18.2%)
Psychosis	2 (1.6%)	3 (3.2%)	0	3 (9.1%)
Other	2 (1.6%)	1 (1.1%)	0	0

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; F, females; M, males; OCD, Obsessive Compulsive Disorder; PTSD, Post-Traumatic Stress Disorder.

The longitudinal investigation involved 63 of these 222 adults, who had pre-COVID-19 pandemic cognitive function data available via MyCognition (MyCognition, 2023). Participants were recruited via social media platforms and MyCognition. Recruitment via MyCognition was conducted in two stages. First, a large group within the MyCognition database who had been assessed since 2017 (*N* = 2894) were invited to participate if they self-reported a confirmed COVID-19 diagnosis. An invitation to participate was then extended to adults with pre-COVID-19 cognitive data who self-reported no COVID-19 history. Participant testing period was March 2021–February 2022 for the COVID group and March 2021–March 2022 for the non-COVID group (recruitment of non-COVID participants stopped after the pandemic-related restrictions in the UK were fully lifted).

The study was approved by the University Research Ethics Committee (26518-A-Sep/2021–34167-1). All participants provided written consent and received £10 (Amazon voucher) for their time.

4.3.2 Measures and Procedure

Demographic, physical, and psychological well-being data were collected using self-report measures administered via Qualtrics (an online survey tool), taking approximately 45 minutes in total. The demographic items included age, sex, ethnicity, education, socio-economic status, existing mental and physical illnesses, and medication use. In addition, COVID participants were asked about their COVID-19 diagnosis, acute symptoms, subjective cognitive impairment (via a single question "Do you believe your cognitive functioning has been impacted due to your diagnosis of COVID-19?") and chronic long-COVID symptoms at the time of participation. Cognitive data were collected via the MyCognition PRO mobile application, taking approximately 15 minutes.

4.3.2.1 Physical and Psychological Well-Being

Physical and psychological well-being were assessed using three self-rated scales:

Short Form Health Survey-36 (SF-36) (Ware & Sherbourne, 1992): SF-36 is a 36-item scale measuring physical, social and emotional functioning, and quality of life through eight

dimensions: physical functioning, physical health, emotional problems, energy, emotional well-being, social functioning, pain and general health.

The Depression, Anxiety and Stress Scale-21 (DASS-21) (Lovibond & Lovibond, 1995): DASS-21 is a 21-item scale assessing levels of depression (dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest, anhedonia, inertia), anxiety (autonomic arousal, skeletal muscle effects, situational anxiety, anxious affect) and stress (levels of chronic non-specific arousal such as problems with relaxation and emotional overactions).

Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989): PSQI is a 19-item, four-point Likert scale assessing daytime dysfunction, use of sleeping medication, sleep disturbances, habitual sleep efficiency, sleep duration, sleep latency and subjective sleep score.

4.3.2.2 Cognitive Function

Cognitive function was assessed online using a self-administered online assessment tool (MyCognition [MyCQ], https://www. mycognition.com/). The MyCQ tool comprises of digital versions of commonly utilised neuropsychological tests validated against the Cambridge Neuropsychological Automated Test Battery (Domen et al., 2019; Reeson et al., 2019) and assesses processing speed, attention, working memory, executive function and memory domains (Bellens et al., 2022).

Processing speed was assessed using a Simple RT task, requiring participants to tap the circle button as quickly as possible when a red circle is presented on the screen (presentation time = one second, inter-stimulus interval = three seconds, 30 stimuli in total). Response accuracy (RA; % correct), average RT (ms) and intraindividual variability in RT were examined.

Attention was assessed using a Choice RT task, requiring participants to tap either the circle or triangle button depending on what shape is presented on the screen. There are 30 trials in total, and each stimulus (circle or triangle) is presented for one second, with a three second inter-stimulus interval. RA (% correct) and average RT (ms) for correct answers were examined.

Working Memory was assessed using the 2-Back task. Participants are asked to tap “Yes” or “No” depending on whether the picture presented to them on the screen (household objects,

food and drink items) matches the picture shown two screens back (50 trials in total). RA (% correct) was used to index task performance.

Executive Function was assessed using the Trail-Making B task, requiring tapping a number and a letter in an ascending and alphabetical order, respectively, to produce an alternating sequence (e.g., 1, A, 2, B). The task has 25 trials (13 numbers, 12 letters). RA (% correct moves) and total task completion time (ms) were examined.

Memory was assessed using a Visual Recognition Memory task. Participants are presented with a set of 24 pictures (each picture for two seconds, inter-stimulus interval = one second) and instructed to remember them. They are then presented with 96 pictures, including 24 pictures presented earlier, and asked to tap either "Yes" or "No" depending on whether they remember seeing the picture earlier. RA (% correct) was used to index task performance.

4.3.3 Statistical Analysis

For the cross-sectional investigation, we first compared the COVID and non-COVID groups on age and body mass index (BMI) (separately) using a 2 (Group: COVID, non-COVID) × 2 (Sex: Males, Females) analysis of variance (ANOVA). Group differences in each of the health and cognitive variables were examined using a 2 (Group) × 2 (Sex) ANOVA, followed by 2 (Group) × 2 (Sex) analyses of covariance (ANCOVA), covarying for age, given that the COVID group, on average, was found to be older than the non-COVID group (Table 4.2). For the two cognitive variables showing a significant Group effect, further (exploratory) ANOVAs were run with Ethnicity (White British versus all other ethnicities) included as an additional between-subjects factor. Any significant interactions were followed up with post hoc comparisons using paired or independent sample *t*-tests as appropriate. As these comparisons were conducted to follow significant main effects or interactions from ANOVAs/ANCOVAs and probed predefined, priori hypotheses, corrections for multiple comparisons (for both cross-sectional and longitudinal investigations) were not considered. Effect sizes, where reported, are partial eta squared (η_p^2; the proportion of variance associated with a factor). In the COVID group, the relationships of cognitive variables with the overall long COVID-19 symptom load (a sum total of individual symptom ratings) were examined using Pearson's correlations, and with each of the long-COVID symptoms (rated 0–7) explored using Spearman rank order

correlations. Pearson's correlations were also used to explore the relationships between all cognitive variables and the physical and mental health measures in the entire sample, and in the COVID and non-COVID groups separately.

For the longitudinal (within-subjects) investigation, the COVID and non-COVID groups were compared on age and BMI using independent sample *t*-tests (sex not analysed due to relatively small number of males). The effect of COVID-19 diagnosis on each of the cognitive variables was then examined using a 2 (Group: COVID, non-COVID) × 2 (Time: Pre-COVID, Post-COVID) ANOVA with Group as a between-subjects and Time as a within-subject factor. Given that poor cognitive function has been linked to more severe acute COVID-19 and hospitalisation (Batty et al., 2021), the relationship between the overall long-COVID symptom load and pre-pandemic cognitive data in the longitudinal COVID sub-sample (n = 29) was also examined using Pearson's correlations.

All analyses were performed using the Statistical Package for Social Sciences (for Windows, version 28; IBM, New York, NY). The data distribution on all variables met the assumptions of parametric statistical procedures. Alpha level for testing the significance of effects was maintained at $p \leq 0.05$.

4.4 Results

4.4.1 Cross-Sectional Investigation

4.4.1.1 Sample Characteristics

The majority of participants in both the COVID (n = 129) and non-COVID (n = 93) groups were White British, held a Bachelor's degree or above and were in some form of employment. The COVID group was, on average, significantly older (Table 4.2), and had more people with at least one physical health problem (n = 58; 44.96%; most commonly related to lungs), compared to the non-COVID group (n = 21; 22.58%). Of various mental health conditions, anxiety, depression, and insomnia were most commonly reported by both groups (Table 4.1).

Within the COVID group, 20 participants (15.5%) had been hospitalised (Tables 4.3 and 4.4). The most prevalent acute symptom (recalled retrospectively) was a high temperature (76.7%).

Table 4.2

Descriptive statistics and group differences (ANOVA and ANCOVA results) in the demographic, mental health and well-being measures for the cross-sectional investigation

	COVID Group *M* (*SD*)				Non-COVID Group *M* (*SD*)				ANOVA *F*(1, 218) (*p*) η_p^2			ANCOVA (covarying for age) *F*(1, 217) (*p*) η_p^2			
	Male (*n* = 23)	Female (*n* = 106)	Total (*N* = 129)	Range	Male (*n* = 32)	Female (*n* = 61)	Total (*N* = 93)	Range	Group Effect	Sex	Group x Sex	Age Effect	Group Effect	Sex	Group x Sex
Demographics															
Age	42.43 (10.99)	40.49 (11.25)	40.84 (11.19)	19-64	34.81 (12.31)	36.21 (12.95)	35.73 (12.68)	18-69	10.00 **(.002)** *.04*	0.02 (.885) *.0*	0.79 (.375) *.004*	n/a	n/a	n/a	n/a
BMI[a]	27.71 (5.80)	29.43 (10.52)	29.12 (9.85)	15.24-86.57	27.32 (7.07)	26.05 (5.39)	26.50 (6.02)	14.53-56.81	1.96 (.163) *.01*	0.03 (.868) *.0*	1.22 (.271) *.01*	10.94 **(.001)** *.05*	0.44 (.506) *.002*	0.05 (.816) *.0*	1.69 (.195) *.01*
Physical Health Status (SF-36)															
Physical functioning	64.35 (29.75)	46.30 (32.51)	49.51 (32.67)	0-100	95.30 (10.99)	86.46 (20.70)	89.50 (18.38)	20-100	68.56 **(<.001)** *.24*	9.81 **(.002)** *.04*	1.15 (.284) *.01*	3.56 (.068) *.02*	60.17 **(<.001)** *.22*	10.02 **(.002)** *.04*	1.41 (.237) *.01*
Physical health	28.26 (40.81)	24.76 (39.42)	25.39 (39.53)	0-100	78.13 (35.21)	75.82 (39.78)	76.61 (38.09)	0-100	66.28 **(<.001)** *.23*	0.22 (.640) *.001*	0.01 (.924) *.0*	1.48 (.226) *.01*	59.52 **(<.001)** *.22*	0.23 (.631) *.001*	0.03 (.866) *.0*
Emotional problems	49.28 (48.06)	37.11 (43.23)	39.28 (44.18)	0-100	73.96 (39.47)	54.10 (46.41)	60.93 (44.94)	0-100	8.87 **(.003)** *.04*	5.24 **(.023)** *.02*	0.30 (.583) *.001*	3.67 (.057) *.02*	11.09 **(.001)** *.05*	5.22 **(.023)** *.02*	0.45 (.506) *.002*
Energy/fatigue	33.48 (19.47)	19.04 (19.86)	21.61 (20.87)	0-80	52.86 (21.80)	42.92 (22.77)	46.34 (22.81)	0-95	41.59 **(<.001)** *.16*	13.20 **(<.001)** *.06*	0.45 (.503) *.002*	0.04 (.852) *.0*	40.08 **(<.001)** *.16*	13.13 **(<.001)** *.06*	0.43 (.512) *.002*
Emotional well-being	62.39 (17.88)	51.47 (21.98)	53.42 (21.65)	4-96	66.88 (18.96)	61.05 (21.85)	63.05 (20.98)	4-100	4.40 **(.037)** *.02*	6.23 **(.013)** *.03*	0.58 (.448) *.003*	8.66 **(.004)** *.04*	7.30 **(.007)** *.03*	6.31 **(.013)** *.03*	0.35 (.553) *.002*
Social functioning	55.98 (27.66)	49.06 (25.74)	50.29 (26.12)	0-100	73.05 (25.02)	71.11 (26.47)	71.77 (25.86)	0-100	22.43 **(<.001)** *.09*	1.15 (.284) *.01*	0.36 (.547) *.002*	1.97 (.162) *.01*	24.36 **(<.001)** *.1*	1.13 (.290) *.01*	0.27 (.604) *.001*
Pain	67.39 (29.47)	51.49 (28.18)	54.32 (28.95)	0-100	87.81 (18.78)	76.23 (25.50)	80.22 (23.95)	0-100	29.01 **(<.001)** *.12*	10.75 **(.001)** *.05*	0.27 (.607) *.001*	2.24 (.136) *.01*	24.68 **(<.001)** *.10*	10.90 **(.001)** *.05*	0.37 (.545) *.002*
General health	57.17 (22.66)	44.67 (21.42)	46.90 (22.08)	0-95	69.22 (21.03)	60.57 (20.82)	63.55 (21.18)	20-100	17.08 **(<.001)** *.07*	9.78 **(.002)** *.04*	0.33 (.569) *.001*	1.78 (.183) *.01*	14.20 **(<.001)** *.06*	9.90 **(.002)** *.04*	0.42 (.516) *.002*
Mental Health (DASS-21)															
Depression	11.57 (9.14)	15.08 (10.71)	14.45 (10.50)	0-42	8.69 (9.79)	11.48 (11.41)	10.52 (10.91)	0-42	3.69 (.056) *.02*	3.49 (.063) *.02*	0.05 (.831) *.0*	4.24 **(.041)** *.02*	5.40 **(.021)** *.02*	3.46 (.064) *.02*	0.01 (.927) *.0*
Anxiety	9.04 (7.28)	10.77 (8.83)	10.47 (8.57)	0-38	5.62 (7.28)	7.93 (8.27)	7.14 (7.98)	0-36	5.62 **(.019)** *.03*	2.34 (.127) *.01*	0.05 (.826) *.0*	11.19 **(.001)** *.05*	9.44 **(.002)** *.04*	2.35 (.127) *.01*	0.18 (.671) *.001*

Stress	12.87 (8.50)	14.87 (9.67)	14.51 (9.47)	0-40	8.75 (7.46)	15.41 (10.82)	13.12 (10.26)	0-42	1.38 (.242) *.01*	8.07 **(.005)** *.04*	2.34 (.128) *.01*	14.71 **(<.001)** *.06*	3.95 **(.048)** *.02*	8.36 **(.004)** *.04*	3.26 (.073) *.02*
								Sleep Quality (PSQI)							
Sleep quality	1.57 (0.79)	1.76 (0.72)	1.73 (0.74)	0-3	1.19 (0.59)	1.44 (0.83)	1.35 (0.76)	0-3	8.78 **(.003)** *.04*	3.70 (.056) *.02*	0.06 (.812) *.0*	0.65 (.422) *.003*	7.44 **(.007)** *.03*	3.73 (.055) *.02*	0.04 (.850) *.0*
Sleep latency	2.09 (1.04)	2.06 (0.95)	2.06 (0.97)	0-3	1.38 (1.04)	1.59 (1.10)	1.52 (1.08)	0-3	13.34 **(<.001)** *.06*	0.33 (.567) *.002*	0.58 (.448) *.003*	0.82 (.367) *.004*	14.13 **(<.001)** *.06*	0.32 (.574) *.001*	0.66 (.417) *.003*
Sleep duration[b]	1.35 (0.98)	1.03 (0.88)	1.09 (0.91)	0-3	0.84 (0.77)	0.90 (0.93)	0.88 (0.87)	0-3	5.00 **(.026)** *.02*	0.86 (.355) *.004*	1.79 (.183) *.01*	0.91 (.341) *.004*	3.95 **(.048)** *.02*	0.84 (.361) *.004*	1.62 (.204) *.01*
Sleep efficiency[c]	1.43 (1.17)	1.43 (1.13)	1.43 (1.14)	0-3	0.72 (1.05)	0.76 (1.01)	0.75 (1.02)	0-3	15.02 **(<.001)** *.07*	0.01 (.905) *.0*	0.02 (.898) *.0*	12.54**(<.001)** *.06*	10.32 **(.002)** *.05*	0.02 (.899) *.0*	0.01 (.939) *.0*
Sleep disturbance	1.48 (0.67)	1.66 (0.62)	1.63 (0.63)	0-3	1.20 (0.54)	1.41 (0.56)	1.33 (0.56)	0-3	8.24 **(.005)** *.04*	4.60 **(.033)** *.02*	0.05 (.831) *.0*	0.02 (.904) *.0*	7.70 **(.006)** *.03*	4.58 **(.033)** *.02*	0.04 (.838) *.0*
Sleep medication[d]	0.26 (0.75)	0.75 (1.24)	0.66 (1.18)	0-3	0.44 (0.98)	0.20 (0.70)	0.28 (0.81)	0-3	1.31 (.253) *.01*	0.57 (.451) *.003*	4.94 **(.027)** *.02*	2.45 (.119) *.01*	0.64 (.426) *.003*	0.60 (.439) *.003*	5.38 **(.021)** *.02*
Daytime dysfunction	1.17 (0.78)	1.45 (0.86)	1.40 (0.85)	0-3	0.84 (0.68)	1.11 (0.80)	1.02 (0.77)	0-3	6.72 **(.010)** *.03*	4.55 **(.034)** *.02*	0.0 (.976) *.0*	3.77 **(.054)** *.02*	8.75 **(.003)** *.04*	4.53 **(.034)** *.02*	0.01 (.932) *.0*
Global score	9.22 (3.70)	10.06 (3.61)	9.91 (3.63)	2-18	6.41 (3.61)	7.31 (3.89)	7.00 (3.80)	1-20	22.41 **(<.001)** *.09*	2.21 (.139) *.01*	0.003 (.955) *.0*	1.38 (.241) *.01*	19.25 **(<.001)** *.08*	2.25 (.135) *.01*	0.0 (.989) *.0*

Significant *p* values are in **bold**.

Sample size reduced [a] by 2 (Non-COVID), [b] by 1 (COVID), [c] by 7 (5 COVID, 2 Non-COVID), [d] by 2 (COVID).

SF-36 (Short Form Health Survey-36): The response ranges between two- and six-point ordered Likert scales. Raw scores are transformed to produce a score between 0 and 100 for each dimension. The higher the score the better the overall health (Ware & Sherbourne, 1992). Internal reliability in this sample: overall scale, Cronbach's *α*=.96; all subscales, Cronbach's *α* >.8, except *α*=.74 for Social Functioning.

DASS-21 (The Depression, Anxiety and Stress Scale-21): Each item is rated by participants on a four-point scale according to how often in the past week it applied to them, ranging from "Did not apply to me at all" (0) to "Applied to me very much or most of the time" (Lovibond & Lovibond, 1995). Higher scores indicate higher levels (severity) of symptoms. Internal reliability in this sample: Depression, Cronbach's *α*=.93; Anxiety, Cronbach's *α=.82;* Stress, Cronbach's *α*=.88.

PSQI (Pittsburgh Sleep Quality Index): Participants answer the PSQI questions by relating them to their past month (Buysse et al., 1989). Each component is scored between "No difficulty" (0) to "Severe difficulty" (3) and tallied up to yield a total score (range 0-21). Higher scores indicate poor sleep quality. Internal reliability in this sample: Global score, Cronbach's *α*=.76.

Table 4.3

COVID-19 diagnosis history and symptoms in COVID group participants

		Cross-Sectional Investigation		Longitudinal Investigation	
		n	% of total	*n*	% of sub-sample total
Confirmed COVID-19 Diagnosis		129	-	30	-
COVID-19 Diagnosis Date	November '19	1	0.8%	1	3.3%
	January '20	2	1.6%	2	6.7%
	March '20	13	10.1%	1	3.3%
	April '20	11	8.5%	2	6.6%
	May '20	2	1.6%	0	0
	June '20	1	0.8%	1	3.3%
	August '20	1	0.8%	0	0
	September '20	5	3.9%	1	3.3%
	October '20	9	7.0%	2	6.6%
	November '20	16	12.4%	5	16.5%
	December '20	23	17.8%	8	26.6%
	January '21	15	11.6%	3	9.9%
	February '21	1	0.8%	0	0
	March '21	2	1.6%	0	0
	May '21	2	1.6%	0	0
	June '21	2	1.6%	1	3.3%
	July '21	2	1.6%	0	0
	August '21	2	1.6%	0	0
	September '21	4	3.1%	2	6.6%
	October '21	5	3.9%	1	3.3%
	November '21	3	2.3%	0	0
	December '21	3	2.3%	0	0
	January '22	3	2.3%	0	0
Hospitalisation due to COVID		20	15.5%	2	6.7%
Acute COVID-19 Symptoms	Temperature	99	76.7%	18	60%
	Dry Cough	86	66.6%	17	56.6%
	Loss of Taste and/or Smell	83	64.3%	21	70%
	Other	83	64.3%	16	69.6%
Subjective Cognitive Function Impairment		101	78.3%	12	41.4%
Subjective Reduced Psychological Well-being		100	77.5%	13	43.3%
Chronic COVID-19 Symptoms (Long COVID)	Abdominal pain	49	38.0%	3	10.3%
	Arrhythmia	72	55.8%	5	17.2%
	Body chills	61	47.3%	3	10.3%
	Breathing problems	91	70.5%	11	37.9%
	Chest pain	69	53.5%	4	13.7%
	Chilblains	19	14.7%	1	1.6%
	Confusion/delirium	77	59.7%	8	27.5%
	Diarrhoea	44	34.1%	4	13.7%
	Dry cough	46	35.7%	8	27.5%
	Exhaustion/fatigue	114	88.4%	19	65.4%
	Hallucinations	19	14.7%	0	0

Headaches	95	73.6%	15	51.7%
Insomnia	101	78.3%	17	58.5%
Irritability	94	72.9%	13	44.7%
Lack of appetite	62	48.1%	7	24.0%
Loss of taste and/or smell	47	36.4%	7	24.0%
Mild cognitive problems	107	82.9%	16	55.0%
Muscle/body ache	97	75.2%	16	55.0%
Sore eyes/conjunctivitis	59	45.7%	7	24.0%
Sore throat	47	36.4%	5	17.2%
Temperature	36	27.9%	4	13.7%
Vomiting/nausea	34	26.4%	4	13.7%
Other	29	22.5%	5	17.2%

Table 4.4

Descriptive statistics and group differences between COVID hospitalised versus non-hospitalised sample (ANOVA and ANCOVA results) in the demographic, mental health and well-being measures for the cross-sectional investigation

		Hospitalised COVID Participants *n* = 20		Non-hospitalised COVID Participants *n* = 109		ANOVA *F*(1, 127) (*p*) η_p^2	ANCOVA (covarying for age) *F*(1, 126) (*p*) η_p^2	
		M (SD)	Range	*M* (SD)	Range	Hospital Effect	Age Effect	Hospital Effect
Demographics	Age	44.25 (11.36)	23-64	40.21 (11.10)	19-64	2.22 (.138) *.02*	n/a	n/a
	BMI	32.21 (10.98)	18.59-62.67	28.56 (9.57)	15.24-86.57	2.34 (.128) *.02*	6.67 **(.011)** *.05*	1.47 (.228) *.01*
Physical Health Status (SF-36)	Physical functioning	36.00 (18.82)	10-85	51.99 (34.10)	0-100	4.15 **(.044)** *.03*	1.09 (.299) *.01*	3.55 (.062) *.03*
	Physical health	10.00 (23.51)	0-100	28.21 (41.26)	0-100	3.66 (.058) *.03*	1.40 (.239) *.01*	3.05 (.083) *.02*
	Emotional problems	8.33 (23.88)	0-100	44.95 (44.86)	0-100	12.67 **(.001)** *.09*	9.18 **(.003)** *.07*	16.30 **(<.001)** *.12*
	Energy/fatigue	15.75 (15.75)	0-55	22.69 (21.56)	0-80	1.88 (.172) *.02*	0.03 (.865) *.0*	1.78 (.185) *.01*
	Emotional well-being	49.80 (18.01)	4-72	54.08 (22.26)	8-96	0.66 (.418) *.01*	11.64 **(.001)** *.09*	1.65 (.201) *.01*
	Social functioning	36.88 (20.06)	0-75	52.75 (26.43)	0-100	6.51 **(.012)** *.05*	3.14 (.079) *.02*	7.75 **(.006)** *.06*
	Pain	40.75 (26.43)	0-90	56.81 (28.81)	0-100	5.38 **(.022)** *.04*	0.36 (.549) *.003*	4.91 **(.029)** *.04*
	General health	42.50 (19.90)	15-75	47.71 (22.45)	0-95	0.94 (.334) *.01*	0.06 (.805) *.0*	0.86 (.357) *.01*
Mental Health (DASS-21)	Depression	15.30 (10.51)	2-42	14.29 (10.54)	0-42	0.15 (.695) *.001*	3.34 (.070) *.03*	0.40 (.528) *.003*
	Anxiety	11.90 (7.77)	0-26	10.20 (8.72)	0-38	0.66 (.418) *.01*	19.75 **(<.001)** *.14*	2.09 (.151) *.02*
	Stress	18.10 (8.81)	6-36	13.85 (9.47)	0-40	3.47 (.065) *.03*	18.85 **(<.001)** *.13*	6.45 **(.012)** *.05*
Sleep Quality (PSQI)	Sleep quality	1.80 (0.70)	0-3	1.72 (0.75)	0-3	0.22 (.640) *.002*	0.31 (.581) *.002*	0.29 (.592) *.002*
	Sleep latency	2.25 (0.91)	0-3	2.03 (0.98)	0-3	0.90 (.346) *.01*	0.57 (.451) *.01*	1.07 (.302) *.01*
	Sleep duration[a]	1.42 (1.12)	0-3	1.03 (0.86)	0-3	3.11 (.080) *.02*	0.003 (.959) *.0*	3.06 (.083) *.02*
	Sleep efficiency[b]	1.94 (1.16)	0-3	1.34 (1.11)	0-3	4.50 **(.036)** *.04*	6.59 **(.012)** *.05*	3.56 (.061) *.03*
	Sleep disturbance	1.75 (0.55)	1-3	1.61 (0.64)	0-3	0.90 (.345) *.01*	0.04 (.843) *.0*	0.98 (.337) *.01*
	Sleep medication[c]	0.42 (1.02)	0-3	0.70 (1.21)	0-3	0.92 (.339) *.01*	0.04 (.841) *.0*	0.95 (.331) *.01*
	Daytime dysfunction	1.80 (0.89)	1-3	1.33 (0.83)	0-3	5.30 **(.023)** *.04*	4.35 **(.039)** *.03*	6.69 **(.011)** *.05*
	Global score	11.10 (3.92)	2-16	9.69 (3.55)	2-18	2.59 (.110) *.02*	0.01 (.914) *.0*	2.57 (.111) *.02*

Significant *p* values are in **bold**.

Abbreviations: BMI, Body Mass Index; DASS-21, The Depression, Anxiety and Stress Scale-21; PSQI, Pittsburgh Sleep Quality Index; SF-36: Short Form Health Survey-36. Sample size reduced [a] by 1 (hospitalised), [b] by 5 (2 hospitalised, 3 non-hospitalised), [c] by 2 (1 hospitalised, 1 non-hospitalised).

At study entry (mean number of days since diagnosis = 263, *SD* = 192.16, range: 20–714), a large proportion of the sample reported subjective cognitive impairment (78.3%), reduced psychological well-being (77.5%), and one or more long-COVID symptoms, most commonly exhaustion/fatigue (88.4%). The overall long-COVID symptom load, however, was not significantly correlated with the number of days since diagnosis [$r(125) = .057$, $p = .527$] or age [$r(126) = .092$, $p = .299$]. Nineteen of 20 hospitalised participants (95%) reported subjective cognitive impairment, and 18 (90%) reported reduced psychological well-being.

4.4.1.2 Mental Health and Psychological Well-Being in COVID versus Non-COVID Participants

There were significant main effects of Group in ANOVA analyses (Table 4.2), with the COVID group having significantly poorer health (SF-36), higher anxiety (DASS-21), and lower sleep quality (PSQI), compared to the non-COVID group. The ANCOVA analyses, with age as a covariate, retained these effects and, in addition, indicated significantly higher depression and stress levels (DASS-21) in the COVID, compared to the non-COVID group (Table 4.2).

There were significant sex differences in physical functioning, emotional problems, energy, emotional well-being, pain, and general health (SF-36), stress (DASS-21), as well as sleep disturbance and daytime dysfunction (PSQI), indicating poorer health and psychological well-being in females compared to males. There were, however, no significant Group × Sex interactions (Table 4.2), except for sleep medication [in females, greater use of sleep medications by COVID compared to non-COVID group, $t(163) = 3.65$, $p < .001$].

Lastly, age was a significant covariate (in ANCOVAs) for BMI, emotional well-being (SF-36), depression, anxiety and stress (DASS21), as well as sleep efficiency and daytime dysfunction (PSQI), indicating poorer health and psychological well-being with older age.

4.4.1.3 Cognitive Function in COVID versus Non-COVID Participants

There were significant main effects of Group indicating significantly greater intra-individual variability in processing speed ($p = .015$) and lower attention RA ($p = .022$) in the COVID compared to non-COVID group (Table 4.5). The Group effect remained significant for processing speed variability ($p = .034$) but lost significance for attention RA ($p = .052$) when

covarying for age, with ANCOVAs additionally revealing longer RTs being associated with older age (Table 4.5). Ethnicity did not show any main or interactive effects (Table 4.5).

Participants who had been hospitalised had longer attention RTs (p = .005) and lower executive function RA (%) (p = .012) than those who did not require hospitalisation (Table 4.6). These effects remained significant when covarying for age, despite older age being associated with poorer performance on both measures.

4.4.1.4 Association between Cognitive Functions and Long-COVID Symptoms

Executive function task completion time, the RTs during processing speed and attention tasks, and attention RA variables were most commonly correlated, with small-to-medium effect sizes, with individual long-COVID symptoms, especially arrythmia, chest pain, and headaches (Table 4.7). The overall long-COVID symptom load was significantly associated with poor performance on all tasks, with small-to-medium-sized correlations (Table 4.8).

4.4.1.5 Association between Cognitive Function, Mental Health and Well-Being

SF-36 dimensions correlated with many cognitive variables, especially executive function, with poorer health being associated with poorer performance (Table 4.9). Depression, anxiety and stress correlated negatively with executive function. Sleep disturbance was associated with poor performance in processing speed, attention, and executive function. These associations were generally stronger in the COVID, relative to non-COVID, group (Table 4.9).

Table 4.5

Descriptive statistics and group differences (ANOVA and ANCOVA results) in cognitive measures for the cross-sectional investigation

		COVID Group *M* (SD)				Non-COVID Group *M* (SD)				ANOVA $F(1, 218)$ (p) η_p^2			ANCOVA (covarying for age) $F(1, 217)$ (p) η_p^2			
		Male (*n* = 23)	Female (*n* = 106)	Total (*N* = 129)	Range	Male (*n* = 32)	Female (*n* = 61)	Total (*N* = 93)	Range	Group Effect	Sex	Group x Sex	Age Effect	Group Effect	Sex	Group x Sex
Processing Speed[a]	Response accuracy (%)	94.87 (9.02)	95.87 (6.56)	95.68 (7.07)	57.14-100	96.36 (8.08)	96.66 (5.15)	96.56 (6.26)	56.67-100	1.11 (.294) *.01*	0.35 (.553) *.002*	0.11 (.746) *.001*	0.41 (.522) *.002*	0.78 (.377) *.004*	0.35 (.556) *.002*	0.09 (.770) *.0*
	RT (correct responses, ms)	352.04 (77.90)	382.45 (81.66)	376.57 (81.52)	275-686	351.32 (66.93)	355.47 (76.96)	354.05 (73.35)	253-746	1.23 (.269) *.01*	1.91 (.168) *.01*	1.11 (.295) *.01*	5.59 **(.019)** *.03*	0.34 (.563) *.002*	2.00 (.159) *.01*	1.37 (.243) *.01*
	RT variability (SD of RT)	84.52 (40.85)	87.21 (42.21)	86.69 (41.80)	22-205	64.00 (34.74)	76.18 (39.11)	72.03 (37.93)	25-182	6.00 **(.015)** *.03*	1.33 (.250) *.01*	0.54 (.462) *.003*	1.35 (.247) *.01*	4.57 **(.034)** *.02*	1.35 (.246) *.01*	0.47 (.495) *.002*
Attention[b]	Response accuracy (%)	94.55 (10.43)	95.23 (8.18)	95.11 (8.58)	51.28-100	97.06 (5.52)	98.16 (4.12)	97.78 (4.66)	73.33-100	5.33 **(.022)** *.03*	0.57 (.451) *.003*	0.03 (.856) *.0*	2.59 (.109) *.01*	3.83 (.052) *.02*	0.59 (.443) *.003*	0.05 (.830) *.0*
	RT (correct responses, ms)	476.76 (101.50)	514.16 (93.76)	507.39 (95.84)	344-830	484.03 (114.70)	461.19 (87.16)	469.15 (97.60)	321-898	2.10 (.149) *.01*	0.21 (.645) *.001*	3.64 (.058) *.02*	31.01**(<.001)** *.13*	0.18 (.670) *.001*	0.21 (.649) *.001*	4.68 **(.032)** *.02*
Working Memory[c]	Response accuracy (%)	92.73 (5.57)	91.85 (8.89)	92.00 (8.40)	52-100	95.07 (4.62)	93.69 (7.44)	94.18 (6.59)	60-100	2.84 (.093) *.01*	0.82 (.366) *.004*	0.04 (.842) *.0*	0.01 (.940) *.0*	2.74 (.099) *.01*	0.81 (.368) *.004*	0.04 (.839) *.0*
Executive Function[d]	Response accuracy (%)	95.40 (5.59)	94.64 (7.55)	94.78 (7.22)	58.14-100	93.80 (9.71)	95.51 (7.96)	94.94 (8.57)	58.14-100	0.08 (.774) *.0*	0.14 (.705) *.001*	0.97 (.326) *.004*	2.93 (.088) *.01*	0.02 (.896) *.0*	0.14 (.712) *.001*	0.73 (.394) *.003*
	Completion time (ms)	29217.00 (11514.15)	34046.42 (20399.68)	33185.36 (19172.91)	11775-162669	31398.80 (11740.80)	29385.68 (12823.20)	30056.72 (12443.24)	12050-97180	0.21 (.645) *.001*	0.28 (.601) *.001*	1.62 (.204) *.01*	0.40 (.527) *.002*	0.09 (.768) *.0*	0.27 (.604) *.001*	1.73 (.189) *.01*
Memory[e]	Recognition accuracy (%)	90.26 (6.96)	89.25 (8.88)	89.42 (8.56)	54.17-98.96	91.15 (7.99)	91.59 (8.40)	91.44 (8.22)	58.33-100	1.43 (.233) *.01*	0.05 (.832) *.0*	0.29 (.592) *.001*	0.34 (.559) *.002*	1.07 (.302) *.01*	0.05 (.825) *.0*	0.33 (.567) *.002*

Significant *p* values are in **bold**.

Abbreviations: ms, milliseconds; RT, reaction time.

Sample size reduced [a] by 12 (10 COVID, 2 Non-COVID), [b] by 17 (13 COVID, 4 Non-COVID), [c] by 5 (2 COVID, 3 Non-COVID), [d] by 3 (Non-COVID), [e] by 2 (COVID).

Further (exploratory) analyses of processing speed RT variability and attention response accuracy (%) with Ethnicity [White British vs All Other Ethnicities] included as an additional between-subjects factor retained the main effects of Group (processing speed RT variability, $p = .006$; attention RA, $p = .042$) but yielded no significant main or interactive effects involving Ethnicity (all p values > .341).

Table 4.6

Descriptive statistics and group differences between COVID hospitalised versus non-hospitalised sample (ANOVA and ANCOVA results) in cognitive measures for the cross-sectional investigation

		Hospitalised COVID Participants *n* = 20		Non-hospitalised COVID Participants *n* = 109		ANOVA $F(1, 127)$ (p) η_p^2	ANCOVA (covarying for age) $F(1, 126)$ (p) η_p^2	
		M (SD)	Range	*M* (SD)	Range	Hospital Effect	Age Effect	Hospital Effect
Processing Speed[a]	Response accuracy (%)	94.09 (9.42)	71.43-100	95.98 (6.55)	57.14-100	1.13 (.289) *.01*	0.16 (.693) *.001*	1.20 (.275) *.01*
	RT (correct responses, ms)	393.00 (87.94)	301-611	373.45 (80.33)	275-686	0.92 (.340) *.01*	0.45 (.506) *.004*	0.77 (.381) *.01*
	RT variability (SD of RT)	93.95 (32.79)	52-186	85.31 (43.30)	22-205	0.68 (.411) *.01*	0.17 (.684) *.001*	0.60 (.441) *.01*
Attention[b]	Response accuracy (%)	94.93 (7.13)	78.79-100	95.14 (8.87)	51.28-100	0.01 (.921) *.0*	0.27 (.608) *.002*	0.002 (.967) *.0*
	RT (correct responses, ms)	562.84 (70.79)	438-714	496.53 (96.63)	344-830	8.07 **(.005)** *.07*	11.89 **(.001)** *.1*	6.62 **(.011)** *.06*
Working Memory[c]	Response accuracy (%)	90.31 (11.38)	52-100	92.39 (7.75)	52-100	0.97 (.327) *.01*	0.42 (.518) *.003*	1.12 (.293) *.01*
Executive Function	Response accuracy (%)	91.06 (11.64)	58.14-100	95.46 (5.91)	71.43-100	6.52 **(.012)** *.05*	8.06 **(.005)** *.06*	8.84 **(.004)** *.07*
	Completion time (ms)	41747.45 (30405.35)	14575-162669	31614.34 (16030.19)	11775-131328	4.86 **(.029)** *.04*	0.03 (.875) *.0*	4.83 **(.030)** *.04*
Memory[c]	Recognition accuracy (%)	88.35 (10.46)	54.17-98.96	89.62 (8.20)	57.14-98.96	0.37 (.543) *.003*	0.13 (.718) *.001*	0.42 (.518) *.003*

Significant *p* values are in **bold**.

Abbreviations: ms, milliseconds; RT, reaction time.

Sample size reduced [a] by 10 (1 hospitalised, 9 non-hospitalised), [b] by 13 (1 hospitalised, 12 non-hospitalised), [c] by 2 (non-hospitalised).

Table 4.7

Correlation between the cognitive variables and the individual chronic long COVID-19 symptoms in the COVID participants

Cross-Sectional Investigation									
	Processing Speed (*n = 119)*			Attention (*n* = 116)		Working Memory (*n* = 127)	Executive Function (*n* = 129)		Memory (*n* = 127)
Individual Long-COVID Symptoms	Response accuracy (%) *rho (p)*	RT correct responses (ms) *rho (p)*	RT variability (SD of RT) *rho (p)*	Response accuracy (%) *rho (p)*	RT Correct Responses (ms) *rho (p)*	Accuracy (%) *rho (p)*	Response accuracy (%) *rho (p)*	Completion time (ms) *rho (p)*	Recognition accuracy (%) *rho (p)*
Abdominal pain	-.075 (.420)	.177 (.055)	.089 (.336)	-.174 (.062)	.119 (.204)	-.076 (.395)	-.139 (.115)	.158 (.074)	-.090 (.314)
Arrhythmia	-.208 **(.023)**	.208 **(.023)**	.195 **(.033)**	-.255 **(.006)**	.253 **(.006)**	-.166 (.063)	-.270 **(.002)**	.293 **(.001)**	-.199 **(.025)**
Body chills	-.053 (.564)	.227 **(.013)**	.125 (.174)	-.155 (.097)	.216 **(.020)**	-.172 (.053)	-.086 (.332)	.193 **(.029)**	.015 (.871)
Breathing problems	-.099 (.285)	.202 **(.027)**	.167 (.070)	-.146 (.118)	.237 **(.011)**	-.130 (.144)	-.234 **(.008)**	.278 **(.001)**	-.169 (.058)
Chest pain	-.091 (.323)	.301 **(.001)**	.171 (.063)	-.237 **(.010)**	.344 **(<.001)**	-.225 **(.011)**	-.293 **(.001)**	.344 **(<.001)**	-.193 **(.030)**
Chilblains	-.136 (.142)	.016 (.862)	.105 (.258)	-.059 (.531)	.070 (.456)	-.256 (.528)	.009 (.918)	.125 (.159)	-.159 (.075)
Confusion/delirium	-.147 (.111)	.160 (.082)	.197 **(.032)**	-.226 **(.015)**	.256 **(.006)**	-.119 (.181)	-.126 (.153)	.173 **(.050)**	-.036 (.685)
Diarrhoea	-.087 (.347)	.265 **(.004)**	.121 (.191)	-.081 (.390)	.125 (.181)	-.215 **(.015)**	-.089 (.314)	.263 **(.003)**	-.106 (.235)
Dry cough	-.006 (.951)	.066 (.473)	.106 (.251)	-.107 (.252)	.057 (.546)	-.119 (.184)	-.077 (.387)	.220 **(.012)**	-.081 (.367)
Exhaustion/fatigue	-.073 (.430)	.280 **(.002)**	.155 (.091)	-.165 (.076)	.283 **(.002)**	-.169 (.057)	-.178 **(.044)**	.272 **(.002)**	-.100 (.262)
Hallucinations	-.249 **(.006)**	.121 (.189)	.162 (.078)	-.222 **(.017)**	.157 (.093)	-.274 **(.002)**	-.013 (.888)	.160 (.070)	.011 (.901)
Headaches	-.123 (.182)	.274 **(.003)**	.269 **(.003)**	-.186 **(.045)**	.315 **(.001)**	-.077 (.392)	-.166 (.061)	.222 **(.011)**	-.152 (.088)
Insomnia	-.104 (.259)	.213 **(.020)**	.146 (.113)	-.177 (.057)	.253 **(.006)**	-.075 (.400)	-.004 (.966)	.151 (.087)	-.056 (.532)
Irritability	-.099 (.286)	.141 (.127)	.168 (.068)	-.188 **(.043)**	.240 **(.009)**	-.109 (.223)	-.097 (.276)	.129 (.146)	-.029 (.749)
Lack of appetite	-.047 (.611)	.185 **(.044)**	.108 (.241)	-.132 (.158)	.189 **(.043)**	-.129 (.148)	-.066 (.459)	.253 **(.004)**	-.143 (.109)
Loss of taste and/or smell	-.059 (.523)	.295 **(.001)**	.091 (.326)	-.137 (.143)	.295 **(.001)**	-.145 (.105)	-.013 (.888)	.189 **(.032)**	-.083 (.351)
Mild cognitive problems	-.050 (.586)	.212 **(.021)**	.131 (.157)	-.176 (.059)	.360 **(<.001)**	-.164 (.065)	-.132 (.135)	.293 **(.001)**	-.099 (.266)
Muscle/body ache	-.062 (.506)	.374 **(<.001)**	.180 **(.050)**	-.180 (.053)	.373 **(<.001)**	-.219 **(.013)**	-.170 (.054)	.345 **(<.001)**	-.116 (.195)
Sore eyes/conjunctivitis	-.086 (.354)	.303 **(.001)**	.116 (.208)	-.112 (.229)	.276 **(.003)**	-.168 (.059)	-.046 (.602)	.261 **(.003)**	.007 (.940)
Sore throat	-.014 (.877)	.075 (.418)	.011 (.907)	-.039 (.677)	.055 (.555)	-.034 (.702)	-.083 (.353)	.187 **(.034)**	-.054 (.546)
Temperature	-.118 (.203)	-.003 (.973)	.080 (.386)	-.135 (.149)	.063 (.500)	-.111 (.214)	-.121 (.171)	.176 **(.046)**	-.005 (.854)
Vomiting/nausea	-.096 (.299)	.232 **(.011)**	.144 (.119)	-.271 **(.003)**	.157 (.093)	-.104 (.246)	-.189 **(.032)**	.274 **(.002)**	-.052 (.561)

Significant *p* values are in **bold**.

Abbreviations: ms, milliseconds; RT, reaction time.

Table 4.8

Associations (Pearson's correlation coefficients) between the cognitive variables and the total long COVID-19 symptom load in the COVID participants

	Processing Speed			Attention		Working Memory	Executive Function		Memory
	Response accuracy (%) *r (p) n* [CI]	RT correct responses (ms) *r (p) n* [CI]	RT variability (SD of RT) *r (p) n* [CI]	Response accuracy (%) *r (p) n* [CI]	RT correct responses (ms) *r (p) n* [CI]	Accuracy (%) *r (p) n* [CI]	Response accuracy (%) *r (p) n* [CI]	Completion time (ms) *r (p) n* [CI]	Recognition accuracy (%) *r (p) n* [CI]
	Cross-sectional Investigation								
Long COVID Symptom Load	-.246 **(.007)** 118 [-0.409, -0.068]	.315 **(.001)** 118 [0.142, 0.469]	.209 **(.023)** 118 [0.029, 0.376]	-.273 **(.003)** 115 [-0.434, -0.095]	.368 **(<.001)** 115 [0.198, 0.516]	-.220 **(.013)** 126 [-0.380, -0.047]	-.240 **(.006)** 128 [-0.397, -0.069]	.289 **(.001)** 128 [0.122, 0.440]	-.253 **(.004)** 126 [-0.410, -0.082]
	Longitudinal (within-Subjects) Investigation - Cognitive Function at Study Entry								
	Cognitive Function at Study Entry								
	-.158 (.422) 28 [-0.502, 0.229]	-.062 (.753) 28 [-0.425, 0.318]	.043 (.828) 28 [-0.336, 0.410]	-.207 (.290) 28 [-0.539, 0.180]	.129 (.513) 28 [-0.256, 0.479]	-.175 (.363) 29 [-0.509, 0.205]	-.012 (.950) 29 [-0.377, 0.356]	.373 **(.046)** 29 [0.008, 0.651]	-.157 (.417) 29 [-0.495, 0.222]
	Pre-pandemic Cognitive Function								
Long COVID Symptom Load	.109 (.573) 29 [-0.268, 0.457]	.089 (.644) 29 [-0.287, 0.441]	.021 (.912) 29 [-0.348, 0.385]	-.075 (.704) 28 [-0.436, 0.307]	.079 (.690) 28 [-0.303, 0.439]	.104 (.598) 28 [-0.280, 0.459]	-.365 (.052) 29 [-0.645, 0.002]	.502 **(.005)** 29 [0.166, 0.734]	-.378 **(.043)** 29 [-0.654, -0.013]

Significant *p* values are in **bold**.

Abbreviations: ms, milliseconds; RT, reaction time.

Table 4.9

Associations (Pearson's correlation coefficients) of the cognitive variables with health and well-being measures for the cross-sectional investigation

	Processing Speed									Attention						Working Memory			Executive Function						Memory		
	Response accuracy (%)			RT correct responses (ms)			RT variability (SD of RT)			Response accuracy (%)			RT correct responses (ms)			Accuracy (%)			Response accuracy (%)			Completion time (ms)			Recognition accuracy (%)		
	r (*p*)			*r* (*p*)			*r* (*p*)			*r* (*p*)			*r* (*p*)			*r* (*p*)			*r* (*p*)			*r* (*p*)			*r* (*p*)		
	All	COV	COV-	All	COV+	COV-	All	COV+	COV-	All	COV+	COV-	All	COV+	COV-	All	COV+	COV-	All	COV+	COV-	All	COV+	COV-	All	COV+	COV-
	N=210	*n*=119	*n*=91	*N*=210	*n*=119	*n*=91	*N*=210	*n*=119	*n*=91	*N*=205	*n*=116	*n*=89	*N*=205	*n*=116	*n*=89	*N*=217	*n*=127	*n*=90	*N*=219	*n*=129	*n*=90	*N*=219	*n*=129	*n*=90	*N*=220	*n*=127	*n*=93
Physical Health Status (SF-36)																											
Physical	.130	.109	.134	-.289	-.317	-.123	-.243	-.159	-.224	.190	.132	-.005	-.324	-.368	-.065	.247	.230	.137	.152	.248	.066	-.246	-.287	-.042	.189	.213	.003
functioning	(.060)	(.238)	(.205)	**(<.001)**	**(<.001)**	(.244)	**(<.001)**	(.085)	**(.033)**	**(.006)**	(.158)	(.961)	**(<.001)**	**(<.001)**	(.546)	**(<.001)**	**(.009)**	(.199)	**(.024)**	**(.005)**	(.536)	**(<.001)**	**(.001)**	(.697)	**(.005)**	**(.016)**	(.979)
Physical	.135	.106	.140	-.166	-.190	.022	-.156	-.096	-.026	.117	.046	-.042	-.260	-.304	-.032	.160	.135	.041	.119	.180	.079	-.120	-.122	-.001	.088	.065	-.027
health	**(.051)**	(.253)	(.186)	**(.016)**	**(.039)**	(.835)	**(.024)**	(.297)	(.807)	(.096)	(.625)	(.695)	**(<.001)**	**(.001)**	(.766)	**(.018)**	(.131)	(.704)	(.079)	**(.041)**	(.459)	(.076)	(.167)	(.993)	(.194)	(.465)	(.794)
Emotional	.095	.151	-.018	.056	-.004	.235	-.013	-.058	.159	.017	.009	-.118	-.007	-.100	.219	.076	.021	.093	.101	.242	-.067	-.014	-.079	.197	.023	.112	-.169
problems	(.170)	(.101)	(.865)	(.417)	(.963)	**(.025)**	(.853)	(.528)	(.133)	(.807)	(.926)	(.271)	(.920)	(.283)	**(.040)**	(.267)	(.814)	(.381)	(.138)	**(.006)**	(.531)	(.841)	(.376)	(.062)	(.732)	(.210)	(.106)
Energy	.137	.093	.160	-.180	-.243	.024	-.153	-.119	-.023	.150	.125	-.033	-.216	-.215	-.058	.135	.065	.101	.092	.126	.071	-.096	-.108	.034	.057	-.021	.023
/fatigue	**(.047)**	(.312)	(.129)	**(.009)**	**(.008)**	(.823)	**(.027)**	(.196)	(.827)	**(.032)**	(.182)	(.762)	**(.002)**	**(.020)**	(.588)	**(.047)**	(.470)	(.344)	(.175)	(.156)	(.508)	(.158)	(.225)	(.752)	(.403)	(.817)	(.827)
Emotional	.140	.095	.183	.016	-.001	.118	-.099	-.049	-.084	.042	.018	-.038	-.022	-.038	.102	.100	.051	.119	.190	.185	.204	-.029	.013	-.062	.090	-.029	.208
well-being	**(.043)**	(.306)	(.083)	(.820)	(.988)	(.265)	(.152)	(.595)	(.426)	(.546)	(.848)	(.724)	(.757)	(.685)	(.343)	(.140)	(.570)	(.263)	**(.005)**	**(.036)**	(.053)	(.674)	(.883)	(.559)	(.183)	(.747)	**(.045)**
Social	.156	.150	.131	-.065	-.134	.174	-.137	-.066	-.085	.118	.007	.174	-.112	-.169	.125	.240	.234	.157	.196	.241	.169	-.135	-.126	-.077	.091	.076	.011
Functioning	**(.024)**	(.103)	(.218)	(.350)	(.145)	(.099)	**(.048)**	(.473)	(.423)	(.093)	(.942)	(.103)	(.110)	(.070)	(.245)	**(<.001)**	**(.008)**	(.139)	**(.004)**	**(.006)**	(.111)	**(.046)**	(.155)	(.473)	(.181)	(.393)	(.916)
Pain	.181	.174	.163	-.277	-.341	-.068	-.300	-.239	-.270	.146	.115	-.037	-.255	-.293	-.041	.211	.205	.083	.154	.182	.148	-.169	-.145	-.145	.129	.168	-.054
	(.009)	(.059)	(.123)	**(<.001)**	**(<.001)**	(.523)	**(<.001)**	**(.009)**	**(.010)**	**(.037)**	(.219)	(.727)	**(<.001)**	**(.001)**	(.703)	**(.002)**	**(.021)**	(.435)	**(.022)**	**(.039)**	(.165)	**(.012)**	(.101)	(.173)	(.057)	(.059)	(.609)
General	.117	.069	.149	-.266	-.312	-.115	-.211	-.161	-.160	.144	.116	.027	-.295	-.322	-.151	.093	.004	.127	.128	.112	.160	-.119	-.086	-.114	.128	.169	-.022
Health	(.092)	(.454)	(.160)	**(<.001)**	**(.001)**	(.279)	**(.002)**	(.081)	(.129)	**(.039)**	(.214)	(.802)	**(<.001)**	**(<.001)**	(.157)	(.173)	(.965)	(.234)	(.058)	(.205)	(.131)	(.079)	(.335)	(.285)	(.058)	(.058)	(.832)
Mental Health (DASS-21)																											
Depression	-.093	-.080	-.088	-.020	.003	-.117	.053	.025	.017	-.038	-.017	.017	.003	.030	-.107	-.136	-.181	-.003	-.207	-.172	-.252	.020	-.025	.068	-.026	.042	-.072
	(.177)	(.384)	(.407)	(.774)	(.978)	(.269)	(.4434)	(.786)	(.872)	(.590)	(.854)	(.878)	(.965)	(.747)	(.319)	**(.046)**	**(.042)**	(.977)	**(.002)**	**(.052)**	**(.017)**	(.771)	(.777)	(.526)	(.698)	(.636)	(.494)
Anxiety	-.190	-.178	-.187	.017	.065	-.116	.093	.121	-.002	-.112	-.113	-.006	.015	.016	-.076	-.142	-.135	-.091	-.291	-.398	-.165	.116	.160	-.033	-.121	-.152	-.027
	(.006)	**(.053)**	(.076)	(.808)	(.485)	(.274)	(.182)	(.188)	(.834)	(.110)	(.226)	(.959)	(.834)	(.861)	(.481)	**(.036)**	(.129)	(.394)	**(<.001)**	**(<.001)**	(.119)	(.088)	(.071)	(.757)	(.073)	(.088)	(.801)
Stress	-.095	-.065	-.129	-.043	-.005	-.116	.060	.008	.108	-.082	-.088	-.048	-.045	-.013	-.114	-.123	-.173	-.023	-.241	-.221	-.264	.057	.012	.138	-.033	.009	-.072
	(0.170)	(.482)	(.223)	(.533)	(.959)	(.271)	(.385)	(.933)	(.307)	(.240)	(.350)	(.655)	(.520)	(.888)	(.289)	(.071)	**(.052)**	(.826)	**(<.001)**	**(.012)**	**(.012)**	(.402)	(.896)	(.195)	(.624)	(.917)	(.490)
Sleep Quality (PSQI)																											

Sleep quality	-.123 (.076)	-.172 (.062)	-.024 (.823)	.054 (.436)	.098 (.289)	-.087 (.412)	**.143 (.038)**	.167 (.069)	.019 (.854)	-.069 (.328)	-.102 (.274)	.145 (.175)	.068 (.334)	.072 (.440)	-.037 (.729)	-.094 (.167)	-.081 (.363)	-.034 (.747)	-.029 (.668)	-.059 (.506)	.009 (.930)	-.023 (.741)	-.078 (.377)	.019 (.856)	.071 (.296)	.039 (.663)	.192 (.065)
Sleep latency	-.048 (.486)	-.080 (.390)	.033 (.757)	.082 (.234)	.133 (.149)	-.071 (.504)	.094 (.175)	.121 (.190)	-.049 (.641)	-.064 (.360)	-.109 (.242)	.193 (.069)	.015 (.830)	.049 (.601)	-.147 (.169)	-.082 (.226)	-.089 (.319)	.009 (.931)	-.109 (.107)	-.051 (.566)	-.174 (.100)	.054 (.427)	.010 (.908)	.076 (.477)	-.006 (.934)	-.064 (.472)	.141 (.178)
Sleep duration	-.140 **(.043)**[a]	-.145 (.118)[a]	-.114 (.284)	-.015 (.827)[a]	.001 (.990)[a]	-.091 (.389)	.112 (.107)[a]	.069 (.458)[a]	.118 (.264)	-.069 (.328)[a]	-.050 (.598)[a]	-.059 (.584)	.075 (.286)[a]	.089 (.343)[a]	.014 (.900)	-.103 (.133)[a]	-.155 (.083)[a]	.035 (.744)	-.093 (.170)[a]	-.135 (.128)[a]	-.040 (.705)	.028 (.679)[a]	.025 (.776)[a]	.001 (.989)	-.120 (.077)[a]	-.189 **(.035)**[a]	.011 (.915)
Sleep efficiency	-.085 (.226)[b]	-.108 (.251)[d]	-.018 (.870)[c]	.077 (.274)[b]	.157 (.095)[d]	-.181 (.092)[c]	.115 (.101)[b]	.132 (.162)[d]	-.020 (.856)[c]	-.067 (.345)[b]	-.064 (.505)[d]	.103 (.346)[c]	.134 (.061)[b]	.212 **(.025)**[d]	-.117 (.285)[c]	-.020 (.771)[b]	-.047 (.611)[d]	.181 (.094)[c]	-.011 (.872)[b]	.048 (.596)[d]	-.076 (.486)[c]	.011 (.868)[b]	-.033 (.713)[d]	.017 (.874)[c]	-.061 (.376)[b]	-.142 (.118)[d]	.149 (.162)[c]
Sleep disturbance	-.171 **(.013)**	-.188 **(.041)**	-.117 (.268)	.233 **(.001)**	.262 **(.004)**	.123 (.246)	.183 **(.008)**	.143 (.120)	.156 (.139)	-.108 (.124)	-.161 (.083)	.158 (.140)	.206 **(.003)**	.236 **(.011)**	.081 (.449)	-.113 (.097)	-.110 (.218)	-.028 (.794)	-.170 **(.012)**	-.190 **(.031)**	-.152 (.152)	.197 **(.003)**	.198 **(.024)**	.147 (.165)	-.081 (.230)	-.150 (.092)	.099 (.347)
Sleep medication	.072 (.304)[c]	.094 (.316)[c]	.056 (.596)	.104 (.136)[c]	.146 (.116)[c]	-.034 (.746)	-.029 (.677)[c]	-.063 (.498)[c]	-.044 (.680)	-.062 (.381)[c]	-.084 (.376)[c]	.113 (.291)	.124 (.077)[c]	.164 (.082)[c]	-.005 (.965)	.065 (.344)[c]	.079 (.383)[c]	.119 (.265)	-.040 (.560)[c]	-.011 (.906)[c]	-.093 (.383)	.055 (.417)[c]	.053 (.553)[c]	.002 (.985)	-.139 **(.041)**[c]	-.163 (.069)[c]	-.038 (.718)
Daytime dysfunction	-.099 (.151)	-.110 (.232)	-.052 (.623)	.025 (.719)	.021 (.817)	-.046 (.662)	.024 (.731)	.004 (.963)	-.043 (.687)	-.025 (.719)	-.010 (.917)	.088 (.411)	.074 (.290)	.079 (.396)	-.035 (.747)	-.036 (.595)	.005 (.958)	-.022 (.836)	-.118 (.082)	-.174 **(.048)**	-.046 (.670)	.030 (.656)	.042 (.633)	-.067 (.530)	-.012 (.862)	-.061 (.493)	.135 (.197)
Global PSQI score	-.118 (.089)	-.154 (.094)	-.028 (.794)	.123 (.074)	.195 **(.034)**	-.083 (.435)	.141 **(.041)**	.126 (.173)	.027 (.801)	-.094 (.181)	-.118 (.209)	.159 (.137)	.154 **(.028)**	.212 **(.022)**	-.052 (.631)	-.085 (.211)	-.090 (.312)	.050 (.638)	-.113 (.095)	-.128 (.148)	-.105 (.326)	.075 (.267)	.050 (.573)	.040 (.707)	-.093 (.169)	-.194 **(.029)**	.137 (.192)

Significant *p* values are in **bold**.

Abbreviations: COV+, COVID group; COV-, Non-COVID group; DASS-21, The Depression, Anxiety and Stress Scale-21; ms, milliseconds; RT, reaction time; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form Health Survey-36.

Sample size reduced [a] by 1, [b] by 7, [c] by 2, [d] by 5.

Table 4.10

Descriptive statistics and changes from pre-pandemic assessment (ANOVA results) in cognitive measures for the longitudinal investigation (sub-sample with pre-pandemic cognitive data)

		Time 1: Pre-COVD-19 Pandemic *M* (SD)			Time 2: During COVID-19 Pandemic *M* (SD)			ANOVA *F*(1, 61) (*p*) η_p^2		
		COVID (*n* = 30)	Non-COVID (*n* = 33)	Total (*N* = 63)	COVID (*n* = 30)	Non-COVID (*n* = 33)	Total (*N* = 63)	Group Effect	Time	Group x Time
Processing Speed[a]	Response accuracy (%)	97.10 (7.21)	96.79 (4.45)	96.94 (5.92)	96.50 (5.07)	95.84 (5.67)	96.16 (5.35)	0.17 (.681) *.003*	0.74 (.393) *.01*	0.04 (.846) *.001*
	RT (correct responses, ms)	331.86 (48.16)	353.17 (59.57)	342.69 (54.86)	338.72 (52.71)	342.70 (62.79)	340.75 (57.59)	0.87 (.354) *0.02*	0.10 (.748) *.002*	2.41 (.126) *.04*
	RT variability (SD of RT)	61.86 (40.49)	77.70 (35.54)	69.92 (38.56)	80.41 (45.01)	71.77 (35.05)	76.02 (40.14)	0.19 (.667) *.003*	1.14 (.291) *.02*	4.29 **(.043)** *.07*
Attention[b]	Response accuracy (%)	97.18 (4.46)	98.14 (4.40)	97.67 (4.42)	97.96 (3.71)	96.32 (7.20)	97.13 (5.76)	0.13 (.722) *.002*	0.28 (.599) *.01*	1.76 (.190) *.03*
	RT (correct responses, ms)	471.57 (86.39)	495.17 (108.56)	483.58 (98.15)	442.18 (64.53)	462.69 (87.93)	452.61 (77.33)	1.03 (.314) *.02*	12.41 **(.001)** *.18*	0.03 (.861) *.001*
Working Memory[c]	Response accuracy (%)	92.81 (9.22)	94.35 (6.28)	93.58 (7.86)	95.66 (4.47)	95.80 (5.05)	95.73 (4.73)	0.361 (.550) *.01*	4.78 **(.033)** *.08*	0.51 (.480) *.01*
Executive Function[d]	Response accuracy (%)	97.00 (4.64)	96.03 (6.30)	96.50 (5.53)	97.20 (4.06)	94.78 (7.57)	95.95 (6.20)	2.09 (.154) *.03*	0.33 (.568) *.01*	0.62 (.434) *.01*
	Completion time (ms)	27173.43 (11845.29)	32866.81 (13489.15)	30111.95 (12938.44)	26701.10 (11223.29)	28917.69 (10631.37)	27845.15 (10889.00)	2.38 (.128) *.04*	1.94 (.168) *.03*	1.20 (.277) *.02*
Memory	Recognition accuracy (%)	90.38 (7.92)	90.16 (6.83)	90.27 (7.31)	90.57 (7.54)	91.23 (10.25)	90.92 (9.00)	0.02 (.904) *.0*	0.37 (.545) *.01*	0.18 (.672) *.003*

Significant *p* values are in **bold**.

Abbreviations: ms, milliseconds; RT, reaction time.

Sample size reduced [a] by 4 (1 COVID, 3 Non-COVID), [b] by 6 (2 COVID, 4 Non-COVID), [c] by 5 (1 COVID, 4 Non-COVID), [d] by 1 (Non-COVID).

4.4.2 Longitudinal (Within-Subjects) Investigation

4.4.2.1 Sample Characteristics

The sub-sample for whom pre-COVID cognitive data were available had similar sample characteristics as the whole sample (Table 4.1).

4.4.2.2 Pre- versus Post-COVID-19 Cognitive Function

In line with the cross-sectional findings, there was a significant Group × Time interaction in RT variability in processing speed (p = .043) (Table 4.10), explained by greater intra-individual variability in the COVID group post-COVID-19 diagnosis (but not acutely unwell) compared to their pre-pandemic scores [$t(28) = 2.01$, p = .05]; there was no such change in the non-COVID group [$t(30) = 0.75$, p = .461]. Additionally, there were main effects of Time on attention task RTs (p = .001) (shorter RTs the second time) and working memory RA (p = .033) (slightly higher the second time), most likely explained by practice-related effects.

4.4.2.3 Association between Cognitive Function and Long-COVID Symptoms

The higher overall long-COVID symptom load correlated with poorer executive function performance at study entry (post-COVID), as well as poorer executive function and memory in pre-pandemic cognitive data (see Table 4.8).

4.5 Discussion

The main aims of this study were to examine the impact of COVID-19 on cognitive function in a UK adult sample (≤69 years), and explore the roles of physical and mental health and long-COVID symptoms in cognitive function in these individuals. The findings showed: (i) significantly larger intra-individual variability in processing speed but no significant impact of COVID-19 on other cognitive measures in our cross-sectional investigation, and a further confirmation of a negative impact of COVID-19 on processing speed variability (but no other cognitive variables) in our within-subjects investigation (pre-pandemic versus post-COVID-19 diagnosis); (ii) poorer attention and executive function in the COVID-19 group participants

who had needed hospitalisation due to COVID-19 relative to those who had not; and (iii) medium-sized negative associations of cognitive performance on all tasks with physical health and long-COVID symptoms (and relatively fewer associations of cognitive variables with anxiety and depression) in the COVID-19 group in the cross-sectional investigation, and (iv) medium-sized negative association between pre-pandemic cognitive function (executive function, memory) and long-COVID symptoms in the longitudinal sample. Further noteworthy findings were: poorer physical and mental health in the COVID relative to non-COVID group; generally reduced psychological well-being in females, relative to males; and longer RTs with increasing age.

Concerning the cognitive impact of COVID-19, our findings indicated only a limited negative impact of COVID-19 history on cognitive function in UK adults <70 years, with only processing speed variability being impacted (with a small effect size) out of nine cognitive function indices examined in both the cross-sectional and longitudinal investigations. This is consistent with the findings of the UK Biobank data-based study (Douaud et al., 2022) which found significant effects of COVID-19 on only two (Trails A and B completion time) out of 10 cognitive function indices examined. We did not detect the impact of COVID-19 as "slower speed" (including Trails B completion time) but rather a "more variable speed" on a task where speed was emphasised. Given that Douaud et al. (2022) did not examine/report intra-individual variability in processing speed, the findings of their and our study combined suggest that intraindividual variability in speed might be relatively more sensitive to COVID-19 in people aged ≤69 years, since our sample had a wider age range of younger adults (18–69) compared to Douaud et al. (2022) study's age range (51–81 years). Elevated intra-individual variability in RTs, reflecting momentary lapses in attention and/or task-irrelevant cognitions and a neural dysfunction involving multiple networks (Lin & McDonough, 2022; Weissman et al., 2006), has also been shown to be a particularly sensitive measure in the context of ageing (Bielak et al., 2014; Dykiert et al., 2012), prediction of future cognitive outcomes (Haynes et al., 2017), and various neurodegenerative diseases (Costa et al., 2019; de Frias et al., 2012). A positive consideration here is that there may be scope for improving/reducing variability in processing speed using continuous cognitive training (Simpson et al., 2012) or mindfulness-based approaches (Antonova et al., 2021), given findings of a more stable performance in long-term meditators compared to meditation-naïve individuals (Kumari et al., 2017), as well

as other reports of improved processing speed following mindfulness practice (Moore & Malinowski, 2009; Slagter et al., 2007).

Against the backdrop of a limited general cognitive impact of COVID-19, our findings suggest reduced cognitive function across multiple domains in people who needed hospitalisation due to COVID-19. This is consistent with recent literature suggesting that brain and cognitive impairment may be more salient in people with a severe infection (He et al., 2023) or hospitalisation (Tassignon et al., 2023), highlighting the need for longitudinal cognitive monitoring and improvement efforts in such cohorts (Davis et al., 2023), for example using non-invasive brain stimulation (Linnhoff et al., 2023; Santana et al., 2023). Furthermore, we found sizable associations between overall long-COVID symptom load and cognitive function across all domains, suggesting that affected individuals may also benefit from longitudinal cognitive monitoring and rehabilitation efforts. Interestingly, further to previous literature linking poorer cognitive function to greater acute COVID-19 severity and hospitalisation (Batty et al., 2021), our finding suggests that poorer cognitive function (executive function, memory) may also be a precursor of long-COVID symptoms. Taken together, our findings indicate that at least a part of COVID-19-related cognitive impairment in cross-sectional studies may reflect reduced pre-infection cognitive level [possibly related to factors, such as low socio-economic status (Sahota et al., 2024; Wang et al., 2023), impulsivity (Sakurai et al., 2020), or low levels of psychological resilience (Jiang et al., 2024; Jung et al., 2021; Yang et al., 2021)]; and that the most robust short-to-medium impact of COVID-19 may be limited to a more variable processing speed. Follow-up assessments of our and other samples are crucially needed to fully chart the cognitive trajectory of COVID-19 and long COVID.

Our further findings confirmed poorer mental health and well-being in COVID-19 survivors (Vanderlind et al., 2021; Vindegaard & Benros, 2020) and suggest that this may continue for some time post-infection. In addition, sex differences (across groups) were observed with women reporting poorer mental health and well-being, which is also in line with previous literature on sex differences in affective disorders (Altemus et al., 2014). Lastly, our finding of longer RTs with increasing age is consistent with previous literature (Madden, 2001).

The limitations of the present study include: (i) most participants being White-British, limiting generalisability of the findings; (ii) significantly older participants, on average, in the COVID than non-COVID groups (due to the open recruitment strategy), though all COVID-related

effects were sustained when covarying for age; and (iii) a reliance on self-report for COVID-19 diagnosis, which cannot rule out that at least some non-COVID group participants may have been pre-symptomatic when assessed. Future research should include more ethnically-diverse samples with consideration to the impact of socio-economic factors and, importantly, assess cognitive function at numerous times post-infection to understand the potential long-term cognitive recovery, especially in association with varying levels of long-COVID symptoms (Hall et al., 2023; Liu et al., 2022).

4.6 Conclusions

We observed a limited cognitive impact of COVID-19 with only intra-individual variability in processing speed being significantly affected (becoming less stable) in an adult UK sample. However, those who required COVID-19-related hospitalisation, did display multifaceted cognitive impairment. Furthermore, long-COVID symptoms were associated with reduced cognitive function (assessed post-COVID-19 diagnosis) but also with poorer executive function and memory prior to the COVID-19 pandemic, suggesting that poorer cognitive function may be a precursor of long-COVID symptoms. Further research is required to understand whether COVID-19 and long COVID continue to impede cognitive function over a longer period of time.

Chapter Five: The Cognitive Trajectory of COVID-19 – An Empirical Study

This chapter has been published as (Appendix K):

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5.1 Chapter Aims and Overview

Chapter Four highlights the negative, yet minimal impact COVID-19 has on cognitive function and psychological well-being in a working-age, non-clinical sample. The cognitive impairment appeared to be worse in participants who required hospitalisation and/or were experiencing long-COVID symptoms. However, it cannot be deduced whether this impairment persists or improves overtime in COVID-19 survivors. The study presented in this chapter therefore builds on the previous findings by following-up participants six-months post the initial assessment.

5.2 Introduction

Since the start of the COVID-19 pandemic, a vast amount of literature has acknowledged the psychological issues and cognitive disruption experienced by survivors (Bertuccelli et al., 2022; Ceban et al., 2022; Crivelli et al., 2022; Schild et al., 2023; Shanbehzadeh et al., 2021; Vanderlind et al., 2021). Living with COVID-19 has become the new normal, yet there is still uncertainty around the longer-term effects of COVID-19 on physical and mental well-being, given marked between-study variability in the proportion of survivors reporting cognitive and mental health impairments post-acute infection (Schou et al., 2021). In a recent review (Tavares-Júnior et al., 2022), 21–65% of adults with long-COVID symptoms (≥12 weeks) were found to have some level of cognitive impairment, while another review (Groff et al., 2021) reported poor mental health for up to six months post a COVID-19 diagnosis. It is unclear at present whether COVID-19-related cognitive impairment and psychological symptoms attenuate or resolve over time and, if so, how long after a COVID-19 diagnosis an improvement can be seen, especially in young and middle-aged adults.

Previous studies have suggested some improvement in cognitive function (Blazhenets et al., 2021; Del Brutto et al., 2022; Galderisi et al., 2024; Larsson et al., 2023; Nersesjan et al., 2022; Poletti et al., 2022) and psychological well-being (Houben-Wilke et al., 2022), especially at longer (≥six months) follow-ups, but these mostly examined older adults (mean age >50 years) (Blazhenets et al., 2021; Del Brutto et al., 2022; Galderisi et al., 2024; Houben-Wilke et al., 2022) and focused on severely ill or hospitalised COVID-19 patients (Galderisi et al., 2024; Larsson et al., 2023; Nersesjan et al., 2022; Poletti et al., 2022). As these groups are likely to need longer to recover from COVID-19 and its adverse cognitive and mental health impacts, with possible co-morbidities exacerbating and/or complicating post-COVID recovery, their findings may not generalise to working-age adults in the general population. A recent study (Cheetham et al., 2023) involving a large sample, though again with an over-representation of middle age adults (≥50 years), showed persistent cognitive deficits at about two years post-infection, especially in individuals who had experienced the symptoms for ≥12 weeks and/or a severe infection, or were experiencing ongoing symptoms. Encouragingly, the sub-group of adults who self-reported a full recovery showed no such deficits (Cheetham et al., 2023). There is clearly a need for further work to fully characterise the cognitive trajectory of COVID-19 in survivors with varying levels of symptoms and younger age groups.

In our recent study (Vakani et al., 2023) investigating the impact of COVID-19 on cognitive function and mental health in a working-age sample (mean age: 38.70 ± 12.08), we had found a limited cognitive impact of COVID-19 diagnosis, with only intra-individual variability in processing speed being significantly increased in COVID-19 survivors, compared to non-COVID controls. There was, however, multifaceted cognitive impairment in association with long-COVID symptoms. Mental health and sleep quality were also worse in COVID-19 survivors, relative to non-COVID controls. Here, with a further assessment (six-month follow-up) of this previously assessed sample (Vakani et al., 2023), we aimed to examine: (i) the longitudinal impact of COVID-19 on cognitive function, mental health, and sleep, first, on average, and then classified by COVID-19-related hospitalisation; and (ii) changes in long-COVID symptom load and their association with cognitive function, mental health and well-being at six months post the initial assessment. Based on previous findings (Blazhenets et al., 2021; Del Brutto et al., 2022; Houben-Wilke et al., 2022; Larsson et al., 2023; Latronico et al., 2022; Poletti et al., 2022), we predicted: (i) a change towards normalisation of cognitive function, mental health, and sleep from study entry (T1) (Vakani et al., 2023) to the six-month follow-up (T2) assessments, on average, in the COVID group, relative to non-COVID group, and (ii) persistently impaired cognitive function, mental health, and sleep in participants with a history of COVID-19-related hospitalisation and/or ongoing long-COVID symptoms.

5.3 Methods

5.3.1 Participants and Design

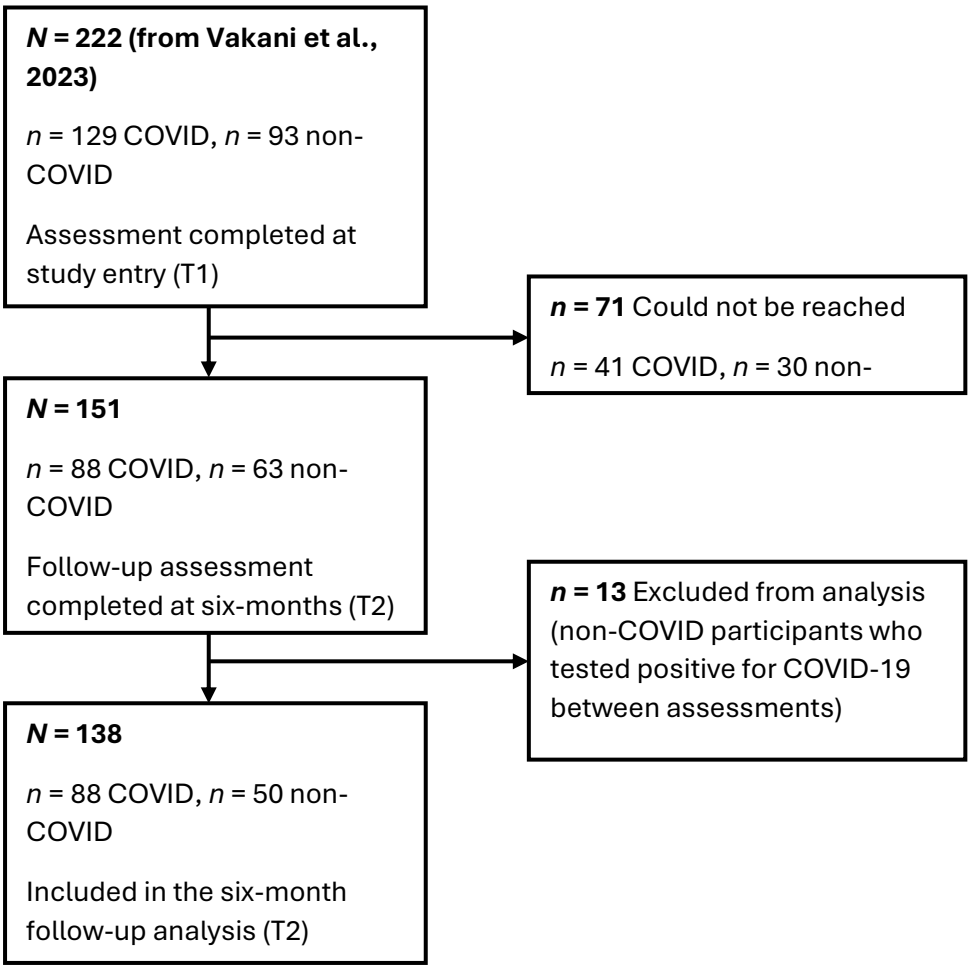
The sample consists of 138 of 222 adults who had been assessed six months earlier (T1; March 2021–March 2022) for our previous study investigating the cognitive impact of COVID-19 in working-age UK adults (Vakani et al., 2023). Of 222 participants (129 with and 93 without a history of COVID diagnosis) assessed at T1 (Vakani et al., 2023), 71 (41 COVID, 30 non-COVID) were lost to the follow-up, and 13 non-COVID (at T1) participants were excluded due to them having tested COVID-19 positive between T1 and T2, leaving 138 participants (mean age: 39.72 ± 11.81) for this investigation (re-assessed at T2; September 2021–October 2022) (see Figure 5.1). Of these 138 participants (current sample), 88 had a history of COVID-19 diagnosis (14 males, 74 females; mean days since diagnosis: 459 ± 180.84; range: 163–895) (to be

referred to as the "COVID group") and 50 had no known history of COVID-19 (11 males, 39 females; to be referred to as the "non-COVID group").

The study was approved by the College of Health, Medicine and Life Sciences Research Ethics Committee, Brunel University London (26518-A-Sep/2021-34167-1). All participants provided informed written consent and received £10 (Amazon voucher) for their time.

Figure 5.1

Study flowchart



5.3.2 Measures and Procedure

As described in Vakani et al. (2023), data on demographics, mental health, and sleep were collected using self-report measures administered via Qualtrics (an online survey tool), taking approximately 45 minutes in total to complete. Additionally, the COVID groups were asked to detail their COVID-19 diagnosis, acute symptoms at the time of infection, subjective

psychological well-being and cognitive impairment, and chronic long-COVID symptoms at both T1 and T2. Cognitive data (T1 and T2) were collected using the self-administered MyCognition (MyCQ) PRO mobile application (MyCognition, 2023), taking approximately 15 minutes to complete.

5.3.3 Assessments

5.3.3.1 Cognitive Function

The MyCQ mobile application tool (approved by the NHS in the UK) assesses processing speed, attention, working memory, executive function, and memory domains, using digital versions of commonly utilised neuropsychological tests validated against the Cambridge Neuropsychological Automated Test Battery (Bellens et al., 2022; Domen et al., 2019; Reeson et al., 2019). As described previously (Vakani et al., 2023), Processing Speed was assessed using a simple reaction time (RT) task, Attention using a choice RT task, Working Memory using the 2-back task, Executive Function using the Trail-Making B task, and memory was assessed using a visual recognition memory task (for further details, see Table 5.1).

Table 5.1

Cognitive domains, tests, and indices examined through MyCognition's mobile application

Cognitive Domains	Cognitive Test	Cognitive Performance Indices
Processing Speed	Simple reaction time (RT)	RA (% correct), average RT (ms), RT variability
Attention	Choice RT	RA (% correct), average RT (ms)
Working Memory	2-back	RA (% correct)
Executive Function	Trail-Making B	RA (% correct moves), total completion time (ms)
Memory	Visual recognition memory	RA (% correct)

Abbreviations: ms, milliseconds; RA, response accuracy; RT, reaction time.

5.3.3.2 Mental Health and Sleep

The following two self-report scales were used:

The Depression, Anxiety and Stress Scale-21 (DASS-21) (Lovibond & Lovibond, 1995) assessed depression, anxiety, and stress with corresponding seven-item sub-scales. Each item is rated by participants on a four-point scale according to how often in the past week it applied to

them. Higher scores indicate higher levels (severity) of symptoms. Internal consistency for all sub-scales was good-to-excellent (Cronbach's $\alpha \geq 0.82$) in this sample.

Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) assessed daytime dysfunction, use of sleeping medication, sleep disturbances, habitual sleep efficiency, sleep duration, sleep latency, and subjective sleep score (scores are derived for component, plus a global score). Participants respond to the PSQI items by relating them to their past month. Higher scores indicate lower sleep quality. The PSQI had an acceptable internal consistency (global score, Cronbach's $\alpha = 0.76$) in this sample.

5.3.4 Statistical Analysis

We first examined the demographic and other characteristics of study participants who provided both T1 and T2 data ($n = 138$) versus those with only T1 data ($n = 84$; not included in any further analysis), out of 222 participants from Vakani et al. (2023), to determine if there were any factors associated with non-volunteering (especially in the COVID group) for T2 assessment.

Next, to examine possible changes from T1 to T2 in the COVID group ($n = 88$), relative to those in the non-COVID group ($n = 50$), we used a 2 (Group: COVID, non-COVID) × 2 (Time: T1, T2) repeated-measures ANOVA, separately for each cognitive variable, with Group as a between-subjects factor and Time as a within-subjects factor. To examine possible differences in cognitive and mental health changes of hospitalised versus non-hospitalised COVID participants, we conducted 3 (Group Hospitalisation: Hospitalised COVID, Non-hospitalised COVID, non-COVID) × 2 (Time: T1, T2) repeated-measures ANOVAs; and confirmed any significant main or interaction effects after covarying for age, given a trend-level age difference between hospitalised and non-hospitalised participants (see Results). To examine a change from T1 to T2 in total long-COVID symptom load (a sum of all symptom ratings), we ran a 2 (Hospitalisation: Hospitalised COVID, Non-hospitalised COVID) × 2 (Time: T1, T2) ANOVA with Hospitalisation as a between-subjects factor and Time as a within-subjects factor, covarying for age. All ANOVAs were initially conducted with Sex entered as another between-subjects factor but Sex was then removed, as there were no main or interactive effects involving Sex, and the current sample has a relatively smaller number of males.

Significant main effects and interactions from ANOVAs were followed up with the analysis of simple main effects and post hoc comparisons, as appropriate. Effect sizes, where reported, are partial eta squared (η_p^2; the proportion of variance associated with a factor). Finally, the relationship between changes (T1 to T2) in total long-COVID symptom load and cognitive function was examined using Pearson's correlations.

All analyses were performed using the Statistical Package for Social Sciences (version 28; IBM, New York, USA). The data distribution on all variables met the assumptions of parametric statistical procedures. Alpha level for testing the significance of effects was maintained at $p \leq 0.05$.

5.4 Results

5.4.1 Sample Characteristics

About two-thirds (62%) of the sample with T1 assessments (*N* = 222) (Vakani et al., 2023) provided T2 data (*n* = 138) (Figure 5.1). Fifteen (75%) of 20 participants with a history of hospitalisation at T1 also provided T2 data. There was no age difference [$t(206) = 0.36$, $p = .72$] between the groups with both T1 and T2 assessments and only T1 assessment. Other characteristics were also comparable for these (T1 and T2, T1 only) groups (Table 5.2). COVID participants who completed both assessments versus those with only T1 assessment also had comparable demographics, COVID-related symptoms (Tables 5.2 and 5.3), as well as cognitive and mental health characteristics (Table 5.4). For the current sample, there was no significant difference in age [$t(136) = 1.66$, $p = .10$] or BMI [$t(136) = 1.66$, $p = .10$] between the COVID (*n* = 88) and non-COVID groups (*n* = 50) (Table 5.5; for demographics, see Table 5.6). Hospitalised COVID participants (*n* = 15) had a higher prevalence of most long-COVID symptoms (Table 5.3) and were also non-significantly older compared to Non-hospitalised COVID participants (*n* = 73) [$t(86) = 1.75$, $p = .08$] (Table 5.7).

Table 5.2

Characteristics of the participants with both T1 and T2 assessments (n = 138; current sample) and those with only T1 assessments [n = 84 of 222 from Vakani et al. (2023) including 41 COVID and 30 non-COVID participants who did not respond and 13 non-COVID participants who were excluded because of becoming COVID positive between T1 and T2]

		Sample from Vakani et al. (2023) (*N* = 222; 129 with and 93 without a COVID history)		COVID Only Group (*n* = 129)	
		T1 & T2 Group (*n* = 138, current investigation)	T1 Only Group (*n* = 84)	T1 & T2 Group (*n* = 88, current investigation)	T1 Only Group (*n* = 41)
		M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Age (Years)		39.72±11.81	37.83±12.45	40.47±10.55	41.63±12.56
		n (% of Total)	*n* (% of Total)	*n* (% of Total)	*n* (% of Total)
Ethnicity	White British	94 (68.1%)	54 (64.3%)	74 (84.1%)	33 (80.5%)
	South Asian	29 (21.0%)	26 (31.0%)	5 (5.7%)	8 (19.5%)
	Other Asian	3 (2.2%)	2 (2.4%)	1 (1.1%)	0
	Black British	1 (0.7%)	2 (2.4%)	1 (1.1%)	0
	Mixed Race	9 (6.5%)	0	6 (6.8%)	0
	Other	2 (1.4%)	0	1 (1.1%)	0
Educational Background	High School	5 (3.6%)	7 (8.3%)	3 (3.4%)	4 (9.8%)
	College/6th Form	26 (18.8%)	5 (6.0%)	19 (21.6%)	1 (2.4%)
	Vocational Qualification	12 (8.7%)	11 (13.1%)	9 (10.2%)	7 (17.1%)
	Bachelor's Degree	45 (32.6%)	38 (45.2%)	28 (31.8%)	22 (53.7%)
	Master's Degree	38 (27.5%)	19 (22.6%)	21 (23.9%)	5 (12.2%)
	PhD or Higher	9 (6.5%)	4 (4.8%)	5 (5.7%)	2 (4.9%)
	Prefer not to say	3 (2.2%)	0	3 (3.4%)	0
Employment Status	Employed Full-time	69 (50.0%)	46 (54.8%)	40 (45.5%)	21 (51.2%)
	Employed Part-time	27 (19.6%)	11 (13.1%)	19 (21.6%)	7 (17.1%)
	Student Full-time	13 (9.4%)	6 (7.1%)	7 (8.0%)	2 (4.9%)
	Student Part-time	1 (0.7%)	2 (2.4%)	0	1 (2.4%)
	Unemployed	1 (0.7%)	1 (1.2%)	1 (1.1%)	0
	Retired	2 (1.4%)	2 (2.4%)	1 (1.1%)	1 (2.4%)
	Semi-retired	4 (2.9%)	2 (2.4%)	2 (2.3%)	1 (2.4%)
	Homemaker	2 (1.4%)	1 (1.2%)	2 (2.3%)	0 (0%)
	Unable to Work	8 (5.8%)	6 (7.1%)	7 (8.0%)	5 (12.2%)
	Other	6 (4.3%)	7 (8.3%)	5 (5.7%)	3 (7.3%)
	Prefer not to say	5 (3.6%)	0	4 (4.5%)	0
Physical Health Conditions	Cancer	3 (2.2.%)	2 (2.4%)	3 (3.4%)	2 (4.9%)
	Diabetes	12 (8.7%)	3 (3.6%)	7 (8.0%)	3 (7.3%)
	Heart Condition	6 (4.3%)	4 (4.8%)	4 (4.5%)	4 (9.8%)
	Immunosuppressed	7 (5.1%)	3 (3.6%)	7 (8.0%)	1 (2.4%)
	Kidney Disease	1 (0.7%)	0	1 (1.1%)	0
	Liver Disease	0	3 (3.6%)	0 (0%)	2 (4.9%)
	Lung Condition	22 (15.9%)	13 (15.5%)	18 (20.5%)	10 (24.4%)
	Neurological Condition	5 (3.6%)	3 (3.6%)	5 (5.7%)	2 (4.9%)
	Obesity	17 (12.3%)	8 (9.5%)	12 (13.6%)	6 (14.6%)
	Organ Transplantation	1 (0.7%)	0	1 (1.1%)	0
Mental Health Conditions	Anorexia Nervosa	2 (1.4%)	2 (2.4%)	1 (1.1%)	1 (2.4%)
	Anxiety	57 (41.3%)	38 (45.2%)	38 (43.2%)	18 (43.9%)
	ADHD	4 (2.9%)	2 (2.4%)	3 (3.4%)	0
	Depression	47 (34.1%)	28 (33.3%)	33 (37.5%)	15 (36.6%)

Eating Disorder(s)	9 (6.5%)	3 (3.6%)	7 (8.0%)	1 (2.4%)
Insomnia	26 (18.8%)	16 (19.0%)	21 (23.9%)	8 (19.5%)
OCD	6 (4.3%)	6 (7.1%)	4 (4.5%)	3 (7.3%)
Panic Disorder	12 (8.7%)	5 (6.0%)	7 (8.0%)	3 (7.3%)
Personality Disorder	4 (2.9%)	1 (1.2%)	3 (3.4%)	1 (2.4%)
Phobias	12 (8.7%)	4 (4.8%)	6 (6.8%)	3 (7.3%)
PTSD	15 (10.9%)	9 (10.7%)	12 (13.6%)	6 (14.6%)
Psychosis	2 (1.4%)	3 (3.6%)	1 (1.1%)	1 (2.4%)
Other	2 (1.4%)	1 (1.2%)	2 (2.3%)	0

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; F, Females; M, Males; OCD, Obsessive Compulsive Disorder; PTSD, Post-Traumatic Stress Disorder.

Table 5.3

Prevalence of COVID-19 symptoms in the COVID participants with both T1 and T2 assessments (n = 88 of 129 from Vakani et al.; classified by hospitalisation history) and those with only T1 assessments (n = 41 of 129 from Vakani et al who did not respond at T2)

		T1 Only Group (*n* = 41)	T1 & T2 Group (all, *n* = 88)		T1 & T2 Group, Classified by Hospitalisation History			
					Hospitalised COVID Group (*n* = 15; 3 M, 12 F)		Non-hospitalised COVID Group (*n* = 73; 11 M, 62 F)	
			T1	T2	T1	T2	T1	T2
		n (% of Total)	*n* (% of Total)	*n* (% of Total)	*n* (% of Total)	*n* (% of Total)	*n* (% of Total)	*n* (% of Total)
Hospitalisation due to COVID		5 (12.2%)	15 (17.0%)		/	/	/	/
Acute COVID-19 Symptoms[a]	Temperature	33 (80.5%)	66 (75.0%)	66 (79.5%)	13 (86.7%)	12 (85.7%)	53 (72.6%)	52 (75.4%)
	Dry Cough	29 (70.7%)	57 (64.8%)	57 (68.7%)	12 (80.0%)	13 (92.9%)	45 (61.6%)	44 (63.8%)
	Loss of Taste and/or Smell	29 (70.7%)	54 (61.4%)	53 (63.9%)	9 (60.0%)	10 (71.4%)	45 (61.6%)	43 (62.3%)
	Other	26 (63.4%)	57 (64.8%)	38 (45.8%)	8 (53.3%)	7 (50.0%)	49 (67.1%)	31 (42.5%)
Chronic COVID-19 Symptoms (Long-COVID)[b]	Abdominal pain	15 (36.6%)	34 (38.6%)	27 (32.9%)	8 (53.3%)	4 (28.6%)	26 (35.6%)	23 (33.8%)
	Arrhythmia	21 (51.2%)	51 (58.0%)	42 (51.2%)	11 (73.3%)	10 (71.4%)	40 (54.8%)	32 (47.1%)
	Body chills	19 (46.3%)	42 (47.7%)	28 (34.1%)	4 (26.7%)	5 (35.7%)	38 (52.1%)	23 (33.8%)
	Breathing problems	27 (65.9%)	64 (72.7%)	52 (63.4%)	14 (93.3%)	13 (92.9%)	50 (68.5%)	39 (57.4%)
	Chest pain	19 (46.3%)	50 (56.8%)	34 (41.5%)	12 (80.0%)	12 (85.7%)	38 (52.1%)	22 (32.4%)
	Chilblains	6 (14.6%)	13 (14.8%)	11 (13.4%)	3 (20.0%)	3 (21.4%)	10 (13.7%)	8 (11.8%)
	Confusion/delirium	28 (68.3%)	49 (55.7%)	51 (62.2%)	11 (73.3%)	11 (78.6%)	38 (52.1%)	40 (58.8%)
	Diarrhoea	14 (34.1%)	30 (34.1%)	24 (29.3%)	7 (46.7%)	6 (42.9%)	23 (31.5%)	18 (26.5%)
	Dry cough	15 (36.6%)	31 (35.2%)	31 (37.8%)	6 (40.0%)	9 (64.3%)	25 (34.2%)	16 (23.5%)
	Exhaustion/fatigue	34 (82.9%)	80 (90.9%)	67 (81.7%)	15 (100.0%)	13 (92.9%)	65 (89.0%)	54 (79.4%)
	Hallucinations	9 (22.0%)	10 (11.4%)	8 (9.76%)	2 (13.3%)	4 (28.6%)	8 (11.0%)	4 (5.9%)
	Headaches	29 (70.7%)	66 (75.0%)	56 (68.3%)	12 (80.0%)	10 (71.4%)	54 (74.0%)	46 (67.6%)
	Insomnia	31 (75.6%)	70 (79.5%)	61 (74.4%)	14 (93.3%)	12 (85.7%)	56 (76.7%)	49 (72.1%)
	Irritability	28 (68.3%)	66 (75.0%)	57 (69.5%)	14 (93.3%)	13 (92.9%)	52 (71.2%)	44 (64.7%)
	Lack of appetite	17 (41.5%)	45 (51.1%)	22 (26.8%)	10 (66.7%)	5 (35.7%)	35 (47.9%)	17 (25.0%)
	Loss of taste and/or smell	16 (39.0%)	31 (35.2%)	22 (26.8%)	7 (46.7%)	5 (35.7%)	24 (32.9%)	17 (25.0%)
	Mild cognitive problems	34 (82.9%)	73 (83.0%)	68 (82.9%)	14 (93.3%)	13 (92.9%)	59 (80.8%)	55 (80.9%)
	Muscle/body ache	29 (70.7%)	68 (77.3%)	59 (72.0%)	12 (80.0%)	12 (85.7%)	56 (76.7%)	47 (69.1%)
	Sore eyes/conjunctivitis	18 (43.9%)	41 (46.6%)	27 (32.9%)	6 (40.0%)	7 (50.0%)	35 (47.9%)	20 (29.4%)
	Sore throat	13 (31.7%)	34 (38.6%)	35 (42.7%)	8 (53.3%)	10 (71.4%)	26 (35.6%)	25 (36.8%)
	Temperature	10 (24.4%)	26 (29.5%)	18 (22.0%)	3 (20.0%)	4 (28.6%)	23 (31.5%)	14 (20.6%)
	Vomiting/nausea	10 (24.4%)	24 (27.3%)	20 (24.4%)	6 (40.0%)	5 (35.7%)	18 (24.7%)	15 (22.1%)
	Other	8 (19.5%)	21 (23.9%)	18 (22.0%)	4 (26.7%)	3 (21.4%)	17 (23.3%)	15 (22.1%)
Subjective Cognitive Function Impairment[a]		32 (78.0%)	69 (78.4%)	66 (79.5%)	14 (93.3%)	13 (86.7%)	55 (75.3%)	53 (72.6%)
Subjective Reduced Psychological Well-being[a]		30 (73.2%)	70 (79.5%)	58 (69.9%)	14 (93.3%)	12 (80.0%)	56 (76.7%)	46 (63.0%)

[a] Data not available for 5 participants at T2 (1 hospitalised, 4 non-hospitalised); [b] Data not available for 6 participants at T2 (1 hospitalised, 5 non-hospitalised).

Table 5.4

Cognitive characteristics at T1 of the participants with both T1 and T2 assessments and those with only T1 assessment

Measures		COVID Group		Non-COVID Group	
		T1 & T2 Group (*n* = 88)	T1 Only Group (*n* = 41)	T1 & T2 Group (*n* = 50)	T1 Only Group (*n* = 43)
		M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Cognitive Function					
Processing Speed	Response accuracy (%)	95.82 (6.27) [a]	95.39 (8.56) [c]	95.78 (7.60) [b]	97.46 (4.09) [b]
	RT (correct responses, ms)	375.89 (80.51) [a]	377.97 (84.60) [c]	354.71 (79.64) [b]	353.29 (66.22) [b]
	RT variability (SD of RT)	88.23 (40.73) [a]	83.54 (44.27) [c]	70.04 (34.67) [b]	74.36 (41.72) [b]
Attention	Response accuracy (%)	95.50 (8.65) [a]	94.24 (8.48) [d]	97.71 (4.48) [c]	97.85 (4.91) [c]
	RT (correct responses, ms)	494.45 (94.54) [a]	536.14 (93.67) [d]	463.52 (92.97) [c]	475.73 (103.53) [c]
Working Memory	Response accuracy (%)	92.44 (8.48) [b]	91.05 (8.25) [b]	92.96 (7.75) [c]	95.58 (4.64) [b]
Executive Function	Response accuracy (%)	94.54 (7.46)	95.27 (6.74)	95.20 (8.44)	94.62 (8.81) [e]
	Completion time (ms)	33626.11 (22201.51)	32239.37 (10144.19)	29598.04 (9665.89)	30630.08 (15341.01) [e]
Memory	Recognition accuracy (%)	89.95 (9.11) [b]	88.29 (7.20) [b]	92.30 (7.50)	90.44 (8.97)
Mental Health and Well-being					
Mental Health (DASS-21)	Depression	14.11 (10.50)	15.17 (10.58)	9.36 (9.69)	11.86 (12.15)
	Anxiety	10.59 (8.75)	10.20 (8.27)	7.04 (7.56)	7.26 (8.53)
	Stress	14.70 (9.26)	14.10 (10.01)	13.28 (10.19)	12.93 (10.45)
Sleep Quality (PSQI)	Global Score	9.95 (3.70)	9.80 (3.51)	6.54 (3.25)	7.53 (4.33)

Abbreviations: ms, milliseconds; RT, Reaction Time.

Sample size reduced [a] by 8; [b] by 1; [c] by 2; [d] by 5; [e] by 3.

Table 5.5

Comparison of T1 and T2 characteristics for the current sample (N = 138), classified by group

		COVID Group (*n* = 88; 14 M, 74 F)		Non-COVID Group (*n* = 50; 11 M, 39 F)	
		T1	T2	T1	T2
		M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Age (Years)		40.47 (10.55)	40.97 (10.42)	37.04 (13.71)	37.52 (13.76)
BMI		28.94 (9.98)	30.13 (12.26)	26.58 (7.03)	26.99 (7.00)
		n (% of Total)	*n* (% of Total)	*n* (% of Total)	*n* (% of Total)
Physical Health Conditions	Cancer	3 (3.4%)	3 (3.4%)	0	0
	Diabetes	7 (8.0%)	6 (6.8%)	5 (10.0%)	3 (6.0%)
	Heart Condition	4 (4.5%)	8 (9.1%)	2 (4.0%)	2 (4.0%)
	Immunosuppressed	7 (8.0%)	8 (9.1%)	0	0
	Kidney Disease	1 (1.1%)	1 (1.1%)	0	0
	Liver Disease	0	0	0	0
	Lung Condition	18 (20.5%)	20 (22.7%)	4 (8.0%)	5 (10.0%)
	Neurological Condition	5 (5.7%)	10 (11.4%)	0	0
	Obesity	12 (13.6%)	10 (11.4%)	5 (10.0%)	3 (6.0%)
	Organ Transplantation	1 (1.1%)	1 (1.1%)	0	0
Mental Health Conditions	Anorexia Nervosa	1 (1.1%)	1 (1.1%)	1 (2.0%)	1 (2.0%)
	Anxiety	38 (43.2%)	38 (43.2%)	19 (38.0%)	18 (36.0%)
	ADHD	3 (3.4%)	3 (3.4%)	1 (2.0%)	2 (4.0%)
	Depression	33 (37.5%)	32 (36.4%)	14 (28.0%)	14 (28.0%)
	Eating Disorder(s)	7 (8.0%)	6 (6.8%)	2 (4.0%)	1 (2.0%)
	Insomnia	21 (23.9%)	24 (27.3%)	5 (10.0%)	6 (12.0%)
	OCD	4 (4.5%)	6 (6.8%)	2 (4.0%)	2 (4.0%)
	Panic Disorder	7 (8.0%)	8 (9.1%)	5 (10.0%)	5 (10.0%)
	Personality Disorder	3 (3.4%)	3 (3.4%)	1 (2.0%)	1 (2.0%)
	Phobias	6 (6.8%)	9 (10.2%)	6 (12.0%)	3 (6.0%)
	PTSD	12 (13.6%)	10 (11.4%)	3 (6.0%)	3 (6.0%)
	Psychosis	1 (1.1%)	1 (1.1%)	1 (2.0%)	1 (2.0%)
	Schizophrenia	0	0	0	1 (2.0%)
	Other	2 (2.3%)	3 (3.4%)	0	1 (2.0%)

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; BMI, Body Mass Index; F, Females; M, Males; OCD, Obsessive Compulsive Disorder; PTSD, Post-Traumatic Stress Disorder.

Table 5.6

Demographic characteristics of the current sample (N = 138)

		COVID Group (*n* = 88; 14 M, 74 F)	Non-COVID Group (*n* = 50; 11 M, 39 F)
		n (% of Total)	*n* (% of Total)
Ethnicity	White British	74 (84.2%)	20 (40.0%)
	South Asian	6 (6.8%)	24 (48.0%)
	Other Asian	1 (1.1%)	3 (6.0%)
	Black British	0	0
	Mixed Race	5 (5.7%)	3 (6.0%)
	Other	2 (2.3%)	0
Educational Background	High School	4 (4.5%)	1 (2.0%)
	College/6th Form	15 (17.0%)	8 (16.0%)
	Vocational Qualification	10 (11.4%)	1 (2.0%)
	Bachelor's Degree	29 (33.0%)	20 (40.0%)
	Master's Degree	21 (23.9%)	15 (30.0%)
	PhD or Higher	5 (5.7%)	4 (8.0%)
	No Education	0	1 (2.0%)
	Prefer not to say	4 (4.5%)	0
Employment Status	Employed Full-time	40 (45.5%)	30 (60.0%)
	Employed Part-time	18 (20.5%)	9 (18.0%)
	Student Full-time	4 (4.5%)	5 (10.0%)
	Student Part-time	1 (1.1%)	1 (2.0%)
	Unemployed	1 (1.1%)	0
	Retired	1 (1.1%)	2 (4.0%)
	Semi-retired	1 (1.1%)	0
	Homemaker	1 (1.1%)	0
	Unable to Work	12 (13.6%)	1 (2.0%)
	Other	7 (8.0%)	2 (4.0%)
	Prefer not to say	2 (2.3%)	0

Abbreviations: F, Females; M, Males.

Table 5.7

T1 characteristics of COVID group participants, classified by hospitalisation history, separately for participants with both T1 and T2 assessments (current sample) or only T1 assessment

		T1 and T2 COVID group (*n* = 88)		T1 only COVID Group (*n* = 41)	
		Hospitalised (*n* = 15; 3 M, 12 F)	Non-hospitalised (*n* = 73; 11 M, 62 F)	Hospitalised (*n* = 5; 1 M, 4 F)	Non-hospitalised (*n* = 36; 8 M, 28 F)
		M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Age (Years)		45.20±10.53	40.10±10.26	42.60±15.13	41.50±12.41
		n (% of Total)	*n* (% of Total)	*n* (% of Total)	*n* (% of Total)
Ethnicity	White British	14 (93.3%)	60 (82.2%)	5 (100.0%)	28 (77.8%)
	South Asian	0	5 (6.8%)	0	8 (22.2%)
	Other Asian	0	1 (1.4%)	0	0
	Black British	0	1 (1.4%)	0	0
	Mixed Race	1 (6.7%)	5 (6.8%)	0	0
	Other	0	1 (1.4%)	0	0
Educational Background	High School	1 (6.7%)	2 (2.7%)	2 (40.0%)	2 (5.6%)
	College/6th Form	2 (13.3%)	17 (23.3%)	0	1 (2.8%)
	Vocational Qualification	4 (26.7%)	5 (6.8%)	1 (20.0%)	6 (16.7%)
	Bachelor's Degree	5 (33.3%)	23 (31.5%)	2 (40.0%)	20 (55.6%)
	Master's Degree	3 (20.0%)	18 (24.7%)	0	5 (13.9%)
	PhD or Higher	0	5 (6.8%)	0	2 (5.6%)
	No Education	0	0	0	0
	Prefer not to say	0	3 (4.1%)	0	0
Employment Status	Employed Full-time	6 (40.0%)	34 (46.6%)	3 (60.0%)	18 (50.0%)
	Employed Part-time	6 (40.0%)	13 (17.8%)	1 (20.0%)	6 (16.7%)
	Student Full-time	1 (6.7%)	6 (8.2%)	0	2 (5.6%)
	Student Part-time	0	0	0	1 (2.8%)
	Unemployed	0	1 (1.4%)	0	0
	Retired	0	1 (1.4%)	0	1 (2.8%)
	Semi-retired	0	2 (2.7%)	0	1 (2.8%)
	Homemaker	1 (6.7%)	1 (1.4%)	0	0
	Unable to Work	1 (6.7%)	6 (8.2%)	1 (20.0%)	4 (11.1%)
	Other	0	5 (6.8%)	0	3 (8.3%)
	Prefer not to say	0	4 (5.5%)	0	0
Physical Health Conditions	Cancer	0	3 (4.1%)	0	2 (5.6%)
	Diabetes	1 (6.7%)	6 (8.2%)	1 (20.0%)	2 (5.6%)
	Heart Condition	1 (6.7%)	3 (4.1%)	1 (20.0%)	3 (8.3%)
	Immunosuppressed	2 (13.3%)	5 (6.8%)	0	1 (2.8%)
	Kidney Disease	0	1 (1.4%)	0	0
	Liver Disease	0	0	1 (20.0%)	1 (2.8%)
	Lung Condition	6 (40.0%)	12 (16.4%)	2 (40.0%)	8 (22.2%)
	Neurological Condition	2 (13.3%)	3 (4.1%)	0	2 (5.6%)
	Obesity	1 (6.7%)	11 (15.1%)	2 (40.0%)	4 (11.1%)
	Organ Transplantation	0	1 (1.4%)	0	0
Mental Health Conditions	Anorexia Nervosa	1 (6.7%)	0	0	1 (2.8%)
	Anxiety	5 (33.3%)	33 (45.2%)	1 (20.0%)	17 (47.2%)
	ADHD	0	3 (4.1%)	0	0
	Depression	5 (33.3%)	28 (38.4%)	1 (20.0%)	14 (38.9%)
	Eating Disorder(s)	1 (6.7%)	6 (8.2%)	0	1 (2.8%)
	Insomnia	3 (20.0%)	18 (24.7%)	0	8 (22.2%)
	OCD	1 (6.7%)	3 (4.1%)	0	3 (8.3%)
	Panic Disorder	0	7 (9.6%)	0	3 (8.3%)
	Personality Disorder	1 (6.7%)	2 (2.7%)	0	1 (2.8%)

Phobias	1 (6.7%)	5 (6.8%)	0	3 (8.3%)
PTSD	2 (13.3%)	10 (13.7%)	1 (20.0%)	5 (13.9%)
Psychosis	0	1 (1.4%)	0	1 (2.8%)
Other	0	2 (2.7%)	0	0

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; F, Females; M, Males; OCD, Obsessive Compulsive Disorder; PTSD, Post-Traumatic Stress Disorder.

5.4.2 Cognitive Function: Changes from T1 to T2

5.4.2.1 COVID versus Non-COVID Participants

For processing speed, we observed a significant Group × Time interaction in intra-individual RT variability [$F(1,126) = 3.77$, $p = .05$, $\eta_p^2 = .03$] (Table 5.8). Follow-up analysis showed significantly larger RT variability in the COVID group compared to the non-COVID group at T1 [$t(126) = 2.63$, $p = .01$], but not at T2 [$t(126) = 0.44$, $p = .67$]. From T1 to T2, there was a trend-level improvement in the COVID group [$t(78) = 1.92$, $p = .06$], with comparable T1 and T2 scores (i.e., no change) in the non-COVID group [$t(48) = 0.99$, $p = .33$] (Table 5.8; Figure 5.2). For attention, there was only a main effect of Group in RTs [$F(1,123) = 4.67$, $p = .03$, $\eta_p^2 = .04$], showing slower RTs on both occasions in the COVID group, relative to the non-COVID group (Table 5.8).

For working memory, executive function, and memory tasks, no significant main effects or interactions were found.

Figure 5.2

Processing speed reaction time (RT) variability in COVID and non-COVID groups at study entry (T1) and six-month follow-up (T2)

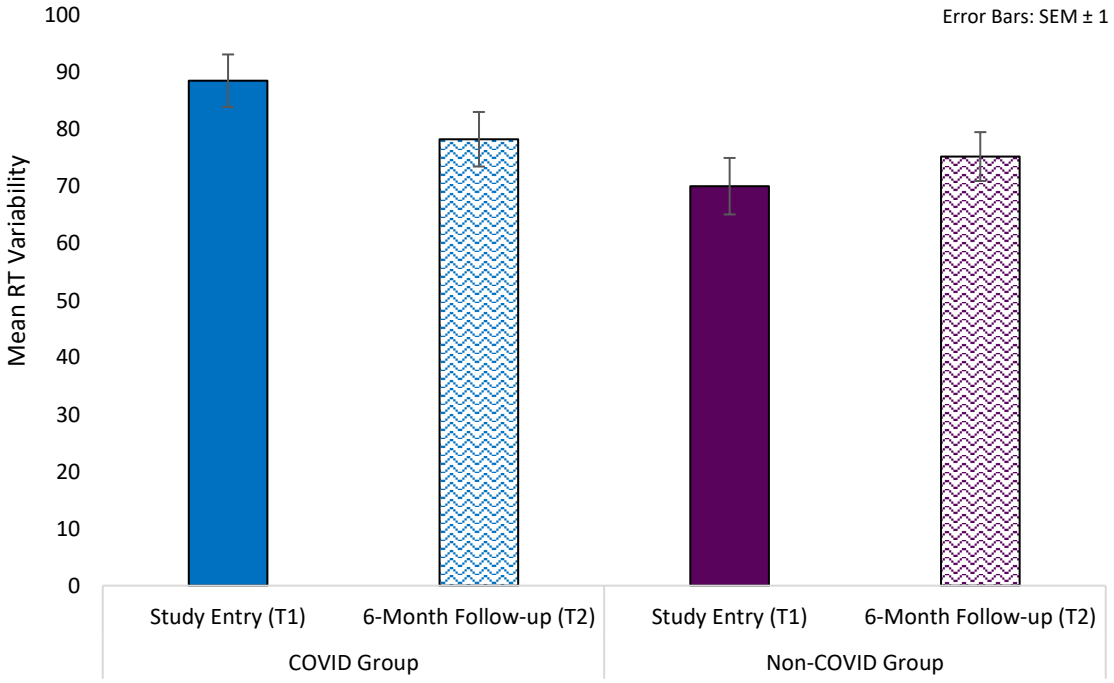


Table 5.8

Descriptive statistics and results of the repeated-measures Group (COVID, non-COVID) x Time (T1, T2) analysis of variance (ANOVA) on cognitive measures

		COVID Group (*n* = 88)		Non-COVID Group (*n* = 50)		Group (COVID, non-COVID) x Time (T1, T2) ANOVA Results											
		T1: Study Entry	T2: Six-Month Follow-up	T1: Study Entry	T2: Six-Month Follow-up	Group				Time				Group x Time			
		M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2
Processing Speed[a]	Response accuracy (%)	95.76 (6.30)	96.71 (4.47)	95.78 (7.60)	96.41 (4.31)	0.03	1,126	.87	*.0*	1.65	1,126	.20	*.01*	0.07	1,126	.80	*.001*
	RT (correct responses, ms)	376.51 (80.83)	367.54 (86.94)	354.71 (79.94)	345.90 (50.58)	2.84	1,126	.09	*.02*	2.29	1,126	.13	*.02*	0.0	1,126	.99	*.0*
	RT variability (SD of RT)	88.54 (40.89)	78.27 (42.53)	70.04 (34.67)	75.24 (29.97)	3.51	1,126	.06	*.03*	0.41	1,126	.53	*.003*	3.77	1,126	**.05**	*.03*
Attention[b]	Response accuracy (%)	95.36 (8.79)	95.02 (9.42)	97.71 (4.48)	95.64 (6.38)	1.55	1,123	.22	*.01*	2.06	1,123	.15	*.02*	1.05	1,123	.31	*.01*
	RT (correct responses, ms)	490.53 (92.15)	494.69 (114.00)	463.52 (92.97)	450.40 (87.67)	4.67	1,123	**.03**	*.04*	0.35	1,123	.56	*.003*	1.29	1,123	.26	*.01*
Working Memory[c]	Response accuracy (%)	92.44 (8.48)	93.53 (7.03)	92.98 (7.83)	94.31(6.14)	0.33	1,132	.57	*.002*	2.79	1,132	.10	*.02*	0.03	1,132	.87	*.0*
Executive Function[d]	Response accuracy (%)	94.48 (7.48)	94.32 (9.02)	95.11 (8.50)	92.56 (12.74)	0.19	1,134	.66	*.001*	1.72	1,134	.19	*.01*	1.34	1,134	.25	*.01*
	Completion time (ms)	33692.22 (22321.50)	32263.90 (23740.74)	29556.16 (9761.48)	33450.29 (31759.02)	0.17	1,134	.68	*.001*	0.37	1,134	.54	*.003*	1.74	1,134	.19	*.01*
Memory[e]	Recognition accuracy (%)	89.95 (9.11)	92.05 (6.38)	92.30 (7.50)	92.56 (6.17)	1.60	1,135	.21	*.01*	2.78	1,135	.10	*.02*	1.71	1,135	.19	*.01*

Significant *p* values are in **bold**.

Abbreviations: ms, milliseconds; RT, Reaction Time.

Sample size reduced [a] by 10 (9 COVID, 1 non-COVID), [b] by 13 (11 COVID, 2 non-COVID), [c] by 4 (1 COVID, 3 non-COVID), [d] by 2 (1 COVID, 1 non-COVID), [e] by 1 (COVID).

5.4.2.2 The Influence of COVID-19-Related Hospitalisation History

For processing speed, there were main effects of Group Hospitalisation for both average RTs [$F(2,125) = 3.71$, $p = .03$, $\eta_p^2 = .06$] and RT variability [$F(2,125) = 3.33$, $p = .04$, $\eta_p^2 = .05$]. Follow-up analysis of RTs showed significantly larger RTs in the Hospitalised COVID group relative to the Non-hospitalised COVID group [$F(1,77) = 3.87$, $p = .05$, $\eta_p^2 = .05$; age covaried: $F(1,76) = 3.36$, $p = .07$, $\eta_p^2 = .04$], as well as the non-COVID group [$F(1,60) = 8.44$, $p = .005$, $\eta_p^2 = .12$; age covaried: $F(1,59) = 6.76$, $p = .01$, $\eta_p^2 = .10$]. The Non-hospitalised COVID and non-COVID groups did not differ from each other [$F(1,113) = 1.24$, $p = .27$, $\eta_p^2 = .01$] (Table 5.9). Follow-up analysis of processing speed RT variability showed that the Hospitalised COVID group had larger RT variability compared to the non-COVID group [$F(1,60) = 8.62$, $p = .005$, $\eta_p^2 = .01$; age covaried: $F(1,59) = 6.83$, $p = .01$, $\eta_p^2 = .10$] but not the Non-hospitalised COVID group [$F(1,77) = 2.63$, $p = .11$, $\eta_p^2 = .03$; age covaried: $F(1,76) = 2.46$, $p = .12$, $\eta_p^2 = .03$] (Table 5.9). There was no significant difference between the Non-hospitalised COVID and non-COVID groups [$F(1,113) = 1.80$, $p = .18$, $\eta_p^2 = .02$].

For attention task RTs, there was a main effect of Group Hospitalisation [$F(2,122) = 7.54$, $p = .001$, $\eta_p^2 = .11$], with larger RTs in the Hospitalised COVID group relative to the Non-hospitalised COVID group [$F(1,75) = 9.60$, $p = .003$, $\eta_p^2 = .11$; age covaried: $F(1,74) = 10.01$, $p = .002$, $\eta_p^2 = .12$] as well as the non-COVID group [$F(1,58) = 15.95$, $p < .001$, $\eta_p^2 = .22$; age covaried: $F(1,57) = 14.23$, $p < .001$, $\eta_p^2 = .20$]. There was no difference between the Non-hospitalised COVID and non-COVID groups [$F(1,111) = 1.82$, $p = .18$, $\eta_p^2 = .02$] (Table 5.9).

For working memory (RA, %), there was only a marginally significant main effect of Time [$F(1,131) = 3.98$, $p = .05$, $\eta_p^2 = .03$; higher RA at T2 than T1], which became non-significant after covarying for age [$F(1,130) = 3.09$, $p = .08$, $\eta_p^2 = .02$] (Table 5.9).

For executive function, there was a main effect of Group Hospitalisation in task completion time (ms) [$F(2,133) = 3.91$, $p = .02$, $\eta_p^2 = .06$], explained by longer completion time (across T1 and T2) in Hospitalised COVID group relative to both the Non hospitalised COVID [$F(1,85) = 6.72$, $p = .011$, $\eta_p^2 = .07$; age covaried: $F(1,84) = 6.11$, $p = .02$, $\eta_p^2 = .07$] and non-COVID [$F(1,62) = 4.15$, $p = .046$, $\eta_p^2 = .06$; age covaried: $F(1,61) = 2.30$, $p = .14$, $\eta_p^2 = .04$] groups. There was no difference between the Non-hospitalised COVID and non-COVID groups [$F(1,119) = 0.61$, $p = .69$, $\eta_p^2 = .001$].

For memory tasks, no significant main effects or interactions were found (Table 5.9).

5.4.3 Mental Health and Sleep: Changes from T1 to T2

5.4.3.1 COVID versus Non-COVID Participants

There were significant main effects of Group in depression [$F(1,136) = 5.09$, $p = .03$, $\eta_p^2 = .04$], anxiety [$F(1,136) = 5.89$, $p = .02$, $\eta_p^2 = .04$], and overall sleep quality [$F(1,136) = 26.49$, $p < .001$, $\eta_p^2 = .16$]. The COVID group had significantly higher depression and anxiety, and lower sleep quality (PSQI) compared to the non-COVID group. Additionally, there was a main effect of Time for depression [$F(1,136) = 4.73$, $p = .03$, $\eta_p^2 = .03$] explained by lower depression at T2 relative to T1 in both groups (Table 5.10). No significant effects (only trends) were found for stress.

5.4.3.2 The Influence of COVID-19-Related Hospitalisation History

For depression, there was a main effect of Group Hospitalisation [$F(2,134) = 2.99$, $p = .05$, $\eta_p^2 = .04$], with no difference between the Non-hospitalised COVID and Hospitalised COVID groups [$F(1,86) = 0.19$, $p = .67$, $\eta_p^2 = .002$] but a trend for higher depression in both Non-hospitalised COVID [$F(1,121) = 3.99$, $p = .05$, $\eta_p^2 = .03$; age covaried: $F(1,120) = 4.35$, $p = .04$, $\eta_p^2 = .04$] and Hospitalised COVID [$F(1,63) = 3.69$, $p = .06$, $\eta_p^2 = .06$; age covaried: $F(1,62) = 3.65$, $p = .06$, $\eta_p^2 = .06$] COVID groups, relative to the non-COVID group (Table 5.11). There was also a trend-level Group Hospitalisation × Time interaction [$F(2,134) = 2.67$, $p = .07$, $\eta_p^2 = .04$], explained by a significant reduction (T1 to T2) in depression in the Non-hospitalised COVID group [$t(72) = 3.31$, $p = .001$], but no significant change in the Hospitalised COVID [$t(14) = 0.68$, $p = .51$] or non-COVID [$t(49) = 0.54$, $p = .59$] groups (Table 5.11).

For anxiety, there was a main effect of Group Hospitalisation [$F(2,134) = 4.13$, $p = .02$, $\eta_p^2 = .06$], with both Hospitalised COVID [$F(1,63) = 3.93$, $p = .05$, $\eta_p^2 = .06$; age covaried: $F(1,62) = 3.89$, $p = .05$, $\eta_p^2 = .06$] and Non-hospitalised COVID [$F(1,121) = 4.85$, $p = .03$, $\eta_p^2 = .04$; age covaried: $F(1,120) = 6.23$, $p = .01$, $\eta_p^2 = .05$] groups showing higher anxiety relative to the non-COVID group (Table 5.11). No difference was found between the Non-hospitalised COVID and Hospitalised COVID groups [$F(1,86) = 0.12$, $p = .73$, $\eta_p^2 = .001$].

Table 5.9

Descriptive statistics and results of the repeated-measures Group Hospitalisation (Hospitalised COVID, Non-hospitalised COVID, non-COVID) x Time (T1, T2) analysis of variance (ANOVA) on cognitive measures

			Hospitalised COVID Group (n = 15)		Non-hospitalised COVID Group (n = 73)		Group Hospitalisation (Hospitalised COVID, Non-hospitalised COVID, non-COVID) x Time (T1, T2) ANOVA Results											
			T1: Study Entry	T2: Six-Month Follow-up	T1: Study Entry	T2: Six-Month Follow-up	Group Hospitalisation				Time				Group Hospitalisation x Time			
			M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2
Processing Speed[a]	Response accuracy (%)	Non-COVID group presented in Table 5.8	94.99 (9.06)	95.45 (5.50)	95.92 (5.68)	96.96 (4.24)	0.38	2,125	.68	*.01*	0.88	1,125	.35	*.01*	0.07	2,125	.93	*.001*
	RT (correct responses, ms)		417.46 (94.65)	401.77 (94.16)	368.44 (76.06)	360.80 (84.58)	3.71	2,125	**.03**	*.06*	2.19	1,125	.14	*.02*	0.08	2,125	.92	*.001*
	RT variability (SD of RT)		99.92 (35.62)	94.77 (35.87)	86.30 (41.73)	75.02 (43.21)	3.33	2,125	**.04**	*.05*	0.58	1,125	.45	*.01*	1.98	2,125	.14	*.03*
Attention[b]	Response accuracy (%)		94.54 (7.03)	92.85 (11.01)	95.51 (9.12)	95.42 (9.15)	1.15	2,122	.32	*.02*	1.48	1,122	.23	*.01*	0.68	2,122	.51	*.01*
	RT (correct responses, ms)		554.17 (75.13)	576.67 (123.67)	478.78 (90.63)	479.55 (106.36)	7.54	2,122	**.001**	*.11*	0.13	1,122	.72	*.001*	0.99	2,122	.38	*.02*
Working Memory[c]	Response accuracy (%)		90.94 (7.37)	94.03 (4.22)	92.75 (8.71)	93.43 (7.50)	0.22	2,131	.81	*.003*	3.98	1,131	**.05**	*.03*	0.58	2,131	.56	*.01*
Executive Function[c]	Response accuracy (%)		91.36 (11.78)	92.72 (12.54)	95.13 (6.16)	94.66 (8.17)	1.06	2,133	.35	*.02*	0.20	1,133	.65	*.002*	0.83	2,133	.44	*.01*
	Completion time (ms)		44595.93 (34257.70)	47056.93 (44537.02)	31420.61 (18486.50)	29182.01 (15352.91)	3.91	2,133	**.02**	*.06*	0.33	1,133	.57	*.002*	1.13	2,133	.33	*.02*
Memory[c]	Recognition accuracy (%)		88.06 (11.49)	90.63 (6.55)	90.34 (8.58)	92.35 (6.35)	1.42	2,134	.25	*.02*	3.63	1,134	.06	*.03*	0.88	2,134	.42	*.01*

Significant *p* values are in **bold**.

Abbreviations: ms, milliseconds; RT, Reaction Time.

Sample size reduced [a] by 9 (2 Hospitalised, 7 non-hospitalised), [b] by 11 (3 Hospitalised, 8 non-hospitalised), [c] by 1 (non-hospitalised).

Table 5.10

Descriptive statistics and results of the repeated-measures Group (COVID, non-COVID) x Time (T1, T2) analysis of variance (ANOVA) on mental health and sleep measures

	COVID Group (*n* = 88)		Non-COVID Group (*n* = 50)		Group (COVID, non-COVID) x Time (T1, T2) ANOVA Results											
	T1: Study Entry	T2: Six-Month Follow-up	T1: Study Entry	T2: Six-Month Follow-up	Group				Time				Group x Time			
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2
Mental Health (DASS-21)																
Depression	14.11 (10.50)	11.61 (10.78)	9.36 (9.69)	8.76 (9.84)	5.09	136	**.03**	*.04*	4.73	136	**.03**	*.03*	1.78	136	.19	*.01*
Anxiety	10.59 (8.75)	10.41 (9.25)	7.04 (7.56)	7.08 (8.13)	5.89	136	**.02**	*.04*	0.02	136	.90	*.0*	0.04	136	.84	*.0*
Stress	14.70 (9.26)	12.95 (9.83)	13.28 (10.19)	12.76 (10.15)	0.25	136	.62	*.002*	3.22	136	.08	*.02*	0.95	136	.33	*.01*
Sleep Quality (PSQI)																
Global Score*	9.95 (3.70)	9.64 (4.00)	6.54 (3.25)	6.76 (3.68)	26.49	136	**<.001**	*.16*	0.04	136	.84	*.0*	1.19	136	.28	*.01*

Significant *p* values are in **bold**.

Abbreviations: ms, milliseconds; RT, Reaction Time.

DASS-21: The Depression, Anxiety and Stress Scale-21. Higher scores indicate higher levels of depression, anxiety and stress.

PSQI: Pittsburgh Sleep Quality Index. Higher scores indicate poor sleep quality.

*The Group Effect was present on all PSQI sub-components, indicating poorer sleep quality in the COVID compared to the non-COVID group.

Table 5.11

Descriptive statistics (non-COVID group presented in Table 5.10) and results of the repeated-measures Group Hospitalisation (Hospitalised COVID, Non-hospitalised COVID, non-COVID) x Time (T1, T2) analysis of variance (ANOVA) on mental health and sleep measures

	Non-COVID group presented in Table 5.10	Hospitalised COVID Group (*n* = 15)		Non-hospitalised COVID Group (*n* = 73)		Group Hospitalisation (Hospitalised COVID, Non-hospitalised COVID, non-COVID) x Time (T1, T2) ANOVA Results											
		T1: Study Entry Total	T2: Six-Month Follow-up Total	T1: Study Entry Total	T2: Six-Month Follow-up Total	Group Hospitalisation				Time				Group x Time			
		M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2
		Mental Health (DASS-21)															
Depression		13.33 (7.43)	14.40 (7.38)	14.27 (11.06)	11.04 (11.30)	2.99	2,134	**.05**	*.04*	1.37	1,134	.24	*.01*	2.67	2,134	.07	*.04*
Anxiety		11.60 (7.49)	10.80 (8.06)	10.38 (9.02)	10.33 (9.52)	4.13	2,134	**.02**	*.06*	0.02	1,134	.88	*.0*	0.10	2,134	.90	*.002*
Stress		17.20 (7.44)	18.27 (8.81)	14.19 (9.55)	11.86 (9.72)	2.79	2,134	.07	*.04*	1.90	1,134	.17	*.01*	1.84	2,134	.16	*.03*
		Sleep Quality (PSQI)															
Global Score		10.80 (4.06)	10.93 (3.85)	9.78 (3.63)	9.37 (4.00)	13.28	2,134	**<.001**	*.17*	0.74	1,134	.39	*.01*	0.79	2,134	.46	*.01*

Significant *p* values are in **bold**.

Abbreviations: ms, milliseconds; RT, Reaction Time.

DASS-21: The Depression, Anxiety and Stress Scale-21. Higher scores indicate higher levels of depression, anxiety and stress.

PSQI: Pittsburgh Sleep Quality Index. Higher scores indicate poor sleep quality.

Finally, there was a main effect of Group Hospitalisation in sleep quality [$F(2,134) = 13.28$, $p < .001$, $\eta_p^2 = .17$], with a lower sleep quality in both Non-hospitalised COVID [$F(1,121) = 21.69$, $p < .001$, $\eta_p^2 = .15$; age covaried: $F(1,120) = 21.05$, $p < .001$, $\eta_p^2 = .15$] and Hospitalised COVID [$F(1,63) = 18.60$, $p < .001$, $\eta_p^2 = .23$; age covaried: $F(1,62) = 15.29$, $p < .001$, $\eta_p^2 = .20$] groups, relative to the non-COVID group. The Non-hospitalised COVID and Hospitalised COVID groups did not differ from each other [$F(1,86) = 1.64$, $p = .20$, $\eta_p^2 = .02$] (Table 5.11).

5.4.4 Long-COVID Symptoms: Changes from T1 to T2 in COVID Participants

A similar pattern of self-reported long-COVID symptoms, with exhaustion and mild cognitive problems being the most prevalent, was seen at T1 and T2 (Figure 5.3), especially in the Hospitalised COVID group (Table 5.3).

Total long-COVID symptom load showed a main effect of Time [$F(1,79) = 4.86$, $p = .03$, $\eta_p^2 = .06$) and, importantly, a Hospitalisation × Time interaction [$F(1,79) = 5.18$, $p = .03$, $\eta_p^2 = .06$], explained by a marked reduction (T1 to T2) in symptom load in Non-hospitalised COVID [$t(67) = 5.25$, $p < .001$] but not in Hospitalised COVID participants [$t(13) = 0.49$, $p = .63$] (Figure 5.4). Long-COVID symptom load did not correlate significantly with the number of days since diagnosis [$r(82) = .16$, $p = .15$].

5.4.4.1 Long-COVID Symptoms, Cognitive Indices, and Mental Health: Inter-Relationships

Higher long-COVID symptom load was associated with poorer performance on most cognitive indices (Table 5.12). The reduction in symptom load from T1 to T2 correlated significantly with an improvement in executive function RA (%) when examined across all COVID participants ($p = .03$), and in Non-hospitalised COVID participants ($p = .003$) (Table 5.12).

Figure 5.3

Prevalence of self-reported chronic COVID-19 (long-COVID) symptoms in the current sample (n = 82 of 88 provided data) at study entry (T1) and the six-month follow-up (T2)

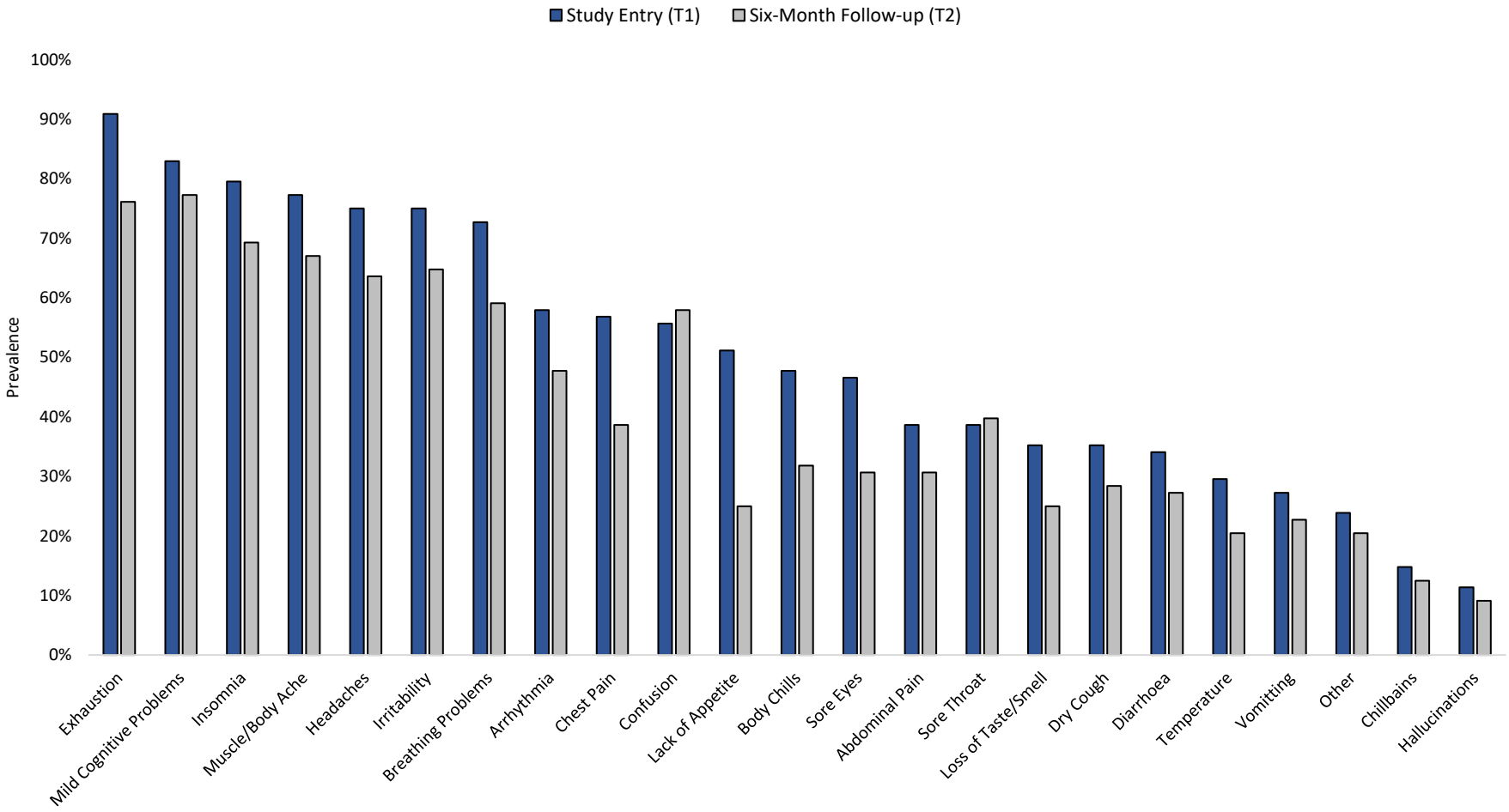


Figure 5.4

Total long-COVID symptom load in COVID participants, classified by hospitalisation history

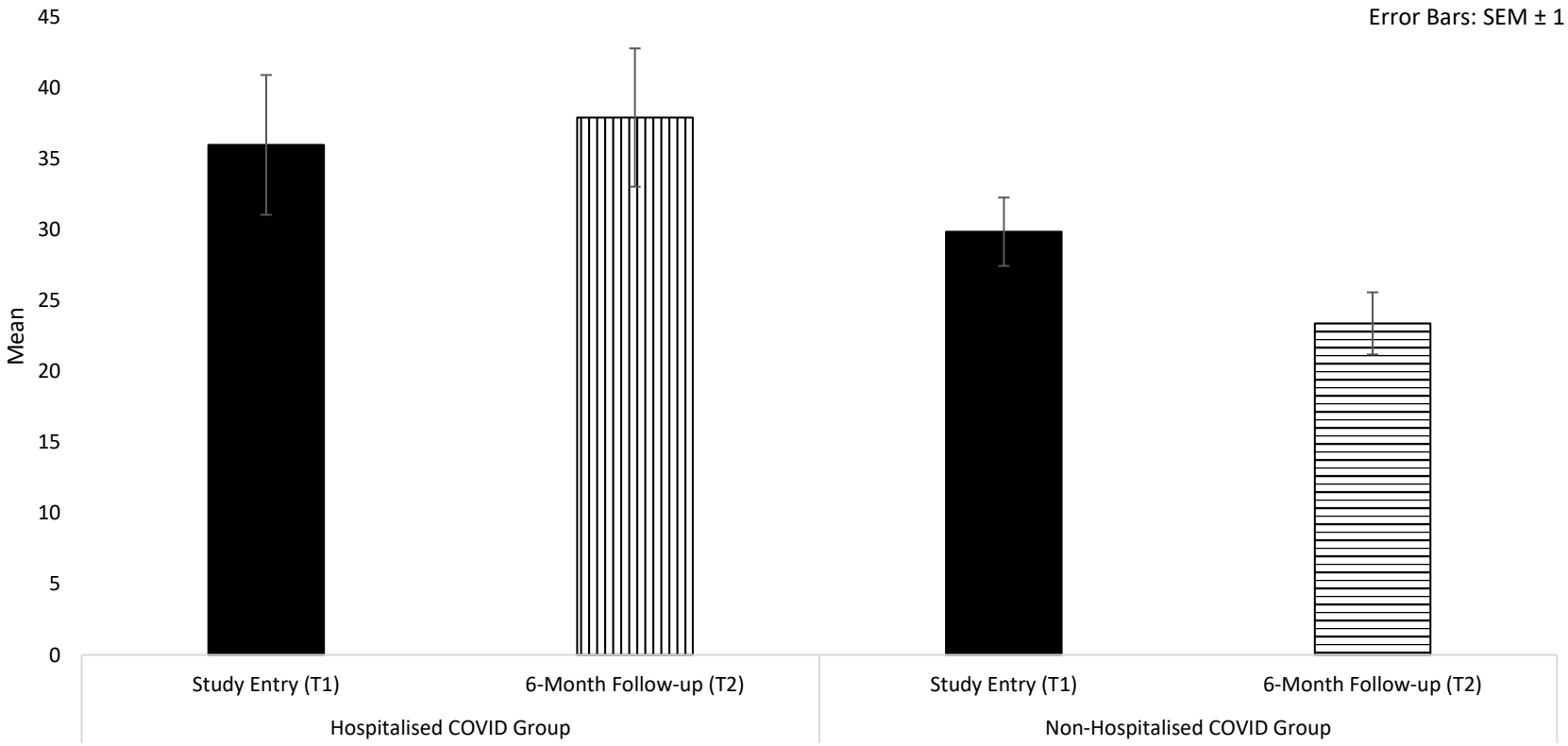


Table 5.12

Associations (Pearson's r) of total long-COVID symptom load (at T1 and T2, and the change from T1 to T2) with cognitive function and mental health (at T1 and T2, and the change from T1 to T2)

		Correlations of total long-COVID symptom load with cognitive function, mental health and sleep						Correlations between decrease in total long-COVID symptom load from T1 to T2[a] and improvement in cognitive function and mental health								
		At T1			At T2[a]			All COVID Participants			Hospitalised Group			Non-Hospitalised Group		
		r	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*
Processing Speed	Response accuracy %	-.21	.06	80	-.10	.40	78	.06	.59	73	.26	.41	12	.002	.99	61
	RT correct responses, ms	.29	**.01**	80	.44	**<.001**	78	-.11	.34	73	.07	.82	12	-.16	.22	61
	RT variability SD of RT	.19	.09	80	.42	**<.001**	78	-.07	.53	73	.14	.67	12	-.13	.31	61
Attention	Response accuracy %	-.21	.07	80	-.32	**.01**	77	.21	.08	71	.39	.23	11	.18	.18	60
	RT correct responses, ms	.31	**.01**	80	.53	**<.001**	77	.00	.00	71	.16	.64	11	-.06	.64	60
Working Memory	Response accuracy %	-.17	.11	87	-.23	**.04**	82	-.11	.32	81	.01	.99	14	-.12	.34	67
Executive Function	Response accuracy %	-.27	**.01**	88	-.21	.06	81	.24	**.03**	81	-.001	1.00	14	.36	**.003**	67
	Completion time ms	.31	**.003**	88	.37	**.001**	81	.09	.41	81	-.31	.29	14	.20	.11	67
Memory	Recognition accuracy %	-.30	**.01**	87	-.45	**<.001**	81	.18	.12	81	.40	.16	14	.10	.42	67
Mental Health (DASS-21)	Depression	.28	**.01**	88	.41	**<.001**	82	.32	**.003**	82	.66	**.01**	14	.21	.08	68
	Anxiety	.54	**<.001**	88	.56	**<.001**	82	.42	**<.001**	82	.62	**.02**	14	.42	**<.001**	68
	Stress	.33	**.002**	88	.36	**.001**	82	.30	**.01**	82	.50	.07	14	.20	.11	68
Sleep Quality (PSQI)	Global Score	.39	**<.001**	88	.46	**<.001**	82	.30	**.01**	82	.36	.20	14	.28	**.02**	68

Significant *p* values are in **bold**.

Abbreviations: ms, milliseconds; RT, Reaction Time.

[a] Long-COVID data not available for 6 participants (1 hospitalised, 5 non-hospitalised).

Table 5.13

Associations (Pearson's r) between the changes in cognitive function and mental health measures

	Processing Speed (*n* = 128)			Attention (*n* = 125)		Working Memory (*n* = 134)	Executive Function (*n* = 136)		Memory (*n* = 137)
	Response accuracy (%)	RT correct responses (ms)	RT variability (SD of RT)	Response accuracy (%)	RT correct responses (ms)	Accuracy (%)	Response accuracy (%)	Completion time (ms)	Recognition accuracy (%)
	r (p)	*r (p)*	*r (p)*	*r (p)*	*r (p)*	*r (p)*	*r (p)*	*r (p)*	*r (p)*
Mental Health (DASS-21)									
Depression	.11 (.20)	-.02 (.87)	.06 (.50)	.004 (.97)	-.17 (.07)	.07 (.45)	.11 (.22)	.04 (.66)	.03 (.72)
Anxiety	.08 (.40)	-.06 (.51)	-.01 (.94)	.14 (.12)	-.03 (.77)	.06 (.53)	.12 (.18)	-.11 (.21)	.12 (.18)
Stress	-.01 (.94)	-.04 (.70)	-.04 (.69)	.11 (.21)	-.04 (.63)	.05 (.56)	.10 (.23)	-.02 (.79)	-.02 (.81)
Sleep Quality (PSQI)									
Global Score	.03 (.70)	-.02 (.87)	-.02 (.83)	.01 (.90)	-.03 (.78)	-.08 (.39)	-.01 (.93)	-.02 (.81)	.19 **(.03)**

Significant *p* values are in **bold**.

Abbreviations: DASS-21, The Depression, Anxiety and Stress Scale-21; ms, milliseconds; PSQI, Pittsburgh Sleep Quality Index; RT, Reaction Time.

Across all participants, the reduction in long-COVID symptom load also correlated with a reduction in depression (p = .003), anxiety (p <.001), stress (p = .01), and improved sleep quality (p = .01); these associations were generally stronger in Hospitalised COVID (r values .36 to .66) relative to Non-hospitalised COVID participants (r values .20 to .42) (Table 5.12). Improved sleep quality correlated with an improvement in memory (r = .19, p = .03); other mental health/ sleep and cognition changes associations, though in the expected direction, were non-significant (Table 5.13).

5.5 Discussion

This investigation focused on charting the cognitive and mental health trajectories of COVID-19 in a UK adult sample (≤ 69 years) that had been assessed six months earlier (T1) (Vakani et al., 2023). The findings showed: (i) a trend-level improvement (from T1 to T2) in processing speed RT variability but a continued slowing on the attention task (longer RTs) in the COVID, relative to the non-COVID group; (ii) within the COVID group, poorer cognitive function (processing speed, attention, executive function) in previously hospitalised, relative to non-hospitalised, participants on both occasions of testing (T1, T2); (iii) higher depression and anxiety, and reduced sleep quality in the COVID group, relative to the non-COVID group, at both T1 and T2, though an improvement in depression was visible in non-hospitalised COVID participants; (iv) reduced overall long-COVID symptom load at T2 compared to T1, particularly in non-hospitalised COVID participants (only a non-significant reduction in hospitalised COVID participants); (v) association between higher long-COVID symptom load and poorer performance on most cognitive indices; (vi) an association between reduced long-COVID symptom load and improved executive function at T2, again observed only in non-hospitalised COVID participants; and (vii) medium-sized associations between reduced long-COVID symptom load and improved mental health and well-being.

Regarding the impact of COVID-19 on cognitive function, in our previous study involving this working-age sample (Vakani et al., 2023) the only cognitive variable to show a robust adverse impact of COVID-19 (regardless of hospitalisation history) was intra-individual variability in processing speed RTs, with larger RT variability in COVID-19 survivors compared to both non-COVID controls and their own pre-pandemic level (sub-sample for whom such data were available). The present investigation, encouragingly, demonstrated a trend towards

normalisation (from T1 to T2) in this measure and thus suggested, on average, only a limited and possibly reversible adverse cognitive effects of COVID-19 in a working-age population. However, participants who had required COVID-19 hospitalisation showed continued cognitive impairment, a finding which is well documented in the literature, with hospitalisation status significantly impacting cognitive function and the speed of any possible recovery months after initial infection and hospitalisation (Diana et al., 2023; Ferrucci et al., 2022; He et al., 2023; Méndez et al., 2022; Miskowiak et al., 2022; Nersesjan et al., 2022; Ollila et al., 2022). Our findings are also consistent with earlier findings of Del Brutto et al. (2022) who observed an improvement towards normalisation in the Montreal Cognitive Assessment scores at 18 months post-infection in older adults (mean age: 62.7 years) who had a history of mild COVID-19 and no hospitalisation and had shown a significant impairment when assessed earlier at six months post-infection. Their findings, taken together with ours, suggest cognitive improvement towards normalisation in COVID-19 survivors, especially without COVID-19-related hospitalisation, and that this recovery may occur relatively earlier (6–12 months post-COVID-19) in younger/working-age samples. Hospitalised COVID participants in our and other samples may show persistent cognitive impairment as a consequence of COVID-19-related structural and/or functional changes in the brain (Díez-Cirarda et al., 2023; Quan et al., 2023), which needs to be explored further.

Regarding total long-COVID symptom load, a significant reduction was observed from T1 to T2, which significantly correlated with improved executive function only in non-hospitalised COVID participants, again suggesting a stronger/faster recovery in those without a hospitalisation history. However, for the majority of the sample, regardless of hospitalisation history, various self-reported long-COVID symptoms were still present at T2, with sizeable associations between long-COVID symptom load and cognitive function, in line with previous findings (Ballouz et al., 2023; Wahlgren et al., 2023).

Mental health and sleep were still impacted at T2 in COVID-19 survivors, irrespective of hospitalisation history, though depression was lower at T2 than T1 in those without COVID-19-related hospitalisation. Notably, sleep appeared to be the most impacted. Interestingly, recent findings show that people with a COVID-19 history are more likely to be a late/evening chronotype, compared to those with no known history of COVID-19 (Han et al., 2022), and late chronotype itself has been associated with poor quality of sleep (Bessot et al., 2023;

Nielsen, 2010; Vardar et al., 2008). There are also suggestions that the lockdowns resulted in delayed chronotype due to the altered social schedule, such as, reduced exposure to sunlight coupled together with longer and later sleeping patterns, which can all contribute to reduced quality of sleep (Bessot et al., 2023; Leone et al., 2020; Sinha et al., 2020). It is possible that those with a history of COVID-19 were more impacted by subsequent lockdowns and shifted more towards eveningness and consequently poor sleep quality.

The strengths of this follow-up study include: (i) the response rate was reasonable with about two-thirds of the original sample (Vakani et al., 2023) available for this investigation, and (ii) the current sample was representative of the original sample. Nonetheless, the limitation of relying on self-report for COVID-19-related information inherent to our earlier study (Vakani et al., 2023) also applies to this study. Despite this limitation, the findings may have important implications. For example, consistently poor(er) performance observed in hospitalised COVID participants on tasks which emphasise speed could negatively impact daily activities such as driving (Wadley et al., 2020) and may present as a bio-marker for accelerated ageing (Nersesjan et al., 2022). Given this, frequent follow-ups of COVID-19 survivors, especially those with COVID-19-related hospitalisation and/or long-COVID symptoms, are needed to assess any potential worsening and/or improvement in cognitive function over time. Moreover, remedial interventions, such as mindfulness training, may help reduce cognitive slowing (Hausswirth et al., 2023) in diverse samples impacted by COVID-19.

5.6 Conclusions

The findings of this follow-up study indicate some cognitive normalisation over a six-month period in young and middle-aged COVID-19 survivors. However, those participants who had required hospitalisation due to COVID-19, compared to those who did not, continued to display multifaceted cognitive impairment. Continuous follow-up assessments are required to determine whether cognitive improvement continues over time in COVID-19 survivors, particularly in hospitalised/long-COVID participants or whether cognitive function in this sub-group worsens further unless addressed by suitable interventions.

Chapter Six: The Role of Persistent COVID-19 Symptoms in Brain Structure and Cognitive Function – An Empirical Study

This chapter has been published as (Appendix K):

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6.1 Chapter Aims and Overview

The existing literature has suggested that COVID-19 survivors, in particular those with post-acute sequalae of COVID-19 have impaired cognitive functioning. Such a prominent cognitive impairment may indicate towards abnormalities in brain structure, and as explored in Chapter Two, COVID-19 has the ability to infiltrate the CNS. This chapter, therefore, presents a study exploring the association of persistent COVID-19 symptoms with subcortical brain volumes and cognitive function, once again, in a working-age, non-clinical population, as well as exploring the mediating role of brain structures in the relationship between persistent COVID-19 symptoms and cognitive function.

6.2 Introduction

Post-acute sequelae of COVID-19 (PASC) is a highly debilitating condition, broadly defined as symptoms that develop during an infection of COVID-19, are continuously experienced ≥12 weeks post-infection, and cannot be attributed to any other plausible condition (Baimukhamedov, 2023; NICE, 2022; Soriano et al., 2022). PASC is often used interchangeably with long COVID, which is a term coined by COVID-19 survivors experiencing persistent COVID-19 symptoms (PCS) (Alwan & Johnson, 2021; Michelen et al., 2021). The prevalence of PASC varies amongst the literature and has been difficult to measure given its novelty and the large array of symptoms (Hastie et al., 2023). Approximately 10-20% of COVID-19 survivors are believed to be experiencing PCS (Davis et al., 2023; Hastie et al., 2023; WHO, 2022), although the ONS estimated that only 3.3% of the UK population (2 million people) were self-reporting PCS (ONS, 2024). O'Mahoney and colleagues, in their meta-analysis of 194 studies (from 2019 to 2022) estimated that 45% of COVID-19 survivors experienced at least one PCS (O'Mahoney et al., 2023). Similarly, a meta-analysis of 31 studies examining the prevalence of PCS reported a regional prevalence of 51% in Asia, 44% in Europe, and 31% in the USA, with a pooled prevalence of 43% in COVID-19 survivors (C. Chen et al., 2022). Regional variations in the prevalence of PCS may be explained by differences in the severity of acute illness, population age, and other co-morbidities (Davis et al., 2023).

Many PCS have been self-reported by survivors, and recently these have been categorised into four different phenotypes (Gentilotti et al., 2023): (i) chronic fatigue-like syndrome (fatigue, memory loss, headaches), (ii) respiratory syndrome (dyspnoea and cough), (iii) chronic pain syndrome (myalgia and arthralgia), and (iv) neurosensorial syndrome (change in taste and smell). Females are generally more likely to report PCS (Bai et al., 2022; Thompson et al., 2022; Tsampasian et al., 2023) with fatigue being the most commonly reported symptom (Cha & Baek, 2024; Healey et al., 2022; Subramanian et al., 2022). PCS post-acute infection have also been associated with substantial impairment in multiple cognitive domains, including but not limited to attention (Graham et al., 2021; Quan et al., 2023), working memory (Graham et al., 2021; Li et al., 2023; Miskowiak et al., 2023), memory (Guo et al., 2022), and executive function (Li et al., 2023; Miskowiak et al., 2023; Quan et al., 2023). Taquet and colleagues (2022) in their large retrospective study (*n* = 856,588, aged 18 to 64 years) reported cognitive deficits, as captured by relevant codes of the International

Statistical Classification of Diseases and Related Health Problems - 10th Revision (ICD-10) (WHO, 2019), in survivors at six months post-diagnosis and this remained true even at the two-year mark, relative to non-COVID controls. Similarly, Zhao et al. (2024) observed a cognitive slowing in long-COVID patients, particularly in the processing speed domain, compared to patients who had previously had a diagnosis of COVID-19 but not developed long COVID, a finding which has also been echoed by Vakani et al. (2024).

The prominent cognitive impairment observed across multiple domains in COVID-19 survivors experiencing PCS may be indicative of abnormalities in the brain's structure (Lu et al., 2020) and/or function (Li et al., 2023; Lu et al., 2020). A number of studies that assessed participants both with and without PASC point towards alterations in the brain, including lower whole-brain (Douaud et al., 2022), total grey matter (GM) (Bendella et al., 2023; Díez-Cirarda et al., 2023; Du et al., 2023; Kumar et al., 2023; but see Duan et al., 2021) and WM volumes (Greene et al., 2024), along with lower volumes of the amygdala (Raman et al., 2023), hippocampus (Raman et al., 2023; Zhou et al., 2023), putamen (Bendella et al., 2023; Deters et al., 2023; Heine et al., 2023; Raman et al., 2023; Tian et al., 2022), pallidum (Deters et al., 2023; Heine et al., 2023), and thalamus (Bendella et al., 2023; Deters et al., 2023; Heine et al., 2023). There is also evidence of dynamic brain changes in long-COVID patients with neuropsychiatric symptoms (Besteher et al., 2022) and larger CSF volume in association with a COVID-19 history (Douaud et al. 2022; Greene et al. 2024).

The neural impact of COVID-19 and its association with cognitive function is an ongoing area of research. Many studies, utilising MRI or electroencephalogram (EEG), have found a correlation between brain abnormalities and reduced cognitive performance post a COVID-19 infection (Andriuta et al., 2022; Bettonagli et al., 2023; Bispo et al., 2022; Cecchetti et al., 2022; Díez-Cirarda et al., 2023; Heine et al., 2023), although, only a handful focus solely on PASC. Andriuta and colleagues (2022) found right-sided WM hypersensitivies, especially in the superior frontal region, to be associated with cognitive slowing and executive dysfunction in patients with post-acute COVID-19 cognitive complains. More recently, Díez-Cirarda and colleagues (2023) found lower GM volume in people with long-COVID symptoms (*n* = 86, mean age: 50.71 years), compared to controls (*n* = 36, mean age: 49.33), and that lower GM volume in patients was correlated with poorer processing speed, attention, and working memory. Heine et al. (2023) observed reduced left thalamus, putamen, and pallidum volumes

in adults with long-COVID symptoms who also had moderate to severe fatigue, approximately seven months post COVID-19 diagnosis (*n* = 50, mean age: 43.40 years), compared to healthy controls (*n* = 47, mean age: 44.5), and also found lower thalamus volume to be significantly associated with poorer short-term memory in the long-COVID group.

The present study aimed to examine the association of any persistent COVID-19 symptoms (overall load as well as specific symptoms) in COVID-19 survivors, with total GM, WM, and CSF volumes as well subcortical brain volumes and cognitive function in a working-age, non-clinical population of COVID-19 survivors (none acutely unwell at the time of investigation). Furthermore, we examined the mediating role of brain structures (that associated with PCS in this sample) in the relationship of PCS with cognitive variables. We expected multifaceted cognitive impairment (Li et al., 2023; Quan et al., 2023; Zhao et al., 2024; Vakani et al., 2024) and reduced GM volumes across the brain (Bendella et al., 2023; Heine et al., 2023; Raman et al., 2023; Zhou et al., 2023) in association with PCS, and expected the volumes of the brain areas associated with PCS to mediate the relationship between PCS and cognitive function (Díez-Cirarda et al., 2023; Heine et al., 2023).

6.3 Materials and Methods

6.3.1 Participants and Design

The study initially involved 50 adults recruited from the general population. All recruited participants were required to (i) be able to communicate in English and be in reasonably good health, (ii) have no potential MRI contraindications (e.g., metal in the body, claustrophobia, pregnancy), and (iii) have no past or current diagnosis of a brain injury and/or psychosis. The study recruitment was open to both individuals with and without a history of COVID-19. However, only seven people without a COVID-19 history volunteered which was insufficient to provide a meaningful non-COVID comparison group (thus not reported hereafter).

The final study sample consists of 43 adults (14 male, 29 female), aged between 24-65 years (mean age: 44.79±10.80), with a previous diagnosis of COVID-19 (65.1% confirmed via polymerase chain reaction test; see Table 6.1 for demographic characteristics), who underwent whole-brain MRI, followed by a cognitive assessment via a mobile application tool,

and a psychometric test online, via Qualtrics, on a single occasion, on average, 731.17 ± 312.41 days post a COVID-19 diagnosis (range: 183-1160).

The study was approved by the College of Health, Medicine and Life Sciences Research Ethics Committee, Brunel University London (34033-A-Sep/2022-41521-1). All participants provided informed written consent and received £25 voucher for their time.

6.3.2 Measures and Procedure

6.3.2.1 Sample Characterisation and Self-Report Measures

A Qualtrics survey, taking approximately 30 minutes to complete, was used to acquire data relating to the participant's COVID-19 diagnosis (date, acute and chronic symptoms, hospitalisation status, subjective cognitive impairment), in addition to demographic data (age, sex, ethnicity, education, occupation, existing mental and physical illnesses), as in our previous studies (Vakani et al., 2023, 2024).

The Qualtrics survey also included two self-report measures assessing mental health and sleep quality. Mental health was assessed using the Depression, Anxiety and Stress Scale-21 (DASS-21) (Lovibond & Lovibond, 1995), a 21-item scale measuring depression, anxiety, and stress. Each DASS-21 item is rated by participants on a four-point Likert scale with higher scores indicating higher levels (severity) of symptoms. Internal consistency for all DASS-21 sub-scales (Depression: Cronbach's α = 0.92; Anxiety: Cronbach's α = 0.75; Stress: Cronbach's α = 0.88) was acceptable-to-excellent in this sample. Quality of sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), which is a 19-item, four-point Likert scale assessing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Higher PSQI scores indicate poorer sleep quality. The PSQI had an acceptable internal consistency in this sample (global score, Cronbach's α = 0.75).

Data relating to acute and chronic COVID-19 symptoms were acquired through a self-report scale (Supplementary Table 1) designed specifically for this study. The scale is broadly based upon symptoms that were mentioned on the UK's NHS website (NHS, 2023). The scale required the participant to rate four acute symptoms (temperature, dry cough, loss of

taste/smell, and other), and 26 chronic symptoms (Supplementary Table 1) on a seven-point Likert scale (Not at all/not applicable to Very Severe). Total PCS load was calculated by tallying together the sum of individual symptom ratings (with each symptom rated 0-7 as already mentioned).

6.3.2.2 MRI: Data Acquisition and Processing

The imaging data were acquired using a 3 Tesla (3T) Magnetom TIM Trio whole-body MRI scanner (Siemens Medical Solutions, Erlangen, Germany), fitted with a 32-channel head coil. For each participant, high-resolution T_1-weighted images were acquired, with the following parameters: inversion time (TI) = 1100 ms, repetition time (TR) = 1830 ms, echo time (TE) = 3.03 ms, flip angle (FA) = 11°, field of view (FOV) = 256 x 256 x 160 mm^3, voxel size = 1 x 1 x 1 mm^3, and a total of 160 images per participant.

All pre-processing and analysis of the T_1-weighted images were performed using FSL [Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/, version 6.0.3] (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Prior to the analysis, removal of non-brain areas was performed on all T_1-weighted images utilising the Brain Extraction Tool (BET) in FSL. This tool uses a set of locally adaptive model forces which adapt to fit the brain's surface (Smith, 2002). Hereafter, GM, WM, CSF, and subcortical brain structures (bilateral accumbens, caudate, pallidum, putamen, thalamus, amygdala, hippocampus) were outlined using FMRIB's Integration Registration and Segmentation Tool (FIRST) (Patenaude et al., 2011). FIRST is a model-based segmentation tool that utilises both shape and appearance models constructed from an atlas of manually segmented images from the Centre for Morphometric Analysis. These manual segmentations are parameterised as surface meshes from which a point distribution is modelled. Utilising the observed intensities from each individual's T_1-weighted image, FIRST finds the most probable shape by searching through linear combinations of shape variation modes, resulting in segmentation for each tissue and subcortical structure per participant. Finally, intracranial volume (ICV) was estimated through the summation of GM, WM, and CSF volumes for each participant. During each step, processed images were carefully inspected by one of the authors (RN) to ensure accuracy of results.

Table 6.1

Demographic characteristics of the sample, classified by hospitalisation history

		Entire Sample (*N* = 43; 14 M, 29 F)	Hospitalised Participants (*n* = 7; 2 M, 5 F)	Non-hospitalised Participants (*n* = 36; 12 M, 24 F)
		n (% of total)	*n* (% of total)	*n* (% of total)
Ethnicity	White British	33 (76.7%)	5 (71.4%)	28 (77.8%)
	South Asian	7 (16.3%)	1 (14.3%)	6 (16.7%)
	Other Asian	1 (2.3%)	0	1 (2.8%)
	Black British	1 (2.3%)	1 (14.3%)	0
	Mixed Race	1 (2.3%)	0	1 (2.8%)
Educational Background	College/6th Form	2 (4.7%)	0	2 (5.6%)
	Vocational Qualification	4 (9.3%)	0	4 (11.1%)
	Bachelor's Degree	11 (25.6%)	3 (42.9%)	8 (22.2%)
	Master's Degree	21 (48.8%)	4 (57.1%)	17 (47.2%)
	PhD or Higher	4 (9.3%)	0	4 (11.1%)
	Prefer not to say	1 (2.3%)	0	1 (2.8%)
Employment Status	Employed Full-time	17 (39.5%)	2 (28.6%)	15 (41.7%)
	Employed Part-time	9 (20.9%)	2 (28.6%)	7 (19.4%)
	Student Part-time	1 (2.3%)	0	1 (2.8%)
	Unemployed	1 (2.3%)	0	1 (2.8%)
	Retired	2 (4.7%)	0	2 (5.6%)
	Unable to Work	11 (25.6%)	3 (42.9%)	8 (22.2%)
	Other	1 (2.3%)	0	1 (2.8%)
	Prefer not to say	1 (2.3%)	0	1 (2.8%)
Main Occupation	Business/Financial Operations	3 (7.0%)	1 (14.3%)	2 (5.6%)
	Clerical/Administrative	1 (2.3%)	0	1 (2.8%)
	Community and Social Services	1 (2.3%)	0	1 (2.8%)
	Education	3 (7.0%)	1 (14.3%)	2 (5.6%)
	Healthcare Profession	22 (51.2%)	3 (42.9%)	18 (50.0%)
	Professional/Scientific/Technical	2 (4.7%)	0	2 (5.6%)
	Retail/Sales Work	1 (2.3%)	0	1 (2.8%)
	Own Business	2 (4.7%)	0	2 (5.6%)
	On Benefits	3 (7.0%)	1 (14.3%)	2 (5.6%)
	Other	4 (9.3%)	1 (14.3%)	4 (11.1%)
	Prefer not to say	1 (2.3%)	0	1 (2.8%)
Physical Health Conditions	Cancer	2 (4.7%)	1 (14.3%)	1 (2.8%)
	Diabetes	1 (2.3%)	0	1 (2.8%)
	Heart Condition	4 (9.3%)	2 (28.6%)	2 (5.6%)

	Immunosuppressed	4 (9.3%)	2 (28.6%)	2 (5.6%)
	Liver Disease	2 (4.7%)	0	2 (5.6%)
	Lung Condition	17 (39.5%)	5 (71.4%)	12 (33.3%)
	Neurological Condition	7 (16.3%)	3 (42.9%)	4 (11.1%)
	Obesity	7 (16.3%)	2 (28.6%)	5 (13.9%)
Mental Health Problems	Anxiety	14 (32.6%)	1 (14.3%)	13 (36.1%)
	ADHD	1 (2.3%)	0	1 (2.8%)
	Depression	19 (44.2%)	3 (42.9%)	16 (44.4%)
	Eating Disorder(s)	2 (4.7%)	0	2 (5.6%)
	Insomnia	11 (25.6%)	2 (28.6%)	9 (25.0%)
	OCD	2 (4.7%)	0	2 (5.6%)
	Panic Disorder	3 (7.0%)	0	3 (8.3%)
	Phobias	3 (7.0%)	0	3 (8.3%)
	PTSD	7 (16.3%)	2 (28.6%)	5 (13.9%)
	Other	3 (7.0%)	1 (14.3%)	2 (5.6%)
COVID Vaccine Uptake	Yes	41 (95.3%)	7 (100.0%)	34 (94.4%)
	No	2 (4.7%)	0	2 (5.6%)
Subjective Cognitive Function Impairment		36 (83.7%)	7 (100.0%)	29 (80.6%)
Subjective Reduced Psychological Well-being		32 (74.4%)	7 (100.0%)	25 (69.4%)

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; F, Females; M, Males; OCD, Obsessive Compulsive Disorder; PTSD, Post-Traumatic Stress Disorder.

6.3.2.3 Cognitive Function

Participants completed a cognitive function assessment via the MyCQ mobile application tool (MyCognition, 2023). The MyCQ mobile application tool has been validated against the Cambridge Neuropsychological Automated Test Battery (Bellens et al., 2022; Domen et al., 2019). It assesses five domains: processing speed, attention, working memory, executive function, and memory, through digital versions of commonly utilised neuropsychological tests, taking approximately 15 min to complete (MyCognition, 2023).

Processing speed was assessed using a Simple Reaction Time (RT) task, with response accuracy (RA; % correct), average RT (ms), and RT variability examined. For this task, participants were required to tap the circle button as quickly as possible when a red circle was shown on the screen.

Attention was assessed using a Choice Reaction Time task, with RA (% correct) and average RT (ms) examined. Participants had to tap either the triangle or circle button based on what shape was presented on the screen.

Working memory was assessed using the 2-Back task, with RA (% correct) used to examine task performance. In this task, participants were asked to tap 'yes' or 'no' based on whether the picture presented to them on the screen matched the picture presented to them two screens back.

Executive function was assessed using the Trail-Making B task, with RA (%, correct moves) and total task completion time (ms) examined. Participants had to produce an alternating sequence consisting of 13 numbers and 12 letters by tapping a number and a letter in ascending and alphabetical order, respectively, (e.g., 1, A, 2, B).

Memory was assessed using a Visual Recognition Memory task, with RA (% correct) used to examine task performance. Participants were presented with a set of 24 images and were instructed to memorise them. They were then presented with another set of 96 images (including the 24 images presented to them earlier), and were asked to select either 'yes' or 'no' based on whether they remembered seeing the image.

6.3.3 Statistical Analysis

Normality checks were performed on total PCS load, MRI data, cognitive indices, DASS-21, and PSQI (global) scores using the Shapiro-Wilk test (Shapiro & Wilk, 1965; Mishra et al., 2019). All of the MRI variables, total PCS load, and sleep quality data met the assumption for normality, but some cognitive indices [processing speed RA (%), RT; attention RA (%); working memory RA (%); executive function RA (%), mean completion time; memory RA (%)] and the DASS-21 variables were non-normally distributed. Given the correlational nature of this study, no data transformation was applied to the non-normally distributed data and instead, non-parametric correlations (Spearman's *rho*) were conducted for the non-normally distributed data.

Pearson's (*r*) correlations were used to examine whether total PCS load and age correlated with brain volumetric data (see Table 6.2 for inter-correlations between subcortical structures), followed by partial correlations controlling for age and ICV. Non-parametric Spearman's (*rho*) correlations were conducted to examine the relationship of total PCS load with cognitive function and then mental health and sleep quality measures (see Table 6.3 for associations between variables), followed by non-parametric partial correlations controlling for age. Spearman's (*rho*) correlations were also conducted to explore the relationship between specific subcortical structures and individual PCS.

Finally, mediation analyses (covarying for age and ICV) were performed using 'PROCESS' toolbox to examine whether the putamen volume (the only subcortical structure that was significantly associated with total PCS load) mediated the association of total PCS load (independent variable) with executive function (RA, completion time) and memory (RA) (outcome variables) (see Figure 6.1); these cognitive variables had significant correlations with both PCS load and putamen volume, and a significant correlation was also present between PCS load and putamen volume (see section 3.2). Given the non-normal distribution of some outcome variables and multiple model testing, the *p* values and 95% confidence intervals were estimated using 10,000 bootstraps, equivalent to $p \leq 0.01$ (Johnston & Faulkner, 2021) (the same pattern of results was obtained when using 5000 bootstraps, Table 6.4). The simple PROCESS mediation model centred the mean for all variables to 0, with all *p* values ± 1 *SD* from the mean.

Table 6.2

Inter-correlations (Pearson's r) between brain volumes

Brain Volumes (Total, mm^3)	CSF	GM		WM		Accumbens		Caudate		Pallidum		Putamen		Thalamus		Amygdala		Hippocampus	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
CSF	1	.19	.23	.40	**.008**	-.06	.73	.09	.57	.52	**<.001**	.19	.22	.32	**.038**	.26	.099	.43	**.004**
GM		1		.81	**<.001**	.70	**<.001**	.61	**<.001**	.48	**.001**	.64	**<.001**	.83	**<.001**	.30	**.049**	.68	**<.001**
WM				1		.65	**<.001**	.50	**.001**	.73	**<.001**	.71	**<.001**	.88	**<.001**	.43	**.004**	.68	**<.001**
Accumbens						1		.42	**.005**	.45	**.003**	.63	**<.001**	.68	**<.001**	.32	**.038**	.51	**<.001**
Caudate								1		.51	**.001**	.47	**.001**	.57	**<.001**	.22	.170	.48	**.001**
Pallidum										1		.61	**<.001**	.72	**<.001**	.53	**<.001**	.50	**.001**
Putamen												1		.62	**<.001**	.28	.064	.47	**.001**
Thalamus														1		.53	**<.001**	.80	**<.001**
Amygdala																1		.47	**.001**
Hippocampus																		1	

Significant *p* values are in **bold**.

Abbreviations: CSF, Cerebral Spinal Fluid; GM, Grey Matter; mm^3, cubic millimetre; WM, White Matter.

Table 6.3

Associations (Spearman's rho) of the cognitive variables with the mental health measures

	Processing Speed (*n* = 40)						Attention (*n* = 39)				Working Memory (*n* = 39)		Executive Function (*n* = 40)				Memory (*n* = 41)	
	Response accuracy (%)		RT (correct responses, ms)		RT variability (SD of RT)		Response accuracy (%)		RT (correct responses, ms)		Response accuracy (%)		Response accuracy (%)		Completion time (ms)		Recognition accuracy (%)	
	rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
Mental Health (DASS-21)																		
Depression	.13	.44	.14	.40	.03	.85	-.17	.31	.09	.60	.04	.82	-.15	.34	.19	.24	-.02	.91
Anxiety	-.27	.10	.28	.08	.21	.19	-.37	**.02**	.13	.45	-.36	**.02**	-.28	.08	.22	.17	-.19	.23
Stress	.05	.74	.16	.34	.03	.84	-.27	.10	.17	.30	-.02	.92	-.20	.21	.25	.12	-.06	.71
Sleep Quality (PSQI)																		
Global Score	-.07	.69	.35	**.03**	.44	**.005**	-.17	.31	.27	.10	-.14	.41	-.20	.21	.19	.24	-.37	**.02**

Significant *p* values are in **bold**.

Abbreviations: DASS-21, The Depression, Anxiety and Stress Scale-21; PSQI, Pittsburgh Sleep Quality Index; RT, Reaction Time; SD, Standard Deviation.

Table 6.4

Mediation effect of putamen volume on the association between total persistent COVID-19 symptom load (independent variable) and cognitive variables (outcome variables)

		Indirect effect		Direct effect		Total effect	
		β	95% [CI]	β	95% [CI]	β	95% [CI]
5,000 Bootstraps	Executive Function – Response accuracy (%)	-0.06	[-0.129, -0.001]	-0.07	[-0.196, 0.059]	-0.13	[-0.254, 0.002]
	Memory - Recognition accuracy (%)	-0.02	[-0.062, 0.023]	-0.12	[-0.220, -0.020]	-0.14	[-0.218, -0.062]
	Sleep Quality (PSQI) - Global Score	0.01	[-0.003, 0.031]	0.11	[0.062, 0.160]	0.12	[0.078, 0.167]
10,000 Bootstraps	Executive Function – Response accuracy (%)	-0.06	[-0.125, -0.002]	-0.07	[-0.196, 0.059]	-0.13	[-0.254, 0.002]
	Memory - Recognition accuracy (%)	-0.02	[-0.063, 0.020]	-0.12	[-0.220, -0.020]	-0.14	[-0.218, -0.062]
	Sleep Quality (PSQI) - Global Score	0.01	[-0.003, 0.030]	0.11	[0.062, 0.160]	0.12	[0.078, 0.167]

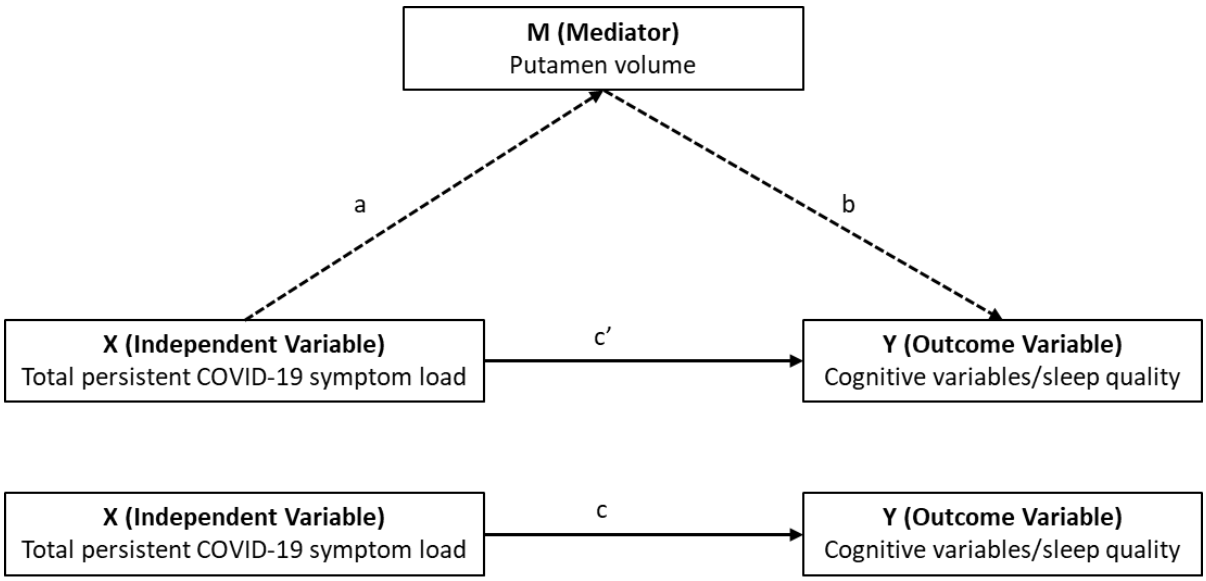
Abbreviations: CI, Confidence Interval; PSQI, Pittsburgh Sleep Quality Index.

Mediating effects were tested following Zhao et al.'s (2010) method: (1) X and M should be correlated, (2) M and Y should be correlated, and (3) the direct effect of X on Y should be attenuated when M is accounted for and the confidence intervals for the indirect effect should not include zero. For the sake of completion, we also examined the mediating role of putamen in PCS association with poor sleep (since sleep correlated with both PCS and putamen volume; see Section 3.4), using the same model parameters as for the cognitive variables.

Analyses were performed using the Statistical Package for Social Sciences (SPSS) software (for Windows, version 28; IBM, New York, USA) and the 'PROCESS' toolbox (v4.1) add-on for SPSS (Hayes, 2018). Alpha level for testing the significance of effects was maintained at $p \leq 0.05$, unless stated otherwise.

Figure 6.1

The simple mediation model illustration



6.4 Results

6.4.1 Sample Characteristics

The majority of the participants were White British, held a Bachelor's degree or above and were in some form of employment, with 51.2% being in the healthcare profession (e.g., doctor, nurse, dentist). In subjective reports, their most common health problem related to

lung function (39.5%), and the most common mental health problem was depression (44.2%), closely followed by anxiety (32.6%), and insomnia (25.6%) (Table 6.1). All but two participants (95.3%) had at least one dose of the COVID-19 vaccine (Table 6.1). Further characteristics of the sample, including MRI volumes, cognitive performance, mental health, and sleep are provided in Table 6.5.

The most prevalent persistent COVID-19 symptoms reported in the entire sample, were mild cognitive problems, muscle/body ache, and exhaustion (Figure 6.2). Total PCS load (total sum of individual symptom ratings) correlated significantly with increasing age [$r(43) = .32$, $p = .04$], but not with the number of days since diagnosis, controlling for age [$r(40) = -.10$, $p = .55$].

6.4.2 Associations between Total Persistent COVID-19 Symptom Load and Brain Volumes

Higher total PCS load was significantly associated with lower putamen volume ($r = -.44$, $p = .003$), and this association remained significant after controlling for age and ICV ($r = -.33$, $p = .03$) (Table 6.6). Of the 26 individual PCS that had been assessed, lack of appetite (*rho* = -.50, $p = .001$), muscle/body ache (*rho* = -.48, $p = .001$), and mild cognitive problems (*rho* = -.44, $p = .003$) correlated most strongly with putamen volume.

The total GM, total WM, and total volumes of all subcortical structures generally had non-significant negative correlations with PCS load [*r* values -.12 (for amygdala) to -.44 (for putamen), and became negligible when controlling for age and ICV (Table 6.6).

6.4.3 Associations of Persistent COVID-19 Symptoms with Cognitive Function and the Mediating Role of Putamen

Higher total PCS load, controlling for age, was associated with lower working memory RA (%) (*rho* = -.33, $p = .05$), lower executive function RA (%) (*rho* = -.41, $p = .009$), longer completion time (ms) in the executive function task (*rho* = .39, $p = .01$), and lower memory RA (%) (*rho* = -.51, $p < .001$) (Table 6.7). Of these cognitive variables, lower RA (%) (*rho* = .34, $p = .03$) and longer completion time (ms) (*rho* = -.44, $p = .005$) in the executive function task and reduced RA (%) in the memory (*rho* = .38, $p = .01$) were significantly correlated with smaller putamen volume (Table 6.8); and all of these remained significant when controlling for age [executive

function RA (%) (*rho* = .33, *p* = .04); executive function completion time (*rho* = -.37, *p* = .02); memory RA (*rho* = .42, *p* = .007)].

The significant association of higher total PCS load with poorer executive function RA (%) was significantly mediated by putamen volume [Model Summary: R^2 = 0.22, $F(4,35) = 3.78$, p = .012], with a significant indirect effect of total PCS load (i.e., mediated by the putamen volume) on executive function RA (%) (β = -0.06, SE = 0.03, 95% CI: [−0.125, -0.002]) and a non-significant direct effect (β = -0.07, SE = 0.06, *p* = .29, 95% CI: [-0.196, 0.059]) (Figure 6.3.1). The mediation model with executive function completion time as an outcome variable yielded no significant direct or indirect effects. For memory RA (%), the overall model was significant [Model Summary: R^2 = 0.26, $F(4,36) = 5.35$, p = .002]; however, the confidence interval for the indirect effect of the total PCS load on memory RA (%) contained zero, indicating that the mediating effect of putamen volume was insignificant (β = -0.02, SE = 0.02, 95% CI: [−0.063, 0.020]). Taken together, these findings suggest that putamen volume robustly mediated the association of total PCS load with executive function RA (%) but not memory RA (%) (Figure 6.3.2).

6.4.4 Persistent COVID-19 Symptoms and Mental Health

Higher total PCS load was significantly associated with higher levels of depression (*rho* = .38, *p* = .01), anxiety (*rho* = .40, *p* = .009), stress (*rho* = .32, *p* = .02), and sleep quality (*rho* = .65, *p* <.001). All of these associations remained significant when covarying for age (Table 6.7). Smaller putamen volume also correlated with poorer sleep quality (*rho* = -.37, *p* = .01) (Table 6.9), and this association remained significant when covarying for age (*rho* = -.37, *p* = .02). The mediation analysis revealed total PCS load to be a significant predictor of sleep quality [Model Summary: R^2 = 0.45, $F(4,38) = 8.20$, p <.001]; with a significant direct effect (β = 0.11, SE = 0.02, 95% CI: [0.062, 0.160]), but insignificant indirect effect with putamen volume as a mediator (β = 0.01, SE = 0.008, 95% CI: [−0.003, 0.030]) (Figure 6.4).

Table 6.5

Characteristics of the sample (N = 43), classified by hospitalisation history

		Entire Sample (*N* = 43)		Hospitalised Participants (*n* = 7)		Non-hospitalised Participants (*n* = 36)	
		M	*SD*	*M*	*SD*	*M*	*SD*
Age (years)		44.79	10.80	51.71	8.48	43.44	10.78
Brain Volumes (Total, mm^3)	Cerebral Spinal Fluid	254958.33	43424.58	261415.29	65021.50	253702.81	39091.03
	Grey Matter	607893.86	61178.09	561499.00	53461.39	616915.08	59052.03
	White Matter	587816.65	57884.76	557449.43	60563.40	593721.39	56317.77
	Intracranial Volume	1450668.84	133168.14	1380363.71	137781.56	1464339.28	129789.69
	Accumbens	943.84	192.95	888.00	262.08	954.69	179.32
	Caudate	7144.84	829.09	7072.29	613.32	7158.94	871.28
	Pallidum	3655.42	353.85	3638.86	482.89	3658.64	331.98
	Putamen	10061.23	920.91	9698.71	701.40	10131.72	949.72
	Thalamus	16652.21	1656.14	15578.86	2075.85	16860.92	1509.11
	Amygdala	3084.79	333.17	2958.00	278.64	3109.44	340.67
	Hippocampus	7880.00	860.85	7401.29	977.82	7973.08	818.91
Cognitive, Mental Health and Well-being Measures							
Processing Speed[a]	Response accuracy (%)	96.52	6.44	98.16	2.54	96.17	6.97
	RT (correct responses, ms)	405.80	112.57	431.14	140.10	400.42	107.68
	RT variability (SD of RT)	87.45	43.09	85.29	27.40	87.91	46.06
Attention[b]	Response accuracy (%)	93.21	12.41	85.12	20.40	94.97	9.50
	RT (correct responses, ms)	529.28	113.50	587.00	145.51	516.66	103.81
Working Memory[b]	Response accuracy (%)	88.83	12.15	87.43	10.50	89.13	12.61
Executive Function[a]	Response accuracy (%)	93.02	9.96	93.08	7.13	93.01	10.55
	Completion time (ms)	45878.60	48309.41	51214.86	29663.94	44746.67	51689.24
Memory[c]	Recognition accuracy (%)	90.35	8.12	93.61	3.58	89.68	8.66
Mental Health (DASS-21)	Depression	12.14	10.65	16.57	13.10	11.28	10.10
	Anxiety	6.60	7.06	8.57	6.71	6.22	7.15
	Stress	11.53	9.40	16.29	9.90	10.61	9.16

Sleep Quality (PSQI)	Global Score	9.47	4.34	10.43	4.20	9.28	4.41
Total Persistent COVID-19 Symptom Load		35.16	24.14	47.86	23.08	32.69	23.87

Note: This table is differentiated by hospitalisation status for information purposes only. Participants who required hospitalisation, relative to those who did not, generally were older, had lower subcortical brain volumes, poorer cognitive performance, poorer mental health and sleep quality, as well as higher total persistent COVID-19 symptom load.

Sample size reduced [a] by 3 (non-hospitalised), [b] by 4 (non-hospitalised), [c] by 2 (non-hospitalised).

Abbreviations: mm^3, cubic millimetre; ms, milliseconds; RT, Reaction Time; SD, Standard Deviation.

DASS-21: The Depression, Anxiety and Stress Scale-21. Higher scores indicate higher levels of depression, anxiety and stress.

PSQI: Pittsburgh Sleep Quality Index. Higher scores indicate poor sleep quality.

Figure 6.2

Prevalence of self-reported chronic COVID-19 (persistent) symptoms, classified by hospitalisation history

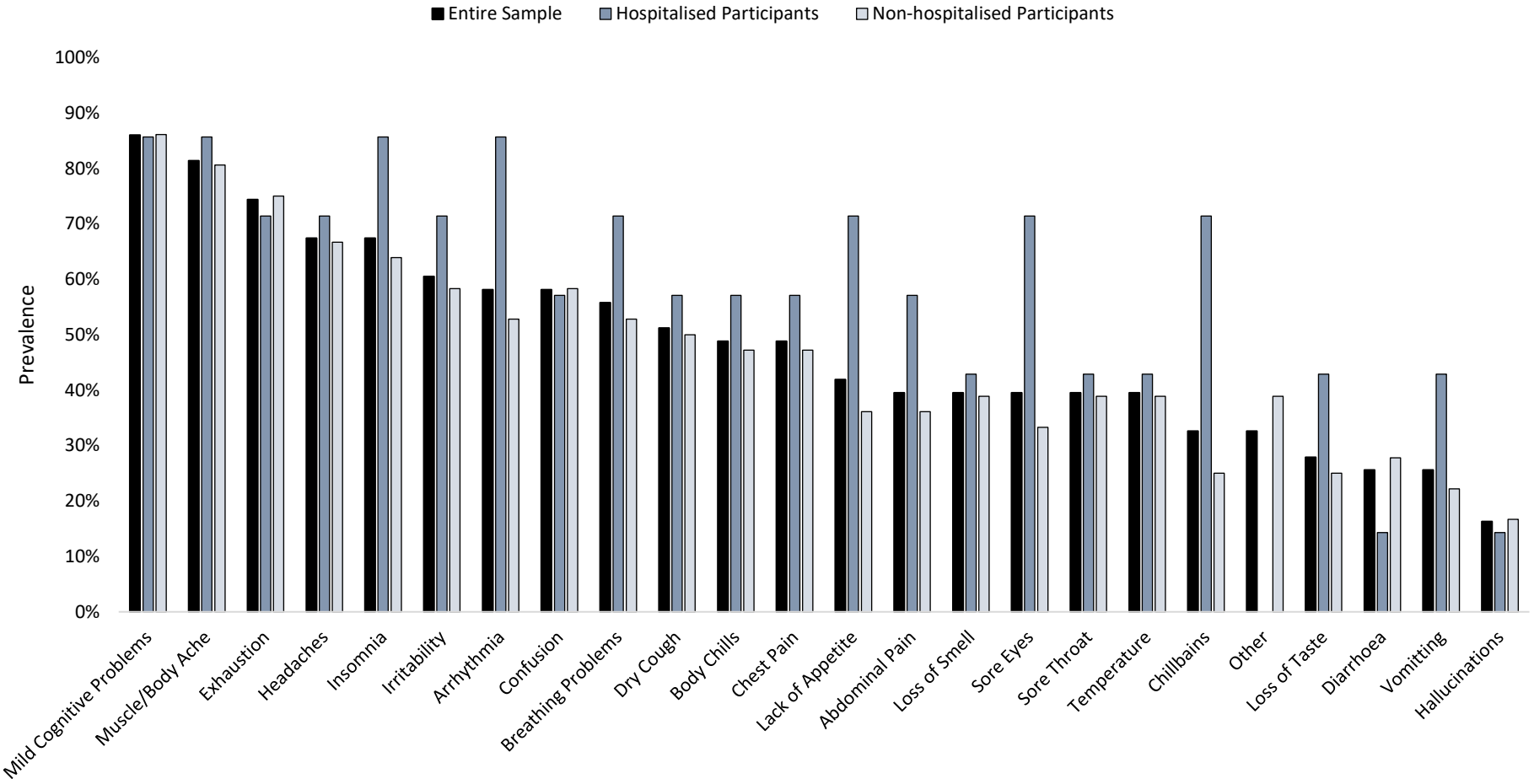


Table 6.6

Associations (Pearson's r) between brain volumes, age, and total persistent COVID-19 symptom load

Brain Volumes (Total, mm^3)		Age		Total persistent COVID-19 symptom load		Persistent COVID-19 symptom load controlling for age and ICV	
		r (*df* = 43)	*p*	*r* (*df* = 43)	*p*	*r* (*df* = 39)	*p*
Cerebral Spinal Fluid		.33	**.03**	-.03	.83	-.03	.86
Grey Matter		-.46	**.002**	-.24	.12	.13	.42
White Matter		-.21	.18	-.27	.09	-.11	.48
Accumbens	Total	-.36	**.02**	-.17	.27	.05	.76
	Left	-.43	**.004**	-.22	.16	.01	.93
	Right	-.20	.19	-.08	.62	.07	.65
Caudate	Total	-.24	.12	-.13	.39	.04	.81
	Left	-.21	.19	-.14	.39	.04	.79
	Right	-.26	.09	-.12	.43	.03	.85
Pallidum	Total	.18	.25	-.20	.20	-.21	.19
	Left	.11	.48	-.17	.29	-.11	.50
	Right	.23	.15	-.22	.16	-.25	.11
Putamen	Total	-.35	**.02**	-.44	**.003**	-.33	**.03**
	Left	-.26	.10	-.39	**.01**	-.28	.08
	Right	-.42	**.01**	-.47	**.002**	-.35	**.02**
Thalamus	Total	-.23	.15	-.24	.12	-.04	.82
	Left	-.24	.12	-.25	.11	-.05	.76
	Right	-.21	.19	-.23	.15	-.02	.89
Amygdala	Total	.15	.33	-.12	.45	-.10	.52
	Left	.08	.60	-.18	.25	-.16	.32
	Right	.17	.29	-.03	.87	-.02	.93
Hippocampus	Total	-.23	.13	-.19	.23	.03	.88
	Left	-.28	.07	-.13	.39	.09	.59
	Right	-.15	.35	-.21	.17	-.06	.72

Significant *p* values are in **bold**.

Abbreviations: ICV, Intracranial Volume; mm^3, cubic millimetre.

Table 6.7

Associations (Spearman's rho) of cognitive, mental health and sleep measures with age and total persistent COVID-19 symptom load

		Age			Total persistent COVID-19 symptom load			Persistent COVID-19 symptom load controlling for age		
		rho	*df*	*p*	*rho*	*df*	*p*	*rho*	*df*	*p*
Cognitive Measures										
Processing Speed	Response accuracy (%)	.06	40	.71	-.06	40	.72	-.08	37	.64
	RT (correct responses, ms)	.35	40	**.03**	.19	40	.24	.11	37	.51
	RT variability (SD of RT)	-.05	40	.76	.25	40	.12	.27	37	.09
Attention	Response accuracy (%)	-.37	39	**.02**	-.28	39	.09	-.19	36	.24
	RT (correct responses, ms)	.53	39	**<.001**	.33	39	**.04**	.22	36	.19
Working Memory	Response accuracy (%)	-.10	39	.53	-.34	39	**.03**	-.33	36	**.05**
Executive Function	Response accuracy (%)	-.07	40	.65	-.42	40	**.008**	-.41	37	**.009**
	Completion time (ms)	.31	40	**.05**	.45	40	**.003**	.39	37	**.01**
Memory	Recognition accuracy (%)	.02	41	.92	-.49	41	**.001**	-.51	38	**<.001**
Mental Health and Sleep Quality Measures										
Mental Health (DASS-21)	Depression	.05	43	.75	.38	43	**.01**	.38	40	**.01**
	Anxiety	.09	43	.58	.40	43	**.009**	.39	40	**.01**
	Stress	.08	43	.59	.32	43	**.02**	.34	40	**.03**
Sleep Quality (PSQI)	Global Score	.10	43	.54	.65	43	**<.001**	.65	40	**<.001**

Significant *p* values are in **bold**.

Abbreviations: DASS-21, The Depression, Anxiety and Stress Scale-21; ms, milliseconds; PSQI, Pittsburgh Sleep Quality Index; RT, Reaction Time; SD, Standard Deviation.

Table 6.8

Associations (Spearman's rho) between brain volumes and cognitive variables

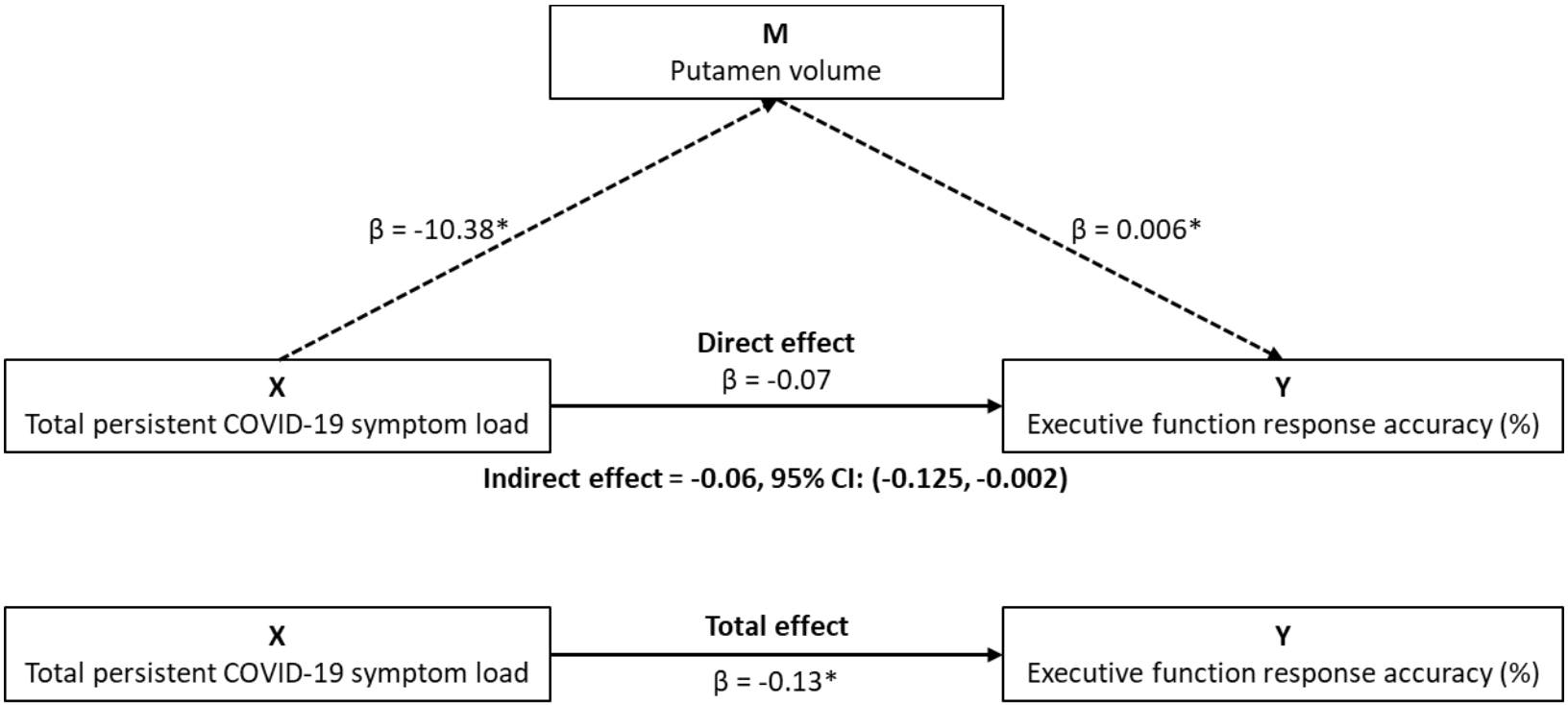
Brain Volumes (Total, mm^3)		Processing Speed (n = 40)						Attention (n = 39)				Working Memory (n = 39)		Executive Function (n = 40)				Memory (n = 41)	
		Response accuracy (%)		RT (correct responses, ms)		RT variability (SD of RT)		Response accuracy (%)		RT (correct responses, ms)		Response accuracy (%)		Response accuracy (%)		Completion time (ms)		Recognition accuracy (%)	
		rho	*p*	*rho*	*p*	*rho*	*P*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
Cerebral Spinal Fluid		-.16	.31	.28	.09	.03	.84	-.08	.64	-.02	.91	.17	.31	-.13	.42	.05	.75	.23	.16
Grey Matter		-.06	.73	-.03	.87	-.22	.18	.31	**.05**	-.29	.07	.19	.24	.11	.50	-.31	.06	.18	.25
White Matter		-.02	.93	-.04	.80	-.30	.06	.19	.26	-.31	**.05**	.20	.22	.12	.46	-.20	.21	.32	**.04**
Accumbens	Total	.13	.42	-.20	.22	-.44	**.005**	.51	**.001**	-.50	**.001**	.12	.46	.07	.67	-.23	.15	.35	**.02**
	Left	.15	.36	-.19	.25	-.30	.06	.46	**.003**	-.52	**.001**	.17	.30	.11	.49	-.31	**.05**	.32	**.04**
	Right	.03	.85	-.18	.28	-.43	**.005**	.48	**.002**	-.32	**.05**	.01	.97	-.06	.70	-.03	.88	.29	.07
Caudate	Total	.14	.40	-.14	.38	-.18	.26	.12	.46	-.32	**.05**	.37	**.02**	.26	.10	-.39	**.01**	.13	.41
	Left	.15	.35	-.11	.49	-.19	.24	.12	.49	-.27	.10	.34	**.04**	.18	.28	-.33	**.04**	.16	.33
	Right	.13	.41	-.16	.34	-.11	.49	.09	.57	-.33	**.04**	.40	**.01**	.30	.06	-.40	**.01**	.07	.67
Pallidum	Total	-.04	.81	-.01	.96	-.31	**.05**	-.04	.83	-.35	**.03**	.17	.31	.32	**.04**	-.36	**.02**	.41	**.009**
	Left	-.01	.96	-.01	.97	-.26	.10	-.03	.84	-.32	**.05**	.24	.13	.26	.10	-.29	.07	.32	**.04**
	Right	-.09	.60	-.04	.79	-.30	.06	-.03	.84	-.33	**.04**	.06	.72	.29	.07	-.36	**.03**	.42	**.007**
Putamen	Total	.12	.46	-.23	.16	-.36	**.02**	.45	**.004**	-.52	**.001**	.003	.98	.34	**.03**	-.44	**.005**	.38	**.01**
	Left	.16	.33	-.25	.12	-.35	**.03**	.38	**.02**	-.42	**.008**	-.02	.92	.28	.08	-.31	**.05**	.37	**.02**
	Right	.09	.58	-.25	.12	-.35	**.03**	.46	**.003**	-.60	**<.001**	.02	.92	.30	.06	-.51	**.001**	.34	**.03**
Thalamus	Total	-.12	.46	-.05	.75	-.22	.17	.21	.21	-.39	**.02**	.20	.23	.02	.90	-.23	.15	.22	.17
	Left	-.15	.35	-.05	.78	-.23	.15	.25	.13	-.38	**.02**	.16	.32	.03	.85	-.23	.15	.22	.17
	Right	-.09	.58	-.03	.86	-.23	.16	.19	.24	-.38	**.02**	.20	.22	.01	.96	-.23	.15	.24	.13
Amygdala	Total	-.11	.50	-.12	.48	-.24	.13	-.08	.63	-.24	.14	.01	.97	-.07	.67	-.02	.90	.18	.26
	Left	-.18	.28	-.15	.36	-.22	.18	-.23	.17	-.19	.26	-.01	.94	-.07	.69	-.03	.87	.06	.70
	Right	.03	.86	-.02	.91	-.25	.12	.06	.73	-.25	.13	.01	.96	.01	.95	-.06	.72	.20	.22
Hippocampus	Total	-.03	.84	-.07	.66	-.21	.20	.37	**.02**	-.28	.08	.20	.22	-.16	.33	-.17	.29	.28	.08
	Left	-.13	.44	-.13	.44	-.17	.29	.33	**.04**	-.29	.08	.07	.66	-.25	.11	-.09	.57	.20	.20
	Right	.06	.74	-.02	.90	-.21	.20	.18	.26	-.22	.19	.26	.11	-.07	.69	-.19	.25	.30	**.05**

Significant *p* values are in **bold**.

Abbreviations: mm^3, cubic millimetre; ms, milliseconds; RT, Reaction Time; SD, Standard Deviation.

Figure 6.3.1

The mediating role of putamen volume between total persistent COVID-19 symptom load and cognitive variables

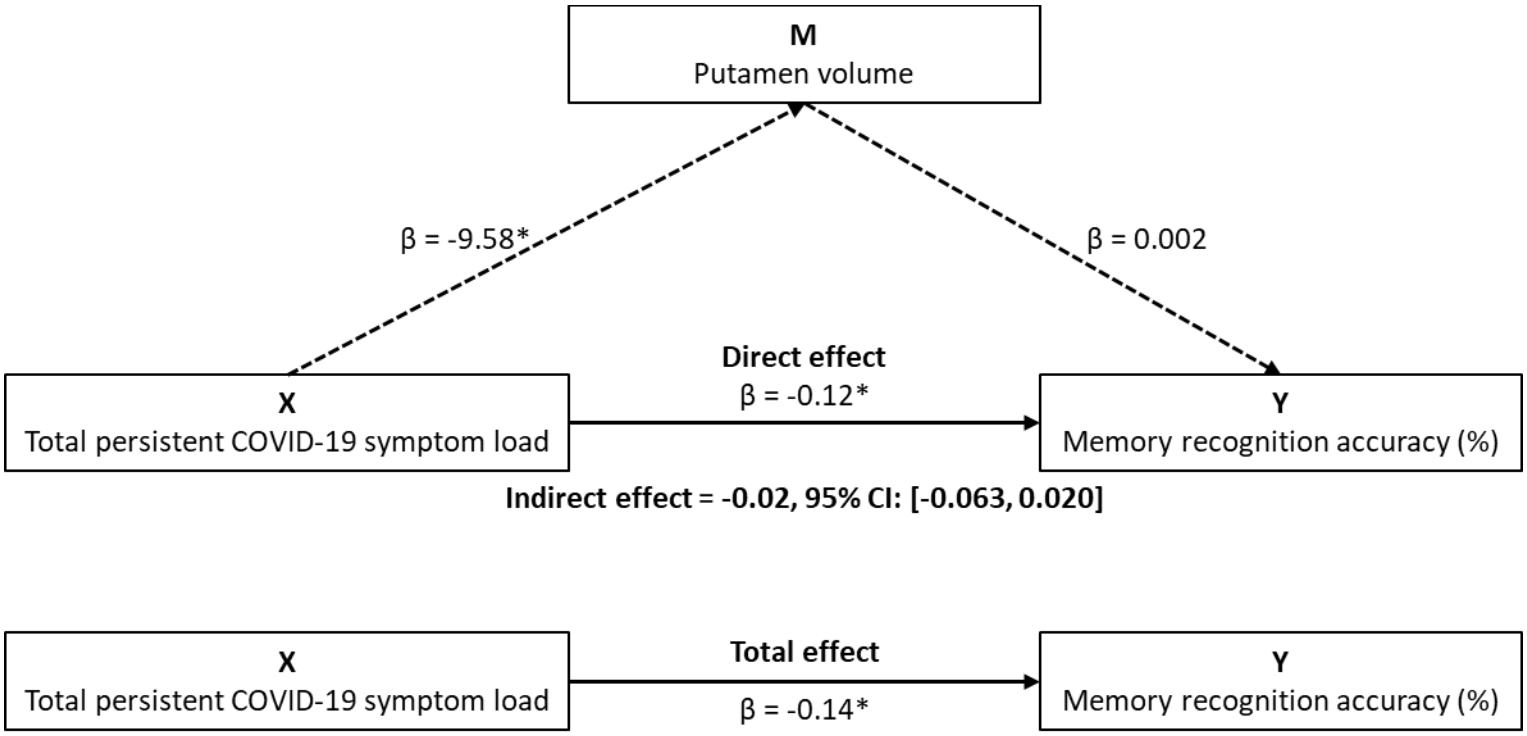


Note: * $p \leq .05$, ** $p \leq .01$.

Abbreviation: CI, Confidence Interval.

Figure 6.3.2

The mediating role of putamen volume between total persistent COVID-19 symptom load and cognitive variables



Note: * $p \leq .05$, ** $p \leq .01$.

Abbreviation: CI, Confidence Interval.

Table 6.9

Associations (Spearman's rho) of brain volumes with mental health measures

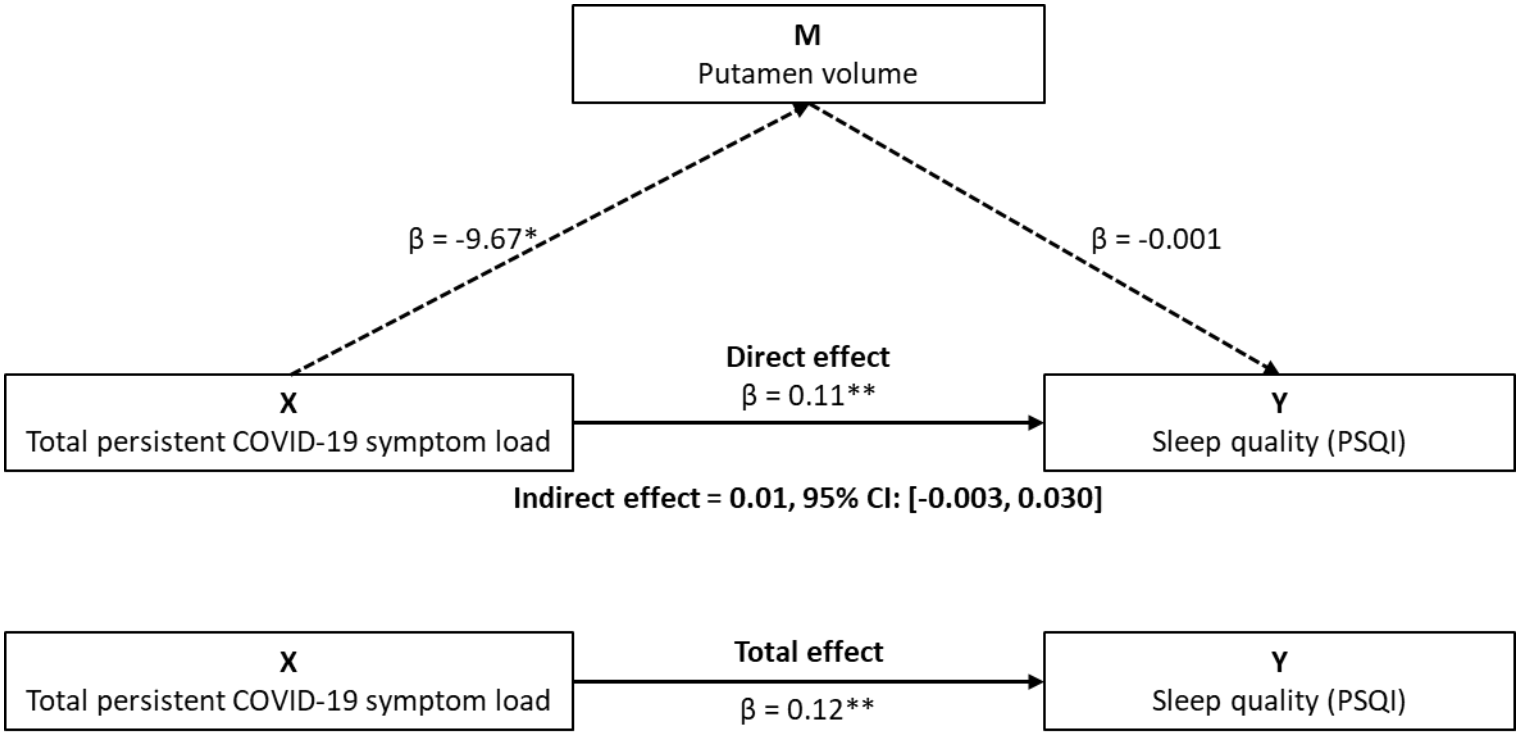
Brain Volumes (Total, mm^3)	Mental Health (DASS-21)						Sleep Quality (PSQI)	
	Depression		Anxiety		Stress		Global Score	
	rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
Cerebral Spinal Fluid	.28	.07	.43	**.004**	.24	.13	.17	.27
Grey Matter	.03	.87	.16	.30	-.05	.74	-.15	.34
White Matter	.13	.41	.19	.21	.11	.48	-.15	.34
Accumbens	.02	.91	.02	.88	-.07	.67	-.34	**.03**
Caudate	-.04	.80	-.09	.58	-.10	.55	-.19	.22
Pallidum	.07	.64	.15	.34	.04	.78	-.18	.25
Putamen	-.14	.39	.05	.76	-.15	.33	-.37	**.01**
Thalamus	.18	.26	.18	.26	.06	.72	-.10	.53
Amygdala	.05	.78	.09	.55	-.10	.51	-.17	.29
Hippocampus	.13	.40	.15	.34	.05	.75	-.10	.52

Significant *p* values are in **bold**.

Abbreviations: DASS-21, The Depression, Anxiety and Stress Scale-21; mm^3, cubic millimetre; PSQI, Pittsburgh Sleep Quality Index.

Figure 6.4

The mediating role of putamen volume between total persistent COVID-19 symptom load and sleep quality



Note: * $p \leq .05$, ** $p \leq .01$.

Abbreviation: CI, Confidence Interval; PSQI, Pittsburgh Sleep Quality Index.

6.5 Discussion

6.5.1 Main Findings

This study investigated the association between persistent COVID-19 symptoms and brain structural volumes, and how PCS load, brain volumes and their intercorrelations might relate to widely reported cognitive impairment in a working-age population. The findings revealed that higher total PCS load (especially lack of appetite, muscle/body ache, and mild cognitive problems) was associated, controlling for age, with lower putamen volume, as well as with poorer cognitive function (working memory, executive function, and memory), mental health, and sleep quality. Lower putamen volume was also associated with poorer executive function and memory performance, and sleep quality, and fully mediated the association of higher PCS load with poorer executive function.

Before discussing these findings in relation to previous research, it is important to consider the COVID-19-related characteristics of our sample. Approximately 88% of the present sample reported at least one PCS, a rate that seems much higher than the predicted incidence rate for long COVID. This could be attributed to the fact that the vast majority of the present sample were frontline medical workers, who in the UK have been severely impacted by long COVID (Bland et al., 2023). For example, in a UK-based study, approximately 76% of medical doctors were experiencing one or more long COVID complication (Bland et al., 2023). The British Medical Association (BMA) also found that 60% of frontline medical workers were impacted in their day-to-day lives due to long COVID, and 18% were no longer able to work (Bland et al., 2023; BMA, 2023). Based upon this recent evidence and the occupation of our participants (Table 6.1), the high incidence rate of PCS in this sample is not a deviation from the norm. On the other hand, it could also be argued that PCS observed in this particular sample are attributed to post-exertional malaise, in which symptoms worsen post any physically and mentally demanding activity (Gross et al., 2023), such as that experienced by healthcare workers in their highly demanding role.

The most frequently self-reported PCS in the present sample was mild cognitive problems (86%), often referred to as ‘brain fog’. With an incidence rate of >50%, this has been one of the most prevalent long-COVID symptom in many previous studies (Ermis et al., 2021; Hosp et al., 2021; Méndez et al., 2021; Miskowiak et al., 2021; Nouraeinejad, 2023). Based on the

symptom categorisation by Gentilotti et al. (2023) that was explored earlier and on the observed symptom profile (Figure 6.2), the current sample appears to fall mainly into either 'chronic fatigue-like syndrome' or 'chronic pain syndrome' (Gentilotti et al., 2023). The continuous experience of mild cognitive problems, or, in other words, 'chronic fatigue-like syndrome', post a COVID-19 diagnosis can have numerous psychosocial consequences (Callan et al., 2022), reflecting a greater impact of the virus on the brain (Davis et al., 2023; Nouraeinejad, 2023).

We found lower putamen volume to be associated with a higher PCS load, most strongly with muscle/body ache and mild cognitive problems. Both of these PCS have been associated with delayed clearance of SARS-CoV-2 viral particles from the upper respiratory tract in the acute stage of the infection (Antar et al., 2023). Prolonged expression of viral particles can cause tissue damage and induce a proinflammatory response (Antar et al., 2023), which may impact the striatum, particularly the putamen (Braga et al., 2023). Our finding of PCS and lower putamen volume is consistent with the current literature indicating that a reduction in putamen volume occurs post a SARS-CoV-2 infection (Bendella et al., 2023; Deters et al., 2023; Heine et al., 2023; Raman et al., 2023; Tian et al., 2022). Putamen volume loss has also been associated with other viruses, such as Human Immunodeficiency Virus (HIV) (Monick et al., 2022; Wright et al., 2016). Although HIV (*Lentivirus*) and SARS-CoV-2 (*β-coronavirus*) are not from the same viral family (Illanes-Álvarez et al., 2021), they both can infiltrate the CNS (Bauer et al., 2022; Chen et al., 2022; Ghaderi et al., 2023; Li et al., 2020; Sepehrinezhad et al., 2020; Wright et al., 2016; Xu & Lazartigues, 2022), and increase proinflammatory cytokines (Illanes-Álvarez et al., 2021). Cytokines in general aid in controlling infections and diseases. However, an excess of cytokines can lead to tissue damage (Darif et al., 2021; Montazersaheb et al., 2022) as well as exacerbate the release of proinflammatory cytokines (Montazersaheb et al., 2022). This overproduction of a protective measure, such as proinflammatory cytokines, towards viruses can lead to further damage, for example, cell death and tissue damage, including those of vital organs (Al-Qahtani et al., 2024; Darif et al., 2021; Fajgenbaum & June, 2020; Montazersaheb et al., 2022). The response can occur directly as a result of the virus or indirectly due to the overdrive of the immune system (Darif et al., 2021). A previous study has shown that an increase in proinflammatory cytokines can affect the striatum in COVID-19 survivors (Braga et al., 2023; Low et al., 2023).

As expected, higher PCS load was negatively associated with performance in the attention, working memory, executive function, and memory domains, replicating our findings in a different sample of working-age adults (Vakani et al., 2023, Vakani et al., 2024). Importantly, the relationship between PCS and executive function was fully mediated by putamen volume. The putamen as part of the striatum (Ghandili & Munakomi, 2024), plays a vital role in learning, language, motor control, and other cognitive function (Fazl & Fleisher, 2018; Ghandili & Munakomi, 2024; Koikkalainen et al., 2007; Luo et al., 2019; Provost et al., 2015). Moreover, previous functional MRI (fMRI) research supports the role of putamen in executive function (Ardila et al., 2018; Monchi et al., 2006; Sylvester et al., 2003). In our previous studies, we observed a multi-domain cognitive impairment in individuals with PCS (Vakani et al., 2023; Vakani et al, 2024), and a reduction in putamen volume has been associated with disrupted global cognitive performance (de Jong et al., 2008; Luo et al., 2019).

We did not find a significant association between PCS and any other brain structural volumes (except putamen), for example, hippocampus (Raman et al., 2023; Zhou et al., 2023). The majority of our sample was highly educated and, given the protective effect of education on brain health and overall cognitive function (Mortby et al., 2014), may have shown a rather limited neural impact of PCS. However, it is also possible that some brain changes associated with COVID-19 or PCS may be expressed more strongly in the presence of other comorbidities or advancing age (Douaud et al. 2022); and the extent and spread of neural changes may further depend on the expressed long COVID phenotype (Gentilotti et al., 2023). Furthermore, some of the PCS related cognitive effects may appear in neuronal function while not being detectable in, or not associating with, volumetric changes in individual brain structures after a COVID-19 infection (Quan et al., 2023; Zhao et al., 2023).

Lastly, this study replicated previously reported associations of long COVID with poor mental health and sleep (Dai et al., 2020; Guo et al., 2020; Mekhael et al., 2022; Moreno et al., 2022; Vanderlind et al., 2021). Our previous work has shown that sleep quality, relative to mental health, was impacted the most due to long COVID and PCS (Vakani et al., 2023; Vakani et al., 2024). Similarly, in this study, PCS load was associated with both poorer mental health and sleep quality, but with a stronger impact on sleep quality. Notably, changes in sleep quality were associated with total PCS load, and not with any brain volumes. Pellitteri et al. (2022) have suggested that poor sleep may be associated with underlying neuroinflammation that

occurs due to COVID-19, yet this association weakens overtime. However, to gauge the trajectory and timeline of this association, a follow-up study would be required.

6.5.2 Limitations

The design of this study lacks a control (comparison) group. The original study design included a group of non-COVID participants; however, following the lifting of the pandemic-related restrictions in the UK, it became difficult to recruit a sufficient number of participants with no exposure to COVID-19 (only seven non-COVID people were assessed; thus, not included). Moreover, the findings from this study are predominantly correlational, therefore further research and replication would be required to confirm these findings. Finally, the sample was predominately female, preventing a meaningful investigation of possible sex differences in the neurobiological impacts of persistent COVID-19 symptoms (Pelà et al., 2022).

6.6 Conclusion

The present study revealed that persistent COVID-19 symptoms may be associated with volume loss in the putamen. PCS was also associated with poor performance in attention, working memory, and executive function, as has been reported consistently in recent studies. Importantly, the relationship between higher PCS load and poorer executive function was found to be fully mediated by lower putamen volume, suggesting a reduction in putamen volume due to persistent symptoms, which then affects executive function. Further research is required to understand whether putamen volume reduction is present in follow-up assessments and continues to mediate the association of PCS with poor executive function, in particular, relative to a control (comparison) group with no history of COVID-19.

Chapter Seven: Overall Discussion

7.1 Chapter Aims and Overview

This final chapter will provide a synthesised review and discussion of the findings from the three empirical studies that were reported in this thesis. Firstly, a brief overview of the research aim(s), hypotheses, and the main findings from each empirical study will be provided, serving as a reminder prior to delving deeper into the overview of the findings. Following on from this, the various strengths and limitations of this research will be outlined. Finally, any future directions the research exploring the impact of COVID-19 on cognitive function, psychological well-being and the brain could take will be explored.

7.2 Overview of Thesis Findings

The overarching aim of this thesis was to understand and examine, both cross-sectionally and longitudinally, the neuropsychological impact of COVID-19 and long COVID, in particular on cognitive function (processing speed, attention, working memory, executive function and memory), psychological well-being (SF-36, DASS-21, and PSQI), and brain structures (through whole brain MRI analysis), in a working-age, non-clinical sample. The research aims, hypotheses, and main findings for each empirical chapter are summarised in Table 7.1.

The findings reported in the first two empirical chapters (Chapters Four and Five) suggest that COVID-19 survivors of a working-age displayed a limited impact of COVID-19 on cognitive function with only processing speed intra-individual variability being significantly impacted, and a trend towards normalisation was observed over a six-month follow-up period. Generally, and in line with previous literature, the findings also suggest that those individuals who required hospitalisation due to their COVID-19 diagnosis and/or were experiencing persistent or long-COVID symptoms displayed a more severe multi-domain cognitive impact, relative to those who were not hospitalised or not experiencing persistent COVID-related symptoms. The final empirical chapter (Chapter Six), similar to the first two, also suggests that in working-age adults COVID-19 has a limited impact on brain volume, with persistent COVID-19 symptoms potentially associated only with volume loss in the putamen. In addition,

consistently, throughout all the empirical chapters, sleep was the most impacted aspect of psychological well-being in COVID-19 survivors.

7.3 Interpretation and Implications of Findings

The consistency observed in these empirical chapters provides a robust understanding of the neuropsychological impact of COVID-19 and long COVID in a working-age, non-clinical sample. The general pattern of a limited cognitive and psychological impairment, with indication of normalisation in scores, as well as limited structural changes in the brain, should be interpreted as a positive outcome for the general population. The positive findings suggest that COVID-19 related neuropsychological disruption is mild at best and short-lived for working-age adults who did not require hospitalisation and/or were not experiencing long-COVID symptoms. There was, however, multifaceted cognitive impairment in the sub-group (15-20% of the sample) that had required hospitalisation and/or had persistent COVID-19 related symptoms as discussed further. Most aspects of psychological well-being (SF-36, DASS-21, and PSQI) were impacted in COVID-19 survivors, more so in participants experiencing long-COVID symptoms, with sleep quality consistently being the most affected. These findings remained consistent even during the follow-up and in the MRI based study. However, throughout the investigations, reduced psychological well-being only significantly correlated with a handful of cognitive indices that were measured, suggesting that psychological well-being, although impacted, cannot fully explain the cognitive impairment observed in COVID-19 survivors.

Another consistent finding throughout the empirical chapters related to the large difference observed between subjectively self-reported cognitive disruption versus the objectively measured cognitive disruption in COVID-19 survivors. Subjectively, a large percentage of participants (<78%) in each empirical study self-reported cognitive disruption post a COVID-19 diagnosis but only a limited cognitive disruption was noted objectively when assessed utilising the MyCQ mobile application (MyCognition, 2023). This finding has also recently been observed in another study that reported a stark difference of 24% between subjective cognitive impairment (33.3%) and objective cognitive impairment (8.9%) in N = 49 (M = 44.2, SD = 13.3) home-isolated COVID-19 survivors (Pihlaja et al., 2023).

Table 7.1

The research aim(s), hypotheses, and main findings from the empirical studies reported in Chapters Four-Six

Chapter	Aim(s)	Hypothesis	Main Findings
Chapter Four: The Cognitive Impact of COVID-19 – An Empirical Study	Examine the effects of COVID-19 on cognitive function in a working-age sample. Examine the associations of long-COVID symptoms and physical and psychological well-being with cognitive function post a COVID-19 diagnosis.	COVID-19 will be associated with a multifaceted cognitive impairment, with the same cognitive indices being impacted in both the cross-sectional and longitudinal investigations. A reduction in physical and mental well-being will be observed in COVID-19 group, compared to the non-COVID group, and long-COVID symptoms will be associated with reduced cognitive function and poor well-being.	Both cross-sectionally and longitudinally, the COVID group showed significantly larger intra-individual variability in processing speed, compared to the non-COVID group. Other cognitive indices were not significantly impacted in the cross-sectional or within-subjects investigations, but participants who had needed hospitalisation due to COVID-19 showed poor attention and executive function relative to those who had not required hospitalisation. Poor health and long-COVID symptoms correlated with poor cognitive function

			across multiple domains in the COVID group.
Chapter Five: The Cognitive Trajectory of COVID-19 – An Empirical Study	Examine the longitudinal impact of COVID-19 on cognitive function, mental health, and sleep, first, on average, and then classified by COVID-19-related hospitalisation status.	A change towards normalisation of cognitive function, mental health, and sleep from study entry (T1) to the six-month follow-up (T2) assessments will be observed in the COVID group, relative to non-COVID group.	A trend-level improvement occurred in intra-individual variability in processing speed in the COVID, relative to the non-COVID group, from T1 to T2. Longer response/task completion times persisted in participants with COVID-19-related hospitalisation relative to those without COVID-19-related hospitalisation and non-COVID controls.
	Examine changes in long-COVID symptom load and their association with cognitive function, mental health and well-being at six months post the initial assessment.	Cognitive function, mental health, and sleep will remain persistently impaired in participants with a history of COVID-19-related hospitalisation and/or in participants experiencing ongoing long-COVID symptoms.	The COVID group continued to self-report poorer mental health, irrespective of hospitalisation history, relative to non-COVID group. There was a significant reduction in long-COVID symptom load, which correlated with improved executive function in non-hospitalised COVID-19 participants.

Chapter Six: The Role of Persistent COVID-19 Symptoms in Brain Structure and Cognitive Function – An Empirical Study	Examine the association of persistent symptoms of COVID-19 (overall load and specific symptoms) with total GM, WM and CSF volumes as well subcortical brain volumes and cognitive function in a working-age, non-clinical population of COVID-19 survivors. Examine the mediating role of brain structures in the relationship of long-COVID symptoms with cognitive variables.	In line with previous literature, COVID-19 survivors experiencing persistent symptoms will show a multifaceted cognitive impairment and reduced GM volumes across the brain. The volumes of the brain areas associated with long-COVID symptoms will mediate the relationship between persistent COVID-19 symptoms and cognitive function disruption.	Higher persistent COVID-19 symptom load was significantly associated with smaller putamen volume, lower response accuracy on working memory, executive function and memory tasks, as well as a longer time to complete the executive function task, and poorer mental health and sleep quality. Smaller putamen volume fully mediated the relationship between persistent COVID-19 symptom load and lower executive function.

Abbreviations: CSF, cerebral spinal fluid; COVID-19, coronavirus disease 2019; GM, grey matter; WM, white matter.

It could be argued that this large disparity between subjective and objective cognitive disruption in COVID-19 survivors is due to the COVID-19 related infodemic. The term infodemic has been around since the SARS-CoV outbreak in the year 2003, yet it has gained significant traction, once again, since the emergence of the novel SARS-CoV-2 infection (Pian et al., 2021; Ries, 2022). The term infodemic encompasses various elements and can be loosely defined as too much information, including some facts coupled together with fear and rumours, amplified by the spread of fake news and misleading information during a disease outbreak, through modern technologies (Cinelli et al., 2020; Pian et al., 2021; WHO, 2024c). A few examples of this include coronavirus being labelled as "public enemy" (Pheasant-Kelly, 2023) and the promotion of conspiracy theories (Ferreira Caceres et al., 2022; Pheasant-Kelly, 2023). Research has found that infodemics can result in increased anxiety, stress, distress, and fear, in other words, a state of psychological panic (Farhoudinia et al., 2024; Pian et al., 2021; Ries, 2022; WHO, 2024), which can all result in maladaptive thinking and impede cognitive function (Akinci et al., 2022; de Kloet et al., 2005; Kulshreshtha et al., 2023; Yuen et al., 2012). Therefore, managing and reducing the levels of anxiety and stress induced by the infodemic, could in turn reduce the high percentage of subjectively reported cognitive impairment. Alternatively, the difference between subjective and objective cognitive impairment in this specific sample could also be due to the MyCQ test battery that was utilised to assess cognitive function. The test battery itself may not be as comprehensive as other well established cognitive assessments, thus unable to capture minute changes in cognitive function. This reason may also explain why other studies have found a more severe impairment in working-age adults (Herrera et al., 2023), relative to the findings presented in this thesis.

Nonetheless, the findings in this thesis generally suggest that any cognitive impairment that was objectively measured and reported, appears to diminish over time. However, this does not seem to be the case for working-age adults who required COVID-19 related hospitalisation or were experiencing long-COVID symptoms. As explored in detail earlier, this finding is in line with the literature suggesting hospitalisation status significantly impedes cognitive recovery in COVID-19 survivors (Diana et al., 2023; Ferrucci et al., 2022; He et al., 2023; Méndez et al., 2022; Miskowiak et al., 2022; Nersesjan et al., 2022; Ollila et al., 2022). Moreover, recent evidence suggests that COVID-19 survivors may experience accelerated brain ageing (Kesler

et al., 2024; Mavrikaki et al., 2021), which is associated with reduced cognitive function (Bishop et al., 2010; Mavrikaki et al., 2021; Murman, 2015). Kesler and colleagues (2024) measured brain age gap between COVID-19 survivors (*M* = 30.3, *SD* = 8.0) and controls (*M* = 30.3, *SD* = 9.0) and found a significant difference between the groups, with brain age being higher in COVID-19 survivors, relative to controls. Moreover, 80% of COVID-19 survivors, compared to only 13% of controls, displayed an accelerated brain age gap, which is also associated with reduced cognitive function (Kesler et al., 2024). It could therefore be argued that individuals who required hospitalisation and/or are experiencing long COVID, show signs of accelerated brain ageing, which in turn acts as a precursor to impaired cognitive function. Although this was not explicitly measured in this thesis, another factor which may hint towards accelerated ageing in COVID-19 survivors is sleep quality. Sleep quality was significantly impacted by COVID-19 in all three empirical studies (Chapters Four-Six), and a recent study has suggested there is a connection between reduced sleep quality and accelerated biological ageing (Carroll & Prather, 2021). Moreover, long COVID was significantly associated with a reduction in putamen volume, and reduced putamen volume has been associated with ageing (Ghandili & Munakomi, 2024; Halkur Shankar et al., 2017). Nonetheless, these effects could be reversible, as healthy cognitive function can also act a protective factor for accelerated ageing (Park et al., 2014; Stern, 2009). Therefore, if timely and adequate rehabilitation to promote healthy cognition and sleep is taken up by COVID-19 survivors who were severely ill, required hospitalisation and/or are experiencing long-COVID symptoms, the speed at which accelerated ageing occurs may slow down. This rehabilitation can take the form of starting a new hobby (Park et al., 2014) and even incorporating physical exercise in daily activities (Christie et al., 2017), both of which are low cost and have proven to sustain healthy cognitive function. In the long-term, this is critical, as accelerated ageing and reduced cognitive function are associated with early onset dementia, therefore early detection and early intervention can halt this progress (Randhawa & Varghese, 2024).

Complications in COVID-19 survivors, such as cognitive dysfunction and accelerated ageing, could be attributed to low grade inflammation, as suggested by recent evidence (Gulen et al., 2023). Post-COVID-19 systemic inflammation can increase the number of proinflammatory cytokines, disrupting the BBB, which can cause damage to the CNS resulting in cognitive dysfunction (Greene et al., 2024; Pan et al., 2024). Moreover, poor sleep quality is associated

with higher rate of inflammation, and systemic inflammation is associated with reduced cognitive function (Jin et al., 2023). Participants in these studies (Chapters Four-Six) may therefore benefit from enhancing their sleep quality, which in turn may increase their cognitive abilities through reducing the systemic inflammation. Although this explanation has gained a significant amount of traction in the literature, the cognitive impairment observed in this sample, in particular in those for whom pre-COVID-19 data were available, could also be explained by reduced cognitive reserves, a theory which is emerging in the COVID-19 field. Cognitive reserve refers to individual differences in task performance and recovery (Stern, 2009), in other words, the plasticity of the brain (Barnett et al., 2006; Costas-Carrera et al., 2022; Stern, 2009, 2012). Cognitive reserves can be impacted by factors such as education level, intellect, and lifestyle (Costas-Carrera et al., 2022). A high level of cognitive reserve is known to be a protective factor against cognitive impairment (Colombo et al., 2024), and is also associated with better cognitive performance (Herrera et al., 2023). Findings from the first empirical chapter (Chapter Four) in this thesis have suggested that participants who displayed a cognitive impairment pre-COVID-19, scored much lower post-COVID-19, relative to those participants who had intact cognitive function pre-COVID-19. It could be argued that this is due to pre-existing low cognitive reserves. Miskowiak and colleagues (2022) also found significant cognitive impairments between long-COVID patients with an existing cognitive impairment, relative to long-COVID patients without an existing cognitive impairment (Miskowiak et al., 2022). Although their study solely focused on long-COVID participants, it still highlights the need to further understand the role of cognitive reserves, in particular in a pre- versus post-COVID-19 research design.

7.4 Strengths and Limitations

A number of strengths and limitations are present in the investigations reported in this thesis. Relative to the vast majority of the existing literature which has focused on older, acutely ill and/or hospitalised COVID-19 survivors, the sample group reported in this thesis was younger, with a relatively low mean age, and none of the participants were acutely ill during the investigation(s). With regards to the limitations, the sample although diverse to some extent, was predominately of a White background which limits the generalisability of the findings to other ethnicities. It is also important to acknowledge the lack of a comparative

control group (non-COVID participants), in the third, MRI based, empirical chapter (Chapter Six). Soon after this final imaging study was initiated, all COVID-19 related restrictions in and around London (UK) were lifted and thus recruiting participants who had no known exposure to COVID-19 became unachievable.

7.5 Future Directions

The empirical studies reported in this thesis are based upon literature suggesting that COVID-19 impacts cognitive function and can cause structural changes in the brain. The first priority would therefore be to conduct follow-up assessments to confirm whether the normalisation observed at six-months post the initial assessment in this sample (Chapter Five), and the limited structural changes observed in the MRI study (Chapter Six), remain. Repeated assessments would provide the opportunity to fully track the trajectory of COVID-19 related cognitive impairments and structural changes, which may be associated with accelerated ageing. At a larger scale, the studies could take into account factors which have been omitted or missed in the present investigations, such as, lifestyle, exercise, diet, and socio-economic background. Moreover, it has been reported that other ethnic groups, such as South Asians, are potentially more susceptible to COVID-19 related complications and deaths (Downes et al., 2021), this may therefore explain the limited cognitive impact visible in this sample but also calls for future research to include a more diverse sample. Important consideration should also be given to the scale(s) which are utilised to assess long COVID. To date, a standardised scale measuring long-COVID symptoms does not exist, making comparisons across studies, countries, and languages more difficult and less reliable. It would therefore be advantageous for the scientific and research communities to introduce a single, multi-language scale measuring long-COVID symptoms, enabling consistent data collection and qualitative analysis for a systemic increase in knowledge on this novel topic. Finally, advanced brain imaging techniques, such as fMRI and diffusion tensor imaging (DTI), along with structural imaging would provide a more cohesive understanding of the neuropathophysiological elements that occur causing impaired cognitive function in COVID-19 survivors. Both fMRI and DTI would detect alterations in structural connectivity (van der Knaap et al., 2024), which may assist in uncovering the underlying mechanisms that cause cognitive disruption.

7.6 Conclusion

This chapter considered the various implications of COVID-19 related cognitive impairment and structural changes in the brain. A potential explanation was provided for the disparity between subjectively self-reported cognitive impairment and objectively assessed cognitive impairment. Generally, the findings in this thesis are positive for society, suggesting that COVID-19 has a limited cognitive impact in working-age adults. However, due consideration was given to the findings which align with recent literature suggesting COVID-19, regardless of severity of illness and age, causes accelerated biological ageing. Overall, taking into account the various methodological strengths and limitations, future research should aim to follow-up participants at regular intervals as well as incorporating advanced neuroimaging techniques.

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Supplementary Material

Supplementary Table 1

Novel COVID-19 scale measuring acute and chronic symptoms

Q: At the time of diagnosis, what symptoms (if any) did you notice and/or experience and how severe were the symptoms?								
Acute Symptoms		Not at all/not applicable	Extremely Minimal	Mild	Moderate	Somewhat Severe	Severe	Very Severe
1	Temperature	☐	☐	☐	☐	☐	☐	☐
2	Dry Cough	☐	☐	☐	☐	☐	☐	☐
3	Loss of taste and/or smell	☐	☐	☐	☐	☐	☐	☐
4	Other (please specify) _____	☐	☐	☐	☐	☐	☐	☐
Q: At the time of this study, what symptoms (if any) are you experiencing from the list below due to your diagnosis of COVID-19 and how severe are they?								
Chronic Symptoms (Persistent COVID-19 Symptoms)		Not at all/not applicable	Extremely Minimal	Mild	Moderate	Somewhat Severe	Severe	Very Severe
1	Abdominal pain	☐	☐	☐	☐	☐	☐	☐
2	Arrhythmia *(too fast/too slow, irregular rhythm of heart)*	☐	☐	☐	☐	☐	☐	☐
3	Body chills	☐	☐	☐	☐	☐	☐	☐
4	Breathing problems/shortness of breath	☐	☐	☐	☐	☐	☐	☐
5	Chest pain	☐	☐	☐	☐	☐	☐	☐
6	Chilblains/purple toes & fingers *(red and/or purple bumps which could be sore)*	☐	☐	☐	☐	☐	☐	☐
7	Confusion/delirium *(feel disorientated, not able to think or speak clearly/quickly)*	☐	☐	☐	☐	☐	☐	☐
8	Diarrhoea *(loose motion 3 or more times in a day)*	☐	☐	☐	☐	☐	☐	☐

9	Dry cough	☐	☐	☐	☐	☐	☐	☐
10	Exhaustion/fatigue	☐	☐	☐	☐	☐	☐	☐
11	Hallucinations	☐	☐	☐	☐	☐	☐	☐
12	Headaches	☐	☐	☐	☐	☐	☐	☐
13	Insomnia *(difficulty getting to sleep or staying asleep for long enough to feel refreshed)*	☐	☐	☐	☐	☐	☐	☐
14	Irritability	☐	☐	☐	☐	☐	☐	☐
15	Lack of appetite	☐	☐	☐	☐	☐	☐	☐
16	Mild cognitive problems *(subtle changes in memory, language, attention)*	☐	☐	☐	☐	☐	☐	☐
17	Muscle/body ache	☐	☐	☐	☐	☐	☐	☐
18	Sore eyes/conjunctivitis	☐	☐	☐	☐	☐	☐	☐
19	Sore throat	☐	☐	☐	☐	☐	☐	☐
20	Taste and/or smell impairment - Loss of smell	☐	☐	☐	☐	☐	☐	☐
21	Taste and/or smell impairment - Distorted sense of smell	☐	☐	☐	☐	☐	☐	☐
22	Taste and/or smell impairment - Loss of taste	☐	☐	☐	☐	☐	☐	☐
23	Taste and/or smell impairment - Distorted sense of taste	☐	☐	☐	☐	☐	☐	☐
24	Temperature	☐	☐	☐	☐	☐	☐	☐
25	Vomiting/nausea	☐	☐	☐	☐	☐	☐	☐
26	Other (please specify) _____	☐	☐	☐	☐	☐	☐	☐

Appendices

Appendix A – Ethical Approval (Empirical Study One)

College of Health, Medicine and Life Sciences Research Ethics Committee (DLS)
Brunel University London
Kingston Lane
Uxbridge
UB8 3PH
United Kingdom

www.brunel.ac.uk

18 February 2021

LETTER OF APPROVAL

APPROVAL HAS BEEN GRANTED FOR THIS STUDY TO BE CARRIED OUT BETWEEN 01/01/2021 AND 30/09/2023

Applicant (s): Miss Krupa Vakani

Project Title: The Effect of COVID-19 on Cognitive Function and Psychological Well-being

Reference: 26518-A-Jan/2021- 30996-1

Dear Miss Krupa Vakani

The Research Ethics Committee has considered the above application recently submitted by you.

The Chair, acting under delegated authority has agreed that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- **Approval is given for remote (online/telephone) research activity only. Face-to-face activity and/or travel will require approval by way of an amendment.**
- **The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee by way of an application for an amendment.**
- In addition to the above, please ensure that you monitor and adhere to all up-to-date local and national Government health advice for the duration of your project.

Please note that:

- Research Participant Information Sheets and (where relevant) flyers, posters, and consent forms should include a clear statement that research ethics approval has been obtained from the relevant Research Ethics Committee.
- The Research Participant Information Sheets should include a clear statement that queries should be directed, in the first instance, to the Supervisor (where relevant), or the researcher. Complaints, on the other hand, should be directed, in the first instance, to the Chair of the relevant Research Ethics Committee.
- The Research Ethics Committee reserves the right to sample and review documentation, including raw data, relevant to the study.
- You may not undertake any research activity if you are not a registered student of Brunel University or if you cease to become registered, including abeyance or temporary withdrawal. As a deregistered student you would not be insured to undertake research activity. Research activity includes the recruitment of participants, undertaking consent procedures and collection of data. Breach of this requirement constitutes research misconduct and is a disciplinary offence.

Professor Christina Victor

Chair of the College of Health, Medicine and Life Sciences Research Ethics Committee (DLS)

Brunel University London

Appendix B – Participant Recruitment Advert (Empirical Study One)

College of Health, Medicine and Life Sciences

Department of Life Sciences

Division of Psychology

PARTICIPANTS NEEDED FOR RESEARCH IN NEUROPSYCHOLOGY AND MENTAL HEALTH

We are looking for participants to take part in a study on:

"The Effect of COVID-19 on Cognitive Function and Psychological Well-being"

You are invited to participate in an online assessment, lasting approximately 45 minutes.

To participate, you need to be 18 years or over.

In appreciation for your time, you will be compensated with a £10 Amazon gift voucher.

For more information about this study, or to take part, please contact:

Principle Investigator: Miss Krupa Vakani (Doctoral Researcher)

Email: krupa.vakani@brunel.ac.uk

This study has been reviewed and granted ethical approval by the College of Health, Medicine and Life Sciences Research Ethics Committee, Brunel University London.

If you have any questions, concerns and/or problems about any aspect of the study, please contact Professor Christina Victor, the Chair of the College of Health, Medicine and Life Sciences Research Ethics Committee via email at christinia.victor@brunel.ac.uk.

Appendix C – Participant Information Sheet: General Population (Empirical Studies One and Two)

College of Health, Medicine and Life Sciences

Department of Life Sciences

PARTICIPANT INFORMATION SHEET

Study title
The Effect of COVID-19 on Cognitive Function and Psychological Well-being.

Invitation paragraph
You are being invited to take part in a psychological research study. Before you continue, it is vital for you to understand why the research is being conducted and what it will involve. Please take your time to read the following information carefully and discuss it with others if you wish. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?
Over the past year, the world has faced a new disease named Coronavirus disease 2019 (COVID-19). This novel disease affects individuals on a physical level when infected. However, some very recent data suggests that COVID-19 could potentially also have an impact on cognitive functioning and psychological well-being.

Therefore, the purpose of this study is to examine the potential impact of COVID-19 on cognitive functioning and psychological well-being both in individuals with and without a confirmed diagnosis of COVID-19.

Why have I been invited to participate?
We are inviting people who are aged 18 or above from the general population to partake in this study. The findings of this study will allow us to determine if there are any changes in cognitive functioning and psychological well-being of people who have tested positive for COVID-19, compared to those who have not tested positive. A minimum of 200 participants will be recruited to take part in this study. Recruitment is on a voluntary basis.

Do I have to take part?
Participation in this study is entirely voluntary, it is up to you to decide whether or not to take part. If you do decide to take part, you will be asked to provide consent prior to commencing the study. If you decide to take part you are still free to withdraw from the research, without giving a reason, up until the point at which you submit your answers. Furthermore, the right to decline and/or withdraw from the study will in no way influence or adversely affect you and/or your rights.

What will happen to me if I take part?

- You will be asked to take part in an online assessment lasting approximately 45 minutes.
- The online assessment will consist of questions which will explore your cognitive functioning and psychological well-being. You will not be expected to answer any question that you do not wish to.
- You will be asked to complete this assessment twice over a period of six months – first, upon entering the study and second, at a six month follow-up.
- You are free to decline and/or withdraw from the study at any time, until the point at which you submit your answers.
- The answers you provide during your online assessment will be collected for research purposes only and are not a form of a diagnostic tool.
- You will be compensated for your time with a £10 Amazon gift voucher (sent to you via email from the University/College Finance Officer).

Are there any lifestyle restrictions?
There are no lifestyle restrictions relevant to this study.

What are the possible disadvantages and risks of taking part?
There are no anticipated disadvantages or risks associated with taking part in this research. If you do, for whatever reason, feel uncomfortable at any point during the research you can terminate your participation without consequence by closing your browser. The principle researcher, Miss Krupa Vakani (krupa.vakani@brunel.ac.uk) is happy to discuss the research with you and answer any questions that you may have. If you are unhappy with any aspect of the research, you can contact Professor Veena Kumari (supervisor to the project leader, Miss Krupa Vakani) whose contact details are at the bottom of this page.

What are the possible benefits of taking part?
There are no direct intended benefits to you when taking part in this study. However, a potential indirect benefit from taking part in this study includes contributing towards knowledge of how COVID-19 impacts cognitive functioning and psychological well-being. You may also feel intrigued and decide to further read into the topic and increase your knowledge base around this subject area.

What if something goes wrong?
If you have any questions, concerns and/or problems about this study, you should seek to contact and speak to a member of the research team. If you remain unhappy and wish to complain formally, you can do this through the University complaints procedure. To complain about the study, you need to contact Professor Christina Victor, the Chair of the College of Health, Medicine and Life Sciences Research Ethics Committee, via email at christina.victor@brunel.ac.uk.

Will my taking part in this study be kept confidential?
Data will be collected with only a participant number to identify it. All information which is collected about you during the course of the research will be stored securely for 10 years. Any information about you which leaves the University will have all your identifying information removed. With your permission, anonymised data will be stored and may be used in future

research, report(s) and/or publication(s) – you can indicate whether or not you give permission for this by way of the Consent Form.

Will I be recorded, and how will the recording be used?
No recording will be made as part of this study.

What will happen to the results of the research study?
The research data will be fully anonymous and analysed by the researcher(s) before being reported. The results will be used primarily for a thesis/final year project and may later be reported at a conference and/or in a scientific journal in the form of a report and/or a publication. The anonymised research data may also be shared with other researchers for further analysis, but at no point will any uniquely identifiable data be shared. If you take part in this research, you can obtain a copy of the publication by contacting the researcher.

Who is organising and funding the research?
This research study is organised by Miss Krupa Vakani in conjunction with Brunel University London and MyCognition, and it is funded by Brunel University London.

What are the indemnity arrangements?
Brunel University London provides appropriate insurance cover for research which has received ethical approval.

Who has reviewed the study?
This study has been reviewed and granted ethical approval by the College of Health, Medicine and Life Sciences Research Ethics Committee.

Research Integrity
Brunel University London is committed to compliance with the Universities UK Research Integrity Concordat. You are entitled to expect the highest level of integrity from the researchers during the course of this research

Contact for further information and complaints
For general information
Researcher: Miss Krupa Vakani, Doctoral Researcher – Centre for Cognitive Neuroscience, Division of Psychology, Department of Life Sciences, Brunel University London. Email: krupa.vakani@brunel.ac.uk

Supervisor: Professor Veena Kumari, Division of Psychology, Department of Life Sciences, Brunel University London, Uxbridge, UB8 3PH. Email: veena.kumari@brunel.ac.uk

For complaints and questions about the conduct of the Research
Professor Christina Victor, Chair College of Health, Medicine and Life Sciences Research Ethics Committee Christina.victor@brunel.ac.uk

Once again, thank you for taking the time to read this Participant Information Sheet.

Appendix D – Consent Form: Database & General Population (Empirical Studies One and Two)

ONLINE CONSENT FORM

College of Health, Medicine and Life Sciences
Department of Life Sciences

The Effect of COVID-19 on Cognitive Function and Psychological Well-being

Miss Krupa Vakani

Ethical approval has been obtained for this study by the College of Health, Medicine and Life Sciences Research Ethics Committee for this study to run from 18/02/21 to 30/09/2023.

Please confirm the following:

	Yes	No
• I have read the Participant Information Sheet.		
• I am over the age of 18.		
• I understand that I will not be referred to by name, or any personal identifying data, in any report(s) and/or publication(s) resulting from this study.		
• I understand that I am free to withdraw from the study:		
- at any time, unless I have submitted my answers, after which I am unable to withdraw my data from the study.		
- without having to give a reason for withdrawing.		
• I agree that my data can be anonymised, stored and used in a thesis/final year project, conference(s), future research, report(s) and/or publication(s) in line with Brunel University's data retention policies.		
• I would like to know about the findings of this study.		
• I am happy to be contacted about future research studies.		
• I agree to take part in this study.		

Appendix E – Debrief Form: General Population (Empirical Studies One and Two)

College of Health, Medicine and Life Sciences
Department of Life Sciences

The Effect of COVID-19 on Cognitive Function and Psychological Well-being

Miss Krupa Vakani

Debrief form

We would like to take this opportunity to say **Thank You** for participating in our study. Your contribution is much appreciated.

The completed research will help to gain an understanding of the impact COVID-19 has on cognitive functioning and psychological well-being. You were invited to take part in the study because you are above the age of 18.

Please be assured, all data collected will be treated in the strictest confidence. You are free to discuss this research by contacting the principle researcher, **Miss Krupa Vakani**, Division of Psychology, Department of Life Sciences, Brunel University London. Email: krupa.vakani@brunel.ac.uk. Please let the principle researcher know if you would like to be kept up-to-date with the progress of the study and if you would like to know the overall results. We regret that we cannot provide individualised feedback, but can offer an overall impression of the results.

We have tried to ensure that this study does not cause any distress. However, if you were unduly or unexpectedly affected by taking part in the study please feel free to feed it back to the principle researcher. If you feel unable for whatever reason what-so-ever to talk with the researcher then please either contact their supervisor (veena.kumari@brunel.ac.uk) or one of the Division of Psychology Research ethics coordinators led by Dr Justin O'Brien (Justin.O'Brien@brunel.ac.uk, +44 (0)1895 266 367).

The following support services may be of interest to you:

MIND
MIND Infoline,
PO BOX 75225,
London,
E15-9FS
Number: 0300 123 3393
Text: 86463
Email: info@mind.org.uk
http://mindinlondon.org.uk/

Samaritans
Chris
Freepost RSRB-KKBY-CYJK
PO Box 9090
STIRLING
FK8 2SA
Number: 116 123 (free 24-hour helpline)
Email: jo@samaritans.org
https://www.samaritans.org/

Rethink Mental Illness
Number: 0300 5000 927
www.rethink.org

Sane
Textcare: www.sane.org.uk/textcare
Email: support@sane.org.uk
http://www.sane.org.uk/home

Once again, thank you for your participation in this study.

Appendix F – Ethical Approval (Empirical Study Three)

College of Health, Medicine and Life Sciences Research Ethics Committee (DLS)
Brunel University London
Kingston Lane
Uxbridge
UB8 3PH
United Kingdom

www.brunel.ac.uk

3 March 2022

LETTER OF APPROVAL

APPROVAL HAS BEEN GRANTED FOR THIS STUDY TO BE CARRIED OUT BETWEEN 15/02/2022 AND 30/09/2023

Applicant (s): Miss Krupa Vakani

Project Title: Investigating the Effects of Long COVID on the Brain

Reference: 34033-A-Feb/2022- 38426-1

Dear Miss Krupa Vakani

The Research Ethics Committee has considered the above application recently submitted by you.

The Chair, acting under delegated authority has agreed that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- Please be clear in the PIS that participants will be invited for two sessions of the FMRI scan and psychological assessment.
- Please update your advert(s) to let participants know that they will be invited to a second session of the scan and assessment
- Please make sure it is clear in your advert and PIS (if appropriate), whether participants will be given a second gift voucher for the second assessment.
- **The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee by way of an application for an amendment.**
- **Please ensure that you monitor and adhere to all up-to-date local and national Government health advice for the duration of your project.**

Please note that:

- Research Participant Information Sheets and (where relevant) flyers, posters, and consent forms should include a clear statement that research ethics approval has been obtained from the relevant Research Ethics Committee.
- The Research Participant Information Sheets should include a clear statement that queries should be directed, in the first instance, to the Supervisor (where relevant), or the researcher. Complaints, on the other hand, should be directed, in the first instance, to the Chair of the relevant Research Ethics Committee.
- Approval to proceed with the study is granted subject to receipt by the Committee of satisfactory responses to any conditions that may appear above, in addition to any subsequent changes to the protocol.
- The Research Ethics Committee reserves the right to sample and review documentation, including raw data, relevant to the study.
- If your project has been approved to run for a duration longer than 12 months, you will be required to submit an annual progress report to the Research Ethics Committee. You will be contacted about submission of this report before it becomes due.
- You may not undertake any research activity if you are not a registered student of Brunel University or if you cease to become registered, including abeyance or temporary withdrawal. As a deregistered student you would not be insured to undertake research activity. Research activity includes the recruitment of participants, undertaking consent procedures and collection of data. Breach of this requirement constitutes research misconduct and is a disciplinary offence.

Professor Louise Mansfield

Chair of the College of Health, Medicine and Life Sciences Research Ethics Committee (DLS)

Appendix G – Participant Recruitment Advert (Empirical Study Three)

Brunel University London

College of Health, Medicine and Life Sciences

Department of Life Sciences

Division of Psychology

PARTICIPANTS NEEDED FOR RESEARCH IN NEUROPSYCHOLOGY AND COVID-19

We are looking for participants to take part in a study on:

"Investigating the Effects of Long COVID on the Brain"

You are invited to participate in an fMRI study, lasting approximately 90 minutes.

You will be invited to take part twice over a period of 6-8 weeks.

To participate, you need to be 18 years or over.

In appreciation for your time, you will be compensated with a £25 Amazon gift voucher.

For more information about this study, or to take part, please contact:

Principle Investigator: Miss Krupa Vakani (Doctoral Researcher)

Email: krupa.vakani@brunel.ac.uk

This study has been reviewed and granted ethical approval by the College of Health, Medicine and Life Sciences Research Ethics Committee, Brunel University London.

If you have any questions, concerns and/or problems about any aspect of the study, please contact Professor Christina Victor, the Chair of the College of Health, Medicine and Life Sciences Research Ethics Committee via email at christinia.victor@brunel.ac.uk.

Appendix H – Participant Information Sheet: General Population (Empirical Study Three)

College of Health, Medicine and Life Sciences

Department of Life Sciences

PARTICIPANT INFORMATION SHEET

Study title

Investigating the Effects of Long COVID on the Brain.

Invitation paragraph

You are being invited to take part in a psychological research study. Before you continue, it is vital for you to understand why the research is being conducted and what it will involve. Please take your time to read the following information carefully and discuss it with others if you wish. Please take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

In 2019 the world saw the emergence of a new disease named Coronavirus disease 2019 (COVID-19). This novel disease has many physical symptoms, including loss of taste and/or smell. Although many individuals recover fully post a COVID-19 infection, some are still experiencing persistent problems, especially with their loss of taste and/or smell, and this may also be associated with changes in cognitive functioning and brain function.

Therefore, the purpose of this study is to examine how the brain responds to different cognitive demands post a COVID-19 diagnosis, compared to that seen in people with no known history of COVID-19. To do this we will use Functional Magnetic Resonance Imaging (fMRI) to explore which regions of the brain are activated when completing certain cognitive tasks. The findings of this study will allow us to determine if there are any changes in the brain of people who have tested positive for COVID-19 and experiencing changes in taste and/or smell for weeks after a COVID-19 diagnosis. We hope that the findings from this study improve our understanding of long COVID-19 and its impact on brain function and structure.

Why have I been invited to participate?

We are inviting people who are aged 18 or above from the general population to partake in this study. A minimum of 30 people with a confirmed diagnosis of COVID-19 (and ongoing

long COVID symptoms) and 30 people with no known history of COVID-19 will be invited. Recruitment is on a voluntary basis.

To ensure that it is safe for you to take part in this study please read the following 15 questions. If you answer YES to any of these questions, you will NOT be able to take part in this study.

1. Have you been fitted with a pacemaker or artificial heart valve?
2. Have you any aneurysm clips or shunts in your body, or a cochlear implant?
3. Have you ever had any metal fragments in your eyes?
4. Have you ever had any metal fragments, e.g., shrapnel in any other part of your body?
5. Have you any surgically implanted metal in any part of your body, other than dental fillings and crowns (e.g., joint replacement or bone reconstruction)
6. Have you ever had any surgery that might have involved metal implants of which you are not aware?
7. Do you wear a denture plate or brace with metal in it?
8. Do you wear a hearing aid?
9. Do you use drug patches attached to your skin?
10. Have you ever suffered from any of: epilepsy, diabetes or thermoregulatory problems?
11. Have you ever suffered from any heart disease?
12. Is there any possibility that you might be pregnant?
13. Have you been sterilised using clips?
14. Do you have a contraceptive coil (IUD) installed?
15. Are you currently breast-feeding an infant?

In addition, you will not be able to take part in this study if you have a current and/or previous diagnosis of psychiatric disorder or if you are claustrophobic.

Do I have to take part?

No. Participation in this study is entirely voluntary, it is up to you to decide whether or not to take part. If you do decide to take part, you will be asked to provide written consent prior to commencing the study. If you decide to take part you are still free to withdraw from the research at any time without giving a reason and you can withdraw your data any time up to 30/09/23. There is no compulsion or academic pressure for you to partake in this study. Furthermore, the right to decline and/or withdraw from the study will in no way influence or adversely affect you and/or your rights.

What will happen to me if I take part?

The study will involve a brain scanning (fMRI) session at Royal Holloway, University of London followed by a psychological assessment that will take place online. You will be invited to take part twice over a period of six weeks – first, upon entering the study and second, at a follow-up session 6-8 weeks after your initial session. Please see the outline below:

We will ask you to:

- Come to the Combined Universities Brain Imaging Centre (CUBIC), located at Royal Holloway, University of London, Egham, England.
- Complete two standardised MRI screening forms:
  - The CUBIC consent form and,
  - Sign and date the study consent form.
- During the brain scanning session, we will ask you to complete some brief cognitive tasks, each taking between 5 and 10 minutes, and in total taking no more than 30 minutes. The tasks will assess your attention and memory; they are designed to be engaging and use a mixture of numbers, words and pictures. In addition, we will also examine how your brain responds to pictures of items that you can smell and/or taste in everyday life. Prior to scanning, your heart rate and oxygen level will also be measured, using a small device placed on the fingertip (called a pulse oximeter) to further explore the correlation between physiological changes and neuropsychological measures.
- The total time you will physically be in the brain scanner would be approximately 60 minutes.
- Once the scan is completed you will be invited to complete an online psychological assessment (i.e. on a computer through a link), lasting approximately 30 minutes.
- The online assessment will consist of questions which will explore your psychological well-being and cognitive functioning. You will not be expected to answer any question that you do not wish to.
- You will be invited to complete this assessment twice over a period of six weeks – first, upon entering the study and second, at a follow-up session 6-8 weeks after your initial session.
- You are free to decline and/or withdraw from the study at any time without giving a reason and you can withdraw your data any time up to 30/09/23.
- The answers you provide during your online assessment will be collected for research purposes only and are not a form of a diagnostic tool.
- You will be compensated for your time with a £25 Amazon gift voucher (sent to you via email from the University/College Finance Officer).

COVID Secure Measures:

- You may be asked to take a rapid lateral flow test for COVID-19 when you arrive for the study session to ensure that you are not infectious and cannot give the virus to others. The researcher assessing and working with you will also be taking a rapid lateral flow test regularly to ensure that they are not infectious and cannot give the virus to you or others.
- You will be required to wear a mask. Researchers will also wear a mask when interacting with you.
- We will ensure that the room is well ventilated during study sessions and maintain social distancing of one meter (or more).
- The researchers and participants will be asked to wash and/or sanitise their hands regularly during the experiment(s) and when traveling to and from campus.
- All members of the research team are fully vaccinated and have also received or booked their booster vaccine doses. When combined with other safety measures,

vaccination reduces the likelihood of transmission of COVID-19 and reduces the risk of serious illness.

Furthermore, any other health and safety regulations implemented at the time by Brunel University London to minimise the risk of you or others catching COVID-19 infection will be strictly followed.

What is an fMRI scan?

- Functional MRI (fMRI) is a totally safe, non-invasive procedure that uses strong magnetic fields to look at your brain (it does not involve the use of any ionising radiation, such as, x-rays). During the scan you will be lying inside a long, quite narrow tube (therefore, to take part it is vital that you are not claustrophobic). Reflecting mirrors, mounted on a plastic surround, are fitted in a position that allows you to view a screen placed at the back of the scanner. It is on this screen that we will present the cognitive tasks. The scans are quite noisy so we give you ear protection (ear plugs) and we also give you an alarm call (a soft rubber bulb) you can squeeze at any time if you are feeling uncomfortable or want to be removed from the scanner. A fully trained CUBIC scan operator will go through the MRI screening form before you go into the scanner to make sure you are safe to enter the magnetic environment. The researchers and scan operator will be able to see you throughout the duration of the scan and will talk to you at regular intervals. Please, on the day of the scan wear comfortable clothes with minimal metal buttons or buckles. You will also be required to remove any keys, coins or any metal jewellery that may interact with the magnetic field (this will be securely stored until you complete the scan).

Are there any lifestyle restrictions?

There are no lifestyle restrictions relevant to this study.

What are the possible disadvantages and risks of taking part?

There are no disadvantages or risks in the taking part of this study that exceed those present in everyday life. All procedures will be conducted in accordance with current guidelines related to COVID-19 and the rigorous safety procedures in place at CUBIC, and therefore do not pose any significant risk. Prior to scanning you will be asked to complete a standardised safety screening form to ensure you have no contra-indications for MR imaging. Currently, there are no known major risks with an MRI scan. Some people may report minor discomforts during the scan due to the space limitation, but you will be given the opportunity to view the scanner before the study starts.

CUBIC is entirely research orientated. As such, brain images that we acquire there are for specific research purposes only and are not suitable for diagnostic opinions. However, although not diagnostic scans, in the unlikely event of a possible structural abnormality being noted incidentally, we will contact your General Practitioner (GP) by letter. You will not be allowed to take part in the study unless you consent for us to contact your UK GP and provide us with your current GP contact details.

You may find some of the questions in the online assessment stressful and/or anxiety provoking. You will not be expected to answer any question that you do not wish to. The answers you provide during your online assessment will be collected for research purposes only and are not a form of a diagnostic tool. If you do, for whatever reason, feel uncomfortable at any point during the research you can terminate your participation without consequence by closing your browser. The principle researcher, Miss Krupa Vakani (krupa.vakani@brunel.ac.uk) is happy to discuss the research with you and answer any questions that you may have. If you are unhappy with any aspect of the research, you can contact Professor Veena Kumari (supervisor to the project leader, Miss Krupa Vakani) whose contact details are at the bottom of this page.

You will be required to travel to the university campus on one occasion. If you need to use public transport to attend these sessions, we advise you to follow government mandated COVID-19 advice, allow social distancing if possible, and wear a face mask. Furthermore, as mentioned earlier, we will take all possible care to minimise the chances of catching COVID-19 infection for you and others involved in this research.

What are the possible benefits of taking part?

There are no direct intended benefits to you when taking part in this study. However, a potential indirect benefit from taking part in this study includes contributing towards knowledge of how COVID-19 and in particular long COVID-19 impacts the brain and its function. You may also feel intrigued and decide to further read into the topic and increase your knowledge base around this subject area.

What if something goes wrong?

If you have any questions, concerns and/or problems about this study, you should seek to contact and speak to a member of the research team. If you are unhappy with any aspect of the research you have taken part in, you can contact Professor Veena Kumari (Project Supervisor) whose contact details are at the bottom of this page. If you remain unhappy and wish to complain formally, you can do this through the University complaints procedure. To complain about the study, you need to contact Professor Louise Mansfield, the Chair of the College of Health, Medicine and Life Sciences Research Ethics Committee, via email at louise.mansfield@brunel.ac.uk.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the University will be anonymised, which means it will have your name, address and any other identifying information removed so that you cannot be identified from it.

In some instances, we may be required to release your details to your GP (please see "*What are the possible disadvantages and risks of taking part?*" above). Otherwise, all the information about your participation in this study will be kept strictly confidential. Your results will be coded with a participant number (for anonymity) and analysed by the researcher(s) before being reported. This anonymisation will occur at the earliest point of data collection. Data will be stored on a University computer for 10 years, while personal details will be stored separately in a locked filing cabinet. Only the named researcher and responsible individuals from Brunel University London will have access to these data. The overall results of the study may be published in scientific journals. However, all personal data will remain confidential, and no identifying data relating to individual participants will be published.

Responsible members of Brunel University London may be given access to the data for monitoring and/or audit of the study to ensure we are complying with regulations. Anyone involved will have a duty of confidentiality to you as a research participant.

Will I be recorded, and how will the recording be used?

No recording will be made as part of this study.

What will happen to the results of the research study?

The research data will be analysed by the researcher(s) before being reported. The results will be used primarily for a thesis/final year project and may later be reported at a conference and/or in a scientific journal in the form of a report and/or a publication. The anonymised research data may also be shared with other researchers for further analysis, but at no point will any uniquely identifiable data be shared. If you take part in this research, you can obtain a copy of the publication by contacting the researcher.

Who is organising and funding the research?

This research is being carried out by researchers from Brunel University London. The study is partly funded via Brunel University London; and we are applying for further funds to support this study.

What are the indemnity arrangements?

Brunel University London provides appropriate insurance cover for research which has received ethical approval.

Who has reviewed the study?

This study has been reviewed and granted ethical approval by the College of Health, Medicine and Life Sciences Research Ethics Committee.

Research Integrity

Brunel University London is committed to compliance with the Universities UK Research Integrity Concordat. You are entitled to expect the highest level of integrity from the researchers during the course of this research

Contact for further information and complaints

For general information

Researcher: Miss Krupa Vakani, Doctoral Researcher – Division of Psychology, Department of Life Sciences, College of Health, Medicine and Life Sciences, Brunel University London. Email: krupa.vakani@brunel.ac.uk

Supervisor: Professor Veena Kumari, Division of Psychology, Department of Life Sciences, Brunel University London, Uxbridge, UB8 3PH. Email: veena.kumari@brunel.ac.uk

For complaints and questions about the conduct of the Research

Professor Louise Mansfield, Chair College of Health, Medicine and Life Sciences Research Ethics Committee louise.mansfield@brunel.ac.uk

Once again, thank you for taking the time to read this Participant Information Sheet.

Appendix I – Consent Form: Database & General Population (Empirical Study Three)

CONSENT FORM

College of Health, Medicine and Life Sciences

Department of Life Sciences

Investigating the Effects of Long COVID on the Brain

Miss Krupa Vakani

APPROVAL HAS BEEN GRANTED FOR THIS STUDY TO BE CARRIED OUT BETWEEN 15/02/2022 AND 30/09/2023

The participant (or their legal representative) should complete the whole of this sheet.		
	YES	NO
Have you read the Participant Information Sheet?		
Have you had an opportunity to ask questions and discuss this study?		
Have you received satisfactory answers to all your questions?		
Do you understand that you will not be referred to by name in any report concerning this study?		
Do you understand that:		
• You are free to withdraw from this study at any time. • You don't have to give any reason for withdrawing. • Choosing not to participate or withdrawing will not affect your rights.		
• You can withdraw your data any time up to 30/09/2023		
The procedures regarding confidentiality have been explained to me.		
I agree that my anonymised data from this study can be stored and shared with other researchers for use in future projects.		
I would like to know about the findings of this study.		
I am happy to be contacted about future research studies.		
Although the brain images we acquire are for specific research purposes only and not suitable for diagnostic opinions, in the unlikely event of a possible abnormality being noted incidentally, do you agree to us contacting your General Practitioner (GP) by letter?		
I agree to take part in this study.		

Signature of research participant:
Print name:
Date:

Appendix J – Consent Form: Database & General Population (Empirical Study Three)

College of Health, Medicine and Life Sciences
Department of Life Sciences

Investigating the Effects of Long COVID on the Brain

Miss Krupa Vakani

Debrief form

We would like to take this opportunity to say **Thank You** for participating in our study. Your contribution is much appreciated.
The completed research will help to gain an understanding of the impact of COVID-19 and long COVID on the brain. We are particularly interested in understanding the effects of COVID-19 in people who are experiencing a persistent (i.e., for more than a few weeks) loss of taste and/or smell or altered taste and/or smell, compared to people who have no known history of COVID-19. You were chosen to take part in the study because you are above the age of 18.

Please be assured, all data collected will be treated in the strictest confidence. You are free to discuss this research by contacting the principle researcher, **Miss Krupa Vakani**, Division of Psychology, Department of Life Sciences, Brunel University London. Email: krupa.vakani@brunel.ac.uk. Please let the principle researcher know if you would like to be kept up-to-date with the progress of the study and if you would like to know the overall results. We regret that we cannot provide individualised feedback, but can offer an overall impression of the results.

We have tried to ensure that this study does not cause any distress. However, if you were unduly or unexpectedly affected by taking part in the study please feel free to feed it back to the principle researcher. If you feel unable for whatever reason what-so-ever to talk with the researcher then please either contact their supervisor (veena.kumari@brunel.ac.uk) or one of the Division of Psychology Research ethics coordinators led by Dr Justin O'Brien (Justin.O'Brien@brunel.ac.uk.

The following support services may be of interest to you:

MIND
MIND Infoline,
PO BOX 75225,
London,
E15-9FS
Number: 0300 123 3393
Text: 86463
Email: info@mind.org.uk
https://www.mind.org.uk/

AbScent - NoseWell
14 London Street,
Andover,
Hampshire,
SP10-2PA
Email: support@abscent.org
https://abscent.org/nosewell

Samaritans
Freepost SAMARITANS LETTERS
Number: 116 123
Email: jo@samaritans.org
https://www.samaritans.org/

The Brain Charity
Number: 0800 008 6417
https://www.thebraincharity.org.uk/

Once again, thank you for your participation in this study.

Appendix K – Published Papers

(i) ***COVID-19 and cognitive function: Evidence for increased processing speed variability in COVID-19 survivors and multifaceted impairment with long-COVID symptoms***

(ii) ***Cognitive and mental health trajectories of COVID-19: Role of hospitalisation and long-COVID symptoms***

(iii) ***Cognitive function and brain structure in COVID-19 survivors: The role of persistent symptoms***

(iv) ***Camera-based visual feedback learning aid for recovering sense of smell and taste in COVID-19 survivors: a proof-of-concept study***

European Psychiatry

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COVID-19 and cognitive function: Evidence for increased processing speed variability in COVID-19 survivors and multifaceted impairment with long-COVID symptoms

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Research Article

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Cognitive function; COVID-19; long-COVID; mental health; well-being

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Abstract

Background. There is increasing evidence for cognitive function to be negatively impacted by COVID-19. There is, however, limited research evaluating cognitive function pre- and post-COVID-19 using objective measures.

Methods. We examined processing speed, attention, working memory, executive function and memory in adults (≤69 years) with a history of COVID-19 (n = 129, none acutely unwell), compared to those with no known history of COVID-19 (n = 93). We also examined cognitive changes in a sub-group of COVID (n = 30) and non-COVID (n = 33) participants, compared to their pre-COVID-19 pandemic level.

Results. Cross-sectionally, the COVID group showed significantly larger intra-individual variability in processing speed, compared to the non-COVID group. The COVID sub-group also showed significantly larger intra-individual variability in processing speed, compared to their pre-COVID level; no significant change occurred in non-COVID participants over the same time scale. Other cognitive indices were not significantly impacted in the cross-sectional or within-subjects investigations, but participants (n = 20) who had needed hospitalisation due to COVID-19 showed poor attention and executive function relative to those who had not required hospitalisation (n = 109). Poor health and long-COVID symptoms correlated with poor cognitive function across domains in the COVID group.

Conclusions. The findings indicate a limited cognitive impact of COVID-19 with only intra-individual variability in processing speed being significantly impacted in an adult UK sample. However, those who required hospitalisation due to COVID-19 severity and/or experience long-COVID symptoms display multifaceted cognitive impairment and may benefit from repeated cognitive assessments and remediation efforts.

Introduction

A growing body of evidence indicates widespread brain and cognitive changes in people with a history of coronavirus disease 2019 (COVID-19), including those who did not show severe symptoms and did not require hospitalisation [1, 2]. According to a systematic review [3], approximately 15–40% of COVID-19 survivors, compared to people without a history of COVID-19, show abnormal performance in one or more cognitive domain(s). More recent cross-sectional studies also indicate attention concentration [4, 5], processing speed [5], memory [6], visuospatial processing [4], executive function [4–6] and general cognitive ability [2] to be negatively impacted by COVID-19. Crivelli et al. [7] in their review of 27 studies observed impaired attention, executive functions and memory in adults who had been assessed at some point, ranging from the acute phase to 7 months after the COVID-19 infection. Most of the existing studies with an objective assessment of cognitive function, however, have utilised cross-sectional designs and focused on adults in late adulthood (mean age across 27 studies = 56.05 years, [7]) who may be particularly vulnerable to negative impacts of COVID-19 [8]. Furthermore, poor cognitive function itself has been linked to greater COVID-19 infection severity and mortality [9], raising the possibility that some of the COVID-19-related cognitive effects may be explained by pre-COVID-19 differences between COVID-19 and non-COVID groups.

The only study published to date (n = 785, age range: 51–81 years, Biobank cohort data, United Kingdom (UK) [10]) to use objective measures of cognitive function both pre- and post-COVID-19 reported a slight impairment in processing speed and executive function (as assessed by the Trail Making Test Trails A and B completion time, respectively) at 141 days, on average, from the COVID-19 diagnosis. There was no significant impact of COVID-19 history on eight

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other cognitive indices derived from six cognitive tests. Furthermore, many COVID-19 survivors report anxiety, depression, sleep difficulties and post-traumatic stress disorder (PTSD) [3, 11, 12] which could cause or exacerbate cognitive difficulties reported by COVID-19 survivors. For many people, COVID-19 also has lasting effects, commonly referred to as long-COVID [13]. In the UK, an estimated 1.9 million people have self-reported long-COVID symptoms at 4 weeks post-infection [14]. A large study (N = 236,379) reported neuropsychiatric diagnosis in 33.62% of patients 6-months post-infection, and this prevalence rate rose to 46.2% for patients who had received intensive care [15]. Although some of these consequences may be due to pre-existing medical and/or psychiatric conditions [16], it seems likely that COVID-19 itself results in short- and long-term neuropsychological symptoms for some people [17], and cognitive disruption may be more salient in association with long-COVID symptoms.

The main aims of the present study, therefore, were to examine: (i) the effects of COVID-19 history on cognitive function in the UK residents of working age (18–69 years); and (ii) the associations of long-COVID symptoms as well as physical and psychological well-being with cognitive function post COVID-19 diagnosis. To achieve these aims, we conducted a cross-sectional investigation of cognitive function and health in individuals with a confirmed COVID-19 diagnosis compared to those with no COVID-19 history (COVID and non-COVID groups, respectively) followed by a longitudinal investigation of participants in the COVID and non-COVID groups for whom pre-COVID-19 pandemic cognitive function data were available through an existing database. Based on the findings of previous reviews [3, 7], we expected multifaceted cognitive impairment, with the same cognitive indices being impacted by COVID-19 history in both the cross-sectional and longitudinal investigations. We further expected reduced physical and mental well-being in the COVID compared to the non-COVID group, and explored whether cognitive profiles associated with COVID-19 are explained, at least in part, by poor health and well-being. Lastly, we expected long-COVID symptoms to be associated with reduced cognitive function and poor well-being.

Methods

Participants and design

The cross-sectional investigation involved 222 adults (mean age = 38.70, SD = 12.08, range: 18–69): 129 with a COVID-19 diagnosis (COVID group) and 93 with no known/confirmed COVID-19 diagnosis (non-COVID group) (see Supplementary Table S1 for the demographic characteristics). The longitudinal investigation involved 63 of these 222 adults, who had pre-COVID-19 pandemic cognitive function data available via MyCognition [18]. Participants were recruited via social media platforms and MyCognition. Recruitment via MyCognition was conducted in two stages. First, a large group within the MyCognition database who had been assessed since 2017 (N = 2894) were invited to participate if they self-reported a confirmed COVID-19 diagnosis. An invitation to participate was then extended to adults with pre-COVID-19 cognitive data who self-reported no COVID-19 history. Participant testing period was March 2021–February 2022 for the COVID group and March 2021–March 2022 for the non-COVID group (recruitment of non-COVID participants stopped after the pandemic-related restrictions in the UK were fully lifted).

The study was approved by the University Research Ethics Committee (26518-A-Sep/2021–34167-1). All participants provided written consent and received £10 (Amazon voucher) for their time.

Measures and procedure

Demographic, physical and psychological well-being data were collected using self-report measures administered via Qualtrics (an online survey tool), taking ~45 min in total. The demographic items included age, sex, ethnicity, education, socio-economic status, existing mental and physical illnesses, and medication use. In addition, COVID participants were asked about their COVID-19 diagnosis, acute symptoms, subjective cognitive impairment (via a single question "Do you believe your cognitive functioning has been impacted due to your diagnosis of COVID-19?") and chronic long-COVID symptoms at the time of participation. Cognitive data were collected via the MyCognition PRO mobile application, taking ~15 min.

Physical and psychological well-being

Physical and psychological well-being were assessed using three self-rated scales:

Short Form Health Survey-36 (SF-36) [19]: SF-36 is a 36-item scale measuring physical, social and emotional functioning, and quality of life through eight dimensions: physical functioning, physical health, emotional problems, energy, emotional well-being, social functioning, pain and general health.

The Depression, Anxiety and Stress Scale-21 (DASS-21) [20]: DASS-21 is a 21-item scale assessing levels of depression (dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest, anhedonia, inertia), anxiety (autonomic arousal, skeletal muscle effects, situational anxiety, anxious affect) and stress (levels of chronic non-specific arousal such as problems with relaxation and emotional overactions).

Pittsburgh Sleep Quality Index (PSQI) [21]: PSQI is a 19-item, four-point Likert scale assessing daytime dysfunction, use of sleeping medication, sleep disturbances, habitual sleep efficiency, sleep duration, sleep latency and subjective sleep score.

Cognitive function

Cognitive function was assessed online using a self-administered online assessment tool (MyCognition [MyCQ], https://www.mycognition.com/). The MyCQ tool comprises of digital versions of commonly utilised neuropsychological tests validated against the Cambridge Neuropsychological Automated Test Battery [22, 23] and assesses processing speed, attention, working memory, executive function and memory domains [24].

Processing speed was assessed using a Simple Reaction Time (RT) task, requiring participants to tap the circle button as quickly as possible when a red circle is presented on the screen (presentation time = 1 s, inter-stimulus interval = 3 s, 30 stimuli in total). Response accuracy (RA; % correct), average RT (ms) and intra-individual variability in RT were examined.

Attention was assessed using a Choice Reaction Time task, requiring participants to tap either the circle or triangle button depending on what shape is presented on the screen. There are 30 trials in total, and each stimulus (circle or triangle) is presented for 1 s, with a 3 s inter-stimulus interval. RA (% correct) and average RT (ms) for correct answers were examined.

Working Memory was assessed using the 2-Back task. Participants are asked to tap "Yes" or "No" depending on whether the picture presented to them on the screen (household objects, food and drink items) matches the picture shown two screens back

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(50 trials in total). RA (% correct) was used to index task performance.

Executive Function was assessed using the Trail-Making B task, requiring tapping a number and a letter in an ascending and alphabetical order, respectively, to produce an alternating sequence (e.g., 1, A, 2, B). The task has 25 trials (13 numbers, 12 letters). RA (% correct moves) and total task completion time (ms) were examined.

Memory was assessed using a Visual Recognition Memory task. Participants are presented with a set of 24 pictures (each picture for 2 s, inter-stimulus interval = 1 s) and instructed to remember them. They are then presented with 96 pictures, including 24 pictures presented earlier, and asked to tap either "Yes" or "No" depending on whether they remember seeing the picture earlier. RA (% correct) was used to index task performance.

Statistical analysis

For the cross-sectional investigation, we first compared the COVID and non-COVID groups on age and body mass index (BMI) (separately) using a 2 (Group: COVID, non-COVID) × 2 (Sex: Males, Females) analysis of variance (ANOVA). Group differences in each of the health and cognitive variables were examined using a 2 (Group) × 2 (Sex) ANOVA, followed by 2 (Group) × 2 (Sex) analyses of co-variance (ANCOVA), covarying for age, given that the COVID group, on average, was found to be older than the non-COVID group (Table 1). For the two cognitive variables showing a significant Group effect (see Results), further (exploratory) ANOVAs were run with Ethnicity (White British vs. all other ethnicities) included as an additional between-subjects factor. Any significant interactions were followed up with post hoc comparisons using paired or independent sample *t*-tests as appropriate. Effect sizes, where reported, are partial eta squared (η_p^2; the proportion of variance associated with a factor). In the COVID group, the relationships of cognitive variables with the overall long COVID-19 symptom load (a sum total of individual symptom ratings) were examined using Pearson's correlations, and with each of the long-COVID symptoms (rated 0–7) explored using Spearman rank order correlations. Pearson's correlations were also used to explore the relationships between all cognitive variables and the physical and mental health measures in the entire sample, and in the COVID and non-COVID groups separately.

For the longitudinal (within-subjects) investigation, the COVID and non-COVID groups were compared on age and BMI using independent sample *t*-tests (sex not analysed due to relatively small number of males). The effect of COVID-19 diagnosis on each of the cognitive variables was then examined using a 2 (Group: COVID, non-COVID) × 2 (Time: Pre-COVID, Post-COVID) ANOVA with Group as a between-subjects and Time as a within-subject factor. Given that poor cognitive function has been linked to more severe acute COVID-19 and hospitalisation [9], the relationship between the overall long-COVID symptom load and pre-pandemic cognitive data in the longitudinal COVID sub-sample (n = 29) was also examined using Pearson's correlations.

All analyses were performed using the Statistical Package for Social Sciences (for Windows, version 28; IBM, New York, NY). The data distribution on all variables met the assumptions of parametric statistical procedures. Alpha level for testing the significance of effects was maintained at $p \leq 0.05$.

Results

Cross-sectional investigation

Sample characteristics

The majority of participants in both the COVID (n = 129) and non-COVID (n = 93) groups were White British, held a Bachelor's degree or above and were in some form of employment. The COVID group was, on average, significantly older (Table 1), and had more people with at least one physical health problem (n = 58; 44.96%; most commonly related to lungs), compared to the non-COVID group (n = 21; 22.58%). Of various mental health conditions, anxiety, depression and insomnia were most commonly reported by both groups (Supplementary Table S1).

Within the COVID group, 20 participants (15.5%) had been hospitalised (Supplementary Tables S2 and S3). The most prevalent acute symptom (recalled retrospectively) was a high temperature (76.7%). At study entry (mean number of days since diagnosis = 263, SD = 192.16, range:20–714), a large proportion of the sample reported subjective cognitive impairment (78.3%), reduced psychological well-being (77.5%), and one or more long-COVID symptoms, most commonly exhaustion/fatigue (88.4%). The overall long-COVID symptom load, however, was not significantly correlated with the number of days since diagnosis [$r(125) = 0.057$, $p = 0.527$] or age [$r(126) = 0.092$, $p = 0.299$]. Nineteen of 20 hospitalised participants (95%) reported subjective cognitive impairment, and 18 (90%) reported reduced psychological well-being.

Mental health and psychological well-being in COVID versus non-COVID participants

There were significant main effects of Group in ANOVA analyses (Table 1), with the COVID group having significantly poorer health (SF-36), higher anxiety (DASS-21), and lower sleep quality (PSQI), compared to the non-COVID group. The ANCOVA analyses, with age as a covariate, retained these effects and, in addition, indicated significantly higher depression and stress levels (DASS-21) in the COVID, compared to the non-COVID group (Table 1).

There were significant sex differences in physical functioning, emotional problems, energy, emotional well-being, pain and general health (SF-36), stress (DASS-21), as well as sleep disturbance and daytime dysfunction (PSQI), indicating poorer health and psychological well-being in females compared to males. There were, however, no significant Group × Sex interactions (Table 1), except for sleep medication [in females, greater use of sleep medications by COVID compared to non-COVID group, $t(163) = 3.65$, $p < 0.001$].

Lastly, age was a significant covariate (in ANCOVAs) for BMI, emotional well-being (SF-36), depression, anxiety and stress (DASS-21), as well as sleep efficiency and daytime dysfunction (PSQI), indicating poorer health and psychological well-being with older age.

Cognitive function in COVID versus non-COVID participants

There were significant main effects of Group indicating significantly greater intra-individual variability in processing speed (p = 0.015) and lower attention RA (p = 0.022) in the COVID compared to non-COVID group (Table 2). The Group effect remained significant for processing speed variability (p = 0.034) but lost formal significance for attention RA (p = 0.052) when covarying for age, with ANCOVAs additionally revealing longer RTs being associated with older age (Table 2). Ethnicity did not show any main or interactive effects (Table 2).

Participants who had been hospitalised had longer attention RTs (p = 0.005) and lower executive function RA (%) (p = 0.012)

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Table 1. Descriptive statistics and group differences (ANOVA and ANCOVA results) in the demographic, mental health and well-being measures for the cross-sectional investigation

	COVID group Mean (SD)				Non-COVID group Mean (SD)			
	Male (n = 23)	Female (n = 106)	Total (N = 129)	Range	Male (n = 32)	Female (n = 61)	Total (N = 93)	Range
Demographics								
Age	42.43	40.49	40.84	19–64	34.81	36.21	35.73	18–69
	(10.99)	(11.25)	(11.19)		(12.31)	(12.95)	(12.68)	
BMI[a]	27.71	29.43	29.12	15.24–86.57	27.32	26.05	26.50	14.53–56.81
	(5.80)	(10.52)	(9.85)		(7.07)	(5.39)	(6.02)	
Physical health status (SF-36)								
Physical functioning	64.35	46.30	49.51	0–100	95.30	86.46	89.50	20–100
	(29.75)	(32.51)	(32.67)		(10.99)	(20.70)	(18.38)	
Physical health	28.26	24.76	25.39	0–100	78.13	75.82	76.61	0–100
	(40.81)	(39.42)	(39.53)		(35.21)	(39.78)	(38.09)	
Emotional problems	49.28	37.11	39.28	0–100	73.96	54.10	60.93	0–100
	(48.06)	(43.23)	(44.18)		(39.47)	(46.41)	(44.94)	
Energy/fatigue	33.48	19.04	21.61	0–80	52.86	42.92	46.34	0–95
	(19.47)	(19.86)	(20.87)		(21.80)	(22.77)	(22.81)	
Emotional well-being	62.39	51.47	53.42	4–96	66.88	61.05	63.05	4–100
	(17.88)	(21.98)	(21.65)		(18.96)	(21.85)	(20.98)	
Social functioning	55.98	49.06	50.29	0–100	73.05	71.11	71.77	0–100
	(27.66)	(25.74)	(26.12)		(25.02)	(26.47)	(25.86)	
Pain	67.39	51.49	54.32	0–100	87.81	76.23	80.22	0–100
	(29.47)	(28.18)	(28.95)		(18.78)	(25.50)	(23.95)	
General health	57.17	44.67	46.90	0–95	69.22	60.57	63.55	20–100
	(22.66)	(21.42)	(22.08)		(21.03)	(20.82)	(21.18)	
Mental health (DASS-21)								
Depression	11.57	15.08	14.45	0–42	8.69	11.48	10.52	0–42
	(9.14)	(10.71)	(10.50)		(9.79)	(11.41)	(10.91)	
Anxiety	9.04	10.77	10.47	0–38	5.62	7.93	7.14	0–36
	(7.28)	(8.83)	(8.57)		(7.28)	(8.27)	(7.98)	
Stress	12.87	14.87	14.51	0–40	8.75	15.41	13.12	0–42
	(8.50)	(9.67)	(9.47)		(7.46)	(10.82)	(10.26)	
Sleep quality (PSQI)								
Sleep quality	1.57	1.76	1.73	0–3	1.19	1.44	1.35	0–3
	(0.79)	(0.72)	(0.74)		(0.59)	(0.83)	(0.76)	
Sleep latency	2.09	2.06	2.06	0–3	1.38	1.59	1.52	0–3
	(1.04)	(0.95)	(0.97)		(1.04)	(1.10)	(1.08)	
Sleep duration[b]	1.35	1.03	1.09	0–3	0.84	0.90	0.88	0–3
	(0.98)	(0.88)	(0.91)		(0.77)	(0.93)	(0.87)	
Sleep efficiency[c]	1.43	1.43	1.43	0–3	0.72	0.76	0.75	0–3
	(1.17)	(1.13)	(1.14)		(1.05)	(1.01)	(1.02)	
Sleep disturbance	1.48	1.66	1.63	0–3	1.20	1.41	1.33	0–3
	(0.67)	(0.62)	(0.63)		(0.54)	(0.56)	(0.56)	
Sleep medication[d]	0.26	0.75	0.66	0–3	0.44	0.20	0.28	0–3
	(0.75)	(1.24)	(1.18)		(0.98)	(0.70)	(0.81)	

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Table 1. *Continued*

	COVID group Mean (SD)				Non-COVID group Mean (SD)			
	Male (n = 23)	Female (n = 106)	Total (N = 129)	Range	Male (n = 32)	Female (n = 61)	Total (N = 93)	Range
Daytime dysfunction	1.17	1.45	1.40	0–3	0.84	1.11	1.02	0–3
	(0.78)	(0.86)	(0.85)		(0.68)	(0.80)	(0.77)	
Global score	9.22	10.06	9.91	2–18	6.41	7.31	7.00	1–20
	(3.70)	(3.61)	(3.63)		(3.61)	(3.89)	(3.80)	

	ANOVA $F(1,218)$ (p) η_p^2			ANCOVA (covarying for age) $F(1,217)$ (p) η_p^2			
	Group effect	Sex	Group × sex	Age effect	Group effect	Sex	Group × sex
Demographics							
Age	10.00 **(0.002)**	0.02 (0.885)	0.790 (0.375)	n/a	n/a	n/a	n/a
	0.44	*0.0*	*0.004*				
BMI[a]	1.96 (0.163)	0.03 (0.868)	1.22 (0.271)	10.94 **(0.001)**	0.44 (0.506)	0.05 (0.816)	1.69 (0.195)
	0.01	*0.0*	*0.01*	*0.05*	*0.002*	*0.0*	*0.01*
Physical health status (SF-36)							
Physical functioning	68.56 **(<0.001)**	9.81 **(0.002)**	1.15 (0.284)	3.56 (0.068)	60.17 **(<0.001)**	10.02 **(0.002)**	1.41 (0.237)
	0.24	*0.04*	*0.01*	*0.02*	*0.22*	*0.04*	*0.01*
Physical health	66.28 **(<0.001)**	0.22 (0.640)	0.01 (0.924)	1.48 (0.226)	59.52 **(<0.001)**	0.23 (0.631)	0.03 (0.866)
	0.23	*0.001*	*0.0*	*0.01*	*0.22*	*0.001*	*0.0*
Emotional problems	8.87 **(0.003)**	5.24 **(0.023)**	0.30 (0.583)	3.67 (0.057)	11.09 **(0.001)**	5.22 **(0.023)**	0.45 (0.506)
	0.04	*0.02*	*0.001*	*0.02*	*0.05*	*0.02*	*0.002*
Energy/fatigue	41.59 **(<0.001)**	13.20 **(<0.001)**	0.45 (0.503)	0.04 (0.852)	40.08 **(<0.001)**	13.13 **(<0.001)**	0.43 (0.512)
	0.16	*0.06*	*0.002*	*0.0*	*0.16*	*0.06*	*0.002*
Emotional well-being	4.40 **(0.037)**	6.23 **(0.013)**	0.58 (0.448)	8.66 **(0.004)**	7.30 **(0.007)**	6.31 **(0.013)**	0.35 (0.553)
	0.02	*0.03*	*0.003*	*0.04*	*0.03*	*0.03*	*0.002*
Social functioning	22.43 **(<0.001)**	1.15 (0.284)	0.36 (0.547)	1.97 (0.162)	24.36 **(<0.001)**	1.13 (0.290)	0.27 (0.604)
	0.09	*0.01*	*0.002*	*0.01*	*0.1*	*0.01*	*0.001*
Pain	29.01 **(<0.001)**	10.75 **(0.001)**	0.27 (0.607)	2.24 (0.136)	24.68 **(<0.001)**	10.90 **(0.001)**	0.37 (0.545)
	0.12	*0.05*	*0.001*	*0.01*	*0.10*	*0.05*	*0.002*
General health	17.08 **(<0.001)**	9.78 **(0.002)**	0.33 (0.569)	1.78 (0.183)	14.20 **(<0.001)**	9.90 **(0.002)**	0.42 (0.516)
	0.07	*0.04*	*0.001*	*0.01*	*0.06*	*0.04*	*0.002*
Mental health (DASS-21)							
Depression	3.69 (0.056)	3.49 (0.063)	0.05 (0.831)	4.24 **(0.041)**	5.40 **(0.021)**	3.46 (0.064)	0.01 (0.927)
	0.02	*0.02*	*0.0*	*0.02*	*0.02*	*0.02*	*0.0*
Anxiety	5.62 **(0.019)**	2.34 (0.127)	0.05 (0.826)	11.19 **(0.001)**	9.44 **(0.002)**	2.35 (0.127)	0.18 (0.671)
	0.03	*0.01*	*0.0*	*0.05*	*0.04*	*0.01*	*0.001*
Stress	1.38 (0.242)	8.07 **(0.005)**	2.34 (0.128)	14.71 **(<0.001)**	3.95 **(0.048)**	8.36 **(0.004)**	3.26 (0.073)
	0.01	*0.04*	*0.01*	*0.06*	*0.02*	*0.04*	*0.02*
Sleep quality (PSQI)							
Sleep quality	8.78 **(0.003)**	3.70 (0.056)	0.06 (0.812)	0.65 (0.422)	7.44 **(0.007)**	3.73 (0.055)	0.04 (0.850)
	0.04	*0.02*	*0.0*	*0.003*	*0.03*	*0.02*	*0.0*
Sleep latency	13.34 **(<0.001)**	0.33 (0.567)	0.58 (0.448)	0.82 (0.367)	14.13 **(<0.001)**	0.32 (0.574)	0.66 (0.417)
	0.06	*0.002*	*0.003*	*0.004*	*0.06*	*0.001*	*0.003*
Sleep duration[b]	5.00 **(0.026)**	0.86 (0.355)	1.79 (0.183)	0.91 (0.341)	3.95 **(0.048)**	0.84 (0.361)	1.62 (0.204)
	0.02	*0.004*	*0.01*	*0.004*	*0.02*	*0.004*	*0.01*
Sleep efficiency[c]	15.02 **(<0.001)**	0.01 (0.905)	0.02 (0.898)	12.54**(<0.001)**	10.32 **(0.002)**	0.02 (0.899)	0.01 (0.939)
	0.07	*0.0*	*0.0*	*0.06*	*0.05*	*0.0*	*0.0*

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Table 1. *Continued*

	ANOVA $F(1,218)$ (p) η_p^2			ANCOVA (covarying for age) $F(1,217)$ (p) η_p^2			
	Group effect	Sex	Group × sex	Age effect	Group effect	Sex	Group × sex
Sleep disturbance	8.24 **(0.005)**	4.60 **(0.033)**	0.05 (0.831)	0.02 (0.904)	7.70 **(0.006)**	4.58 **(0.033)**	0.04 (0.838)
	0.04	*0.02*	*0.0*	*0.0*	*0.03*	*0.02*	*0.0*
Sleep medication[d]	1.31 (0.253)	0.57 (0.451)	4.94 **(0.027)**	2.45 (0.119)	0.64 (0.426)	0.60 (0.439)	5.38 **(0.021)**
	0.01	*0.003*	*0.02*	*0.01*	*0.003*	*0.003*	*0.02*
Daytime dysfunction	6.72 **(0.010)**	4.55 **(0.034)**	0.0 (0.976)	3.77 (0.054)	8.75 **(0.003)**	4.53 **(0.034)**	0.01 (0.932)
	0.03	*0.02*	*0.0*	*0.02*	*0.04*	*0.02*	*0.0*
Global score	22.41 **(<0.001)**	2.21 (0.139)	0.003 (0.955)	1.38 (0.241)	19.25 **(<0.001)**	2.25 (0.135)	0.0 (0.989)
	0.09	*0.01*	*0.0*	*0.01*	*0.08*	*0.01*	*0.0*

SF-36 (Short Form Health Survey-36): The response ranges between two- and six-point ordered Likert scales. Raw scores are transformed to produce a score between 0 and 100 for each dimension. The higher the score the better the overall health (19.47). Internal reliability in this sample: overall scale, Cronbach's $\alpha = 0.96$; all subscales, Cronbach's $\alpha > 0.8$, except $\alpha = 0.74$ for Social Functioning.

DASS-21 (The Depression, Anxiety and Stress Scale-21): Each item is rated by participants on a four-point scale according to how often in the past week it applied to them, ranging from "Did not apply to me at all" (0) to "Applied to me very much or most of the time" (3). Higher scores indicate higher levels (severity) of symptoms. Internal reliability in this sample: Depression, Cronbach's $\alpha = 0.93$; Anxiety, Cronbach's $\alpha = 0.82$; Stress, Cronbach's $\alpha = 0.88$.

PSQI (Pittsburgh Sleep Quality Index): Participants answer the PSQI questions by relating them to their past month (21). Each component is scored between "No difficulty" (0) to "Severe difficulty" (3) and tallied up to yield a total score (range 0–21). Higher scores indicate poor sleep quality. Internal reliability in this sample: Global score, Cronbach's $\alpha = 0.76$.

[a]Sample size reduced by 2 (non-COVID).
[b]Sample size reduced by 1 (COVID).
[c]Sample size reduced by 7 (5 COVID, 2 non-COVID).
[d]Sample size reduced by 2 (COVID).

than those who did not require hospitalisation (Table 3). These effects remained significant when covarying for age, despite older age being associated with poorer performance on both measures.

Association between cognitive functions and long-COVID symptoms

Executive function task completion time, the RTs during processing speed and attention tasks, and attention RA variables were most commonly correlated, with small-to-medium effect sizes, with individual long-COVID symptoms, especially arrythmia, chest pain and headaches (Supplementary Table S4). The overall long-COVID symptom load was significantly associated with poor performance on all tasks, with small-to-medium-sized correlations (Table 4).

Association between cognitive function, mental health and well-being

SF-36 dimensions correlated with many cognitive variables, especially executive function, with poorer health being associated with poorer performance (Table 5). Depression, anxiety and stress correlated negatively with executive function. Sleep disturbance was associated with poor performance in processing speed, attention and executive function. These associations were generally stronger in the COVID, relative to non-COVID, group (Table 5).

Longitudinal (within-subjects) investigation

Sample characteristics

The sub-sample for whom pre-COVID cognitive data were available had similar sample characteristics as the whole sample (Supplementary Table S1).

Pre- versus post-COVID-19 cognitive function

In line with the cross-sectional findings, there was a significant Group × Time interaction in RT variability in processing speed ($p = 0.043$; Table 6), explained by greater intra-individual variability in the COVID group post-COVID-19 diagnosis (but not acutely unwell) compared to their pre-pandemic scores [$t(28)=2.01$, $p = 0.05$]; there was no such change in the non-COVID group [$t(30)=0.75$, $p = 0.461$]. Additionally, there were main effects of Time on attention task RTs ($p = 0.001$) (shorter RTs the second time) and working memory RA ($p = 0.033$) (slightly higher the second time), most likely explained by practice-related effects.

Association between cognitive function and long-COVID symptoms

The higher overall long-COVID symptom load correlated with poorer executive function performance at study entry (post-Covid), as well as poorer executive function and memory in pre-pandemic cognitive data (see Table 4).

Discussion

The main aims of this study were to examine the impact of COVID-19 on cognitive function in a UK adult sample (≤69 years), and explore the roles of physical and mental health and long-COVID symptoms in cognitive function in these individuals. The findings showed: (i) significantly larger intra-individual variability in processing speed but no significant impact of COVID-19 on other cognitive measures in our cross-sectional investigation, and a further confirmation of a negative impact of COVID-19 on processing speed variability (but no other cognitive variables) in our within-subjects investigation (pre-pandemic vs. post-COVID-19 diagnosis); (ii) poorer attention and executive function in the COVID-19 group participants who had needed hospitalisation due to COVID-19 relative to those who had not; and (iii) medium-sized negative associations of cognitive performance on all tasks with physical health and long-COVID symptoms (and relatively fewer associations of cognitive variables with anxiety and depression) in the COVID-19 group in the cross-sectional investigation, and (iv) medium-sized negative association between pre-pandemic cognitive function (executive function, memory) and long-COVID

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Table 2. Descriptive statistics and group differences (ANOVA and ANCOVA results) in cognitive measures for the cross-sectional investigation

		COVID group Mean (SD)				Non-COVID group Mean (SD)			
		Male (n = 23)	Female (n = 106)	Total (N = 129)	Range	Male (n = 32)	Female (n = 61)	Total (N = 93)	Range
Processing speed[a]	Response accuracy (%)	94.87	95.87	95.68	57.14–100	96.36	96.66	96.56	56.67–100
		(9.02)	(6.56)	(7.07)		(8.08)	(5.15)	(6.26)	
	RT (correct responses, ms)	352.04	382.45	376.57	275–686	351.32	355.47	354.05	253–746
		(77.90)	(81.66)	(81.52)		(66.93)	(76.96)	(73.35)	
	RT variability (SD of RT)	84.52	87.21	86.69	22–205	64.00	76.18	72.03	25–182
		(40.85)	(42.21)	(41.80)		(34.74)	(39.11)	(37.93)	
Attention[b]	Response accuracy (%)	94.55	95.23	95.11	51.28–100	97.06	98.16	97.78	73.33–100
		(10.43)	(8.18)	(8.58)		(5.52)	(4.12)	(4.66)	
	RT (correct responses, ms)	476.76	514.16	507.39	344–830	484.03	461.19	469.15	321–898
		(101.50)	(93.76)	(95.84)		(114.70)	(87.16)	(97.60)	
Working memory[c]	Response accuracy (%)	92.73	91.85	92.00	52–100	95.07	93.69	94.18	60–100
		(5.57)	(8.89)	(8.40)		(4.62)	(7.44)	(6.59)	
Executive function[d]	Accuracy (%)	95.40	94.64	94.78	58.14–100	93.80	95.51	94.94	58.14–100
		(5.59)	(7.55)	(7.22)		(9.71)	(7.96)	(8.57)	
	Completion time (ms)	29,217.00	34,046.42	33,185.36	11,775–162,669	31,398.80	29,385.68	30,056.72	12050–97180
		(11,514.15)	(20,399.68)	(19,172.91)		(11,740.80)	(12,823.20)	(12,443.24)	
Memory[e]	Recognition accuracy (%)	90.26	89.25	89.42	54.17–98.96	91.15	91.59	91.44	58.33–100
		(6.96)	(8.88)	(8.56)		(7.99)	(8.40)	(8.22)	

		ANOVA $F(1, 218)$ (p) η_p^2			ANCOVA (covarying for age) $F(1, 217)$ (p) η_p			
		Group effect	Sex	Group × sex	Age effect	Group effect	Sex	Group × sex
Processing speed[a]	Response accuracy (%)	1.11 (0.294)	0.35 (0.553)	0.11 (0.746)	0.41 (0.522)	0.78 (0.377)	0.35 (0.556)	0.09 (0.770)
		0.01	*0.002*	*0.001*	*0.002*	*0.004*	*0.002*	*0.0*
	RT (correct responses, ms)	1.23 (0.269)	1.91 (0.168)	1.11 (0.295)	5.59 **(0.019)**	0.34 (0.563)	2.00 (0.159)	1.37 (0.243)
		0.01	*0.01*	*0.01*	*0.03*	*0.002*	*0.01*	*0.01*
	RT variability (SD of RT)	6.00 **(0.015)**	1.33 (0.250)	0.54 (0.462)	1.35 (0.247)	4.57 **(0.034)**	1.35 (0.246)	0.47 (0.495)
		0.03	*0.01*	*0.003*	*0.01*	*0.02*	*0.01*	*0.002*
Attention[b]	Response accuracy (%)	5.33 **(0.022)**	0.57 (0.451)	0.03 (0.856)	2.59 (0.109)	3.83 (0.052)	0.59 (0.443)	0.05 (0.830)
		0.03	*0.003*	*0.0*	*0.01*	*0.02*	*0.003*	*0.0*
	RT (correct responses, ms)	2.10 (0.149)	0.21 (0.645)	3.64 (0.058)	31.01**(<0.001)**	0.18 (0.670)	0.21 (0.649)	4.68 **(0.032)**
		0.01	*0.001*	*0.02*	*0.13*	*0.001*	*0.001*	*0.02*
Working memory[c]	Response accuracy (%)	2.84 (0.093)	0.82 (0.366)	0.04 (0.842)	0.01 (0.940)	2.74 (0.099)	0.81 (0.368)	0.04 (0.839)
		0.01	*0.004*	*0.0*	*0.0*	*0.01*	*0.004*	*0.0*
Executive function[d]	Accuracy (%)	0.08 (0.774)	0.14 (0.705)	0.97 (0.326)	2.93 (0.088)	0.02 (0.896)	0.14 (0.712)	0.73 (0.394)
		0.0	*0.001*	*0.004*	*0.01*	*0.0*	*0.001*	*0.003*
	Completion time (ms)	0.21 (0.645)	0.28 (0.601)	1.62 (0.204)	0.40 (0.527)	0.09 (0.768)	0.27 (0.604)	1.73 (0.189)
		0.001	*0.001*	*0.01*	*0.002*	*0.0*	*0.001*	*0.01*
Memory[e]	Recognition accuracy (%)	1.43 (0.233)	0.05 (0.832)	0.29 (0.592)	0.34 (0.559)	1.07 (0.302)	0.05 (0.825)	0.33 (0.567)
		0.01	*0.0*	*0.001*	*0.002*	*0.01*	*0.0*	*0.002*

Note: Further (exploratory) analyses of processing speed RT variability and attention response accuracy (%) with Ethnicity (White British vs. All Other Ethnicities) included as an additional between-subjects factor retained the main effects of Group (processing speed RT variability, p = 0.006; attention RA, p = 0.042) but yielded no significant main or interactive effects involving Ethnicity (all p values > 0.341).

[a]Sample size reduced by 12 (10 COVID, 2 non-COVID).

[b]Sample size reduced by 17 (13 COVID, 4 non-COVID).

[c]Sample size reduced by 5 (2 COVID, 3 non-COVID).

[d]Sample size reduced by 3 (non-COVID).

[e]Sample size reduced by 2 (COVID).

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Table 3. Descriptive statistics and group differences between COVID hospitalised versus non-hospitalised sample (ANOVA and ANCOVA results) in cognitive measures for the cross-sectional investigation

		Hospitalised COVID participants n = 20		Non-hospitalised COVID participants n = 109		ANOVA $F(1,127)$ (p) η_p^2	ANCOVA (covarying for age) $F(1,126)$ (p) η_p^2	
		Mean (SD)	Range	Mean (SD)	Range	Hospital effect	Age effect	Hospital effect
Processing speed[a]	Response accuracy (%)	94.09 (9.42)	71.43–100	95.98 (6.55)	57.14–100	1.13 (0.289) *0.01*	0.16 (0.693) *0.001*	1.20 (0.275) *0.01*
	RT (correct responses, ms)	393.00 (87.94)	301–611	373.45 (80.33)	275–686	0.92 (0.340) *0.01*	0.45 (0.506) *0.004*	0.77 (0.381) *0.01*
	RT variability (SD of RT)	93.95 (32.79)	52–186	85.31 (43.30)	22–205	0.68 (0.411) *0.01*	0.17 (0.684) *0.001*	0.60 (0.441) *0.01*
Attention[b]	Response accuracy (%)	94.93 (7.13)	78.79–100	95.14 (8.87)	51.28–100	0.01 (0.921) *0.0*	0.27 (0.608) *0.002*	0.002 (0.967) *0.0*
	RT (correct responses, ms)	562.84 (70.79)	438–714	496.53 (96.63)	344–830	8.07 **(0.005)** *0.07*	11.89 **(0.001)** *0.1*	6.62 **(0.011)** *0.06*
Working memory[c]	Response accuracy (%)	90.31 (11.38)	52–100	92.39 (7.75)	52–100	0.97 (0.327) *0.01*	0.42 (0.518) *0.003*	1.12 (0.293) *0.01*
Executive function	Accuracy (%)	91.06 (11.64)	58.14–100	95.46 (5.91)	71.43–100	6.52 **(0.012)** *0.05*	8.06 **(0.005)** *0.06*	8.84 **(0.004)** *0.07*
	Completion time (ms)	41,747.45 (30,405.35)	14,575–162,669	31,614.34 (16,030.19)	11,775–13,1328	4.86 **(0.029)** *0.04*	0.03 (0.875) *0.0*	4.83 **(0.030)** *0.04*
Memory[c]	Recognition accuracy (%)	88.35 (10.46)	54.17–98.96	89.62 (8.20)	57.14–98.96	0.37 (0.543) *0.003*	0.13 (0.718) *0.001*	0.42 (0.518) *0.003*

[a]Sample size reduced by 10 (1 hospitalised, 9 non-hospitalised).
[b]Sample size reduced by 13 (1 hospitalised, 12 non-hospitalised).
[c]Sample size reduced by 2 (non-hospitalised).

Table 4. Associations (Pearson correlation coefficients) between the cognitive variables and the total long COVID-19 symptom load in the COVID participants

	Processing speed			Attention		Working memory	Executive function		Memory
	Response accuracy (%) r (p) n [CI]	RT correct responses (ms) r (p) n [CI]	RT variability (SD of RT) r (p) n [CI]	Response accuracy (%) r (p) n [CI]	RT correct responses (ms) r (p) n [CI]	Accuracy (%) r (p) n [CI]	Response accuracy (%) r (p) n [CI]	Completion time (ms) r (p) n [CI]	Recognition accuracy (%) r (p) n [CI]
Cross-sectional investigation									
Long COVID symptom load	−0.246 **(0.007)** 118	0.315 **(0.001)** 118	0.209 **(0.023)** 118	−0.273 **(0.003)** 115	0.368 **(<0.001)** 115	−0.220 **(0.013)** 126	−0.240 **(0.006)** 128	0.289 **(0.001)** 128	−0.253 **(0.004)** 126
	[−0.409, −0.068]	[0.142, 0.469]	[0.029, 0.376]	[−0.434, −0.095]	[0.198, 0.516]	[−0.380, −0.047]	[−0.397, −0.069]	[0.122, 0.440]	[−0.410, −0.082]
Longitudinal (within-subjects) investigation – cognitive function at study entry									
Long COVID symptom load	Cognitive function at study entry								
	−0.158 (0.422) 28	−0.062 (0.753) 28	0.043 (0.828) 28	−0.207 (0.290) 28	0.129 (0.513) 28	−0.175 (0.363) 29	−0.012 (0.950) 29	0.373 **(0.046)** 29	−0.157 (0.417) 29
	[−0.502, 0.229]	[−0.425, 0.318]	[−0.336, 0.410]	[−0.539, 0.180]	[−0.256, 0.479]	[−0.509, 0.205]	[−0.377, 0.356]	[0.008, 0.651]	[−0.495, 0.222]
	Pre-pandemic cognitive function								
	0.109 (0.573) 29	0.089 (0.644) 29	0.021 (0.912) 29	−0.075 (0.704) 28	0.079 (0.690) 28	0.104 (0.598) 28	−0.365 (0.052) 29	0.502 **(0.005)** 29	−0.378 **(0.043)** 29
	[−0.268, 0.457]	[−0.287, 0.441]	[−0.348, 0.385]	[−0.436, 0.307]	[−0.303, 0.439]	[−0.280, 0.459]	[−0.645, 0.002]	[0.166, 0.734]	[−0.654, −0.013]

Table 5. Associations (Pearson correlation coefficients) of the cognitive variables with health and well-being measures for the cross-sectional investigation

	Processing speed				Attention				Working memory				Executive function				Memory	
	Response accuracy (%) *r* (*p*)		RT correct responses (ms) *r* (*p*)		RT variability (SD of RT) *r* (*p*)		Response accuracy (%) *r* (*p*)		RT correct responses (ms) *r* (*p*)		Accuracy (%) *r* (*p*)		Response accuracy (%) *r* (*p*)		Completion time (ms) *r* (*p*)		Recognition accuracy (%) *r* (*p*)	
	COV + *n* = 119	COV−*n* = 91	COV + *n* = 119	COV−*n* = 91	COV + *n* = 119	COV−*n* = 91	COV + *n* = 116	COV−*n* = 89	COV + *n* = 116	COV−*n* = 89	COV + *n* = 127	COV−*n* = 90	COV + *n* = 129	COV−*n* = 90	COV + *n* = 129	COV−*n* = 90	COV + *n* = 127	COV−*n* = 93
Physical health status (SF-36)																		
Physical functioning	0.109 (0.238)	0.134 (0.205)	−0.317 **(<0.001)**	−0.123 (0.244)	−0.159 (0.085)	−0.224 **(0.033)**	0.132 (0.158)	−0.005 (0.961)	−0.368 **(<0.001)**	−0.065 (0.546)	0.230 **(0.009)**	0.137 (0.199)	0.248 **(0.005)**	0.066 (0.536)	−0.287 **(0.001)**	−0.042 (0.697)	0.213 **(0.016)**	0.003 (0.979)
Physical health	0.106 (0.253)	0.140 (0.186)	−0.190 **(0.039)**	0.022 (0.835)	−0.096 (0.297)	−0.026 (0.807)	0.046 (0.625)	−0.042 (0.695)	−0.304 **(0.001)**	−0.032 (0.766)	0.135 (0.131)	0.041 (0.704)	0.180 **(0.041)**	0.079 (0.459)	−0.122 (0.167)	−0.001 (0.993)	0.065 (0.465)	−0.027 (0.794)
Emotional problems	0.151 (0.101)	−0.018 (0.865)	−0.004 (0.963)	0.235 **(0.025)**	−0.058 (0.528)	0.159 (0.133)	0.009 (0.926)	−0.118 (0.271)	−0.100 (0.283)	0.219 **(0.040)**	0.021 (0.814)	0.093 (0.381)	0.242 **(0.006)**	−0.067 (0.531)	−0.079 (0.376)	0.197 (0.062)	0.112 (0.210)	−0.169 (0.106)
Energy/fatigue	0.093 (0.312)	0.160 (0.129)	−0.243 **(0.008)**	0.024 (0.823)	−0.119 (0.196)	−0.023 (0.827)	0.125 (0.182)	−0.033 (0.762)	−0.215 **(0.020)**	−0.058 (0.588)	0.065 (0.470)	0.101 (0.344)	0.126 (0.156)	0.071 (0.508)	−0.108 (0.225)	0.034 (0.752)	−0.021 (0.817)	0.023 (0.827)
Emotional well-being	0.095 (0.306)	0.183 (0.083)	−0.001 (0.988)	0.118 (0.265)	−0.049 (0.595)	−0.084 (0.426)	0.018 (0.848)	−0.038 (0.724)	−0.038 (0.685)	0.102 (0.343)	0.051 (0.570)	0.119 (0.263)	0.185 **(0.036)**	0.204 (0.053)	0.013 (0.883)	−0.062 (0.559)	−0.029 (0.747)	0.208 **(0.045)**
Social Functioning	0.150 (0.103)	0.131 (0.218)	−0.134 (0.145)	0.174 (0.099)	−0.066 (0.473)	−0.085 (0.423)	0.007 (0.942)	0.174 (0.103)	−0.169 (0.070)	0.125 (0.245)	0.234 **(0.008)**	0.157 (0.139)	0.241 **(0.006)**	0.169 (0.111)	−0.126 (0.155)	−0.077 (0.473)	0.076 (0.393)	0.011 (0.916)
Pain	0.174 (0.059)	0.163 (0.123)	−0.341 **(<0.001)**	−0.068 (0.523)	−0.239 **(0.009)**	−0.270 **(0.010)**	0.115 (0.219)	−0.037 (0.727)	−0.293 **(0.001)**	−0.041 (0.703)	0.205 **(0.021)**	0.083 (0.435)	0.182 **(0.039)**	0.148 (0.165)	−0.145 (0.101)	−0.145 (0.173)	0.168 (0.059)	−0.054 (0.609)
General health	0.069 (0.454)	0.149 (0.160)	−0.312 **(0.001)**	−0.115 (0.279)	−0.161 (0.081)	−0.160 (0.129)	0.116 (0.214)	0.027 (0.802)	−0.322 **(<0.001)**	−0.151 (0.157)	0.004 (0.965)	0.127 (0.234)	0.112 (0.205)	0.160 (0.131)	−0.086 (0.335)	−0.114 (0.285)	0.169 (0.058)	−0.022 (0.832)
Mental health (DASS-21)																		
Depression	−0.080 (0.384)	−0.088 (0.407)	0.003 (0.978)	−0.117 (0.269)	0.025 (0.786)	0.017 (0.872)	−0.017 (0.854)	0.017 (0.878)	0.030 (0.747)	−0.107 (0.319)	−0.181 **(0.042)**	−0.003 (0.977)	−0.172 **(0.052)**	−0.252 **(0.017)**	−0.025 (0.777)	0.068 (0.526)	0.042 (0.636)	−0.072 (0.494)
Anxiety	−0.178 **(0.053)**	−0.187 (0.076)	0.065 (0.485)	−0.116 (0.274)	0.121 (0.188)	−0.002 (0.834)	−0.113 (0.226)	−0.006 (0.959)	0.016 (0.861)	−0.076 (0.481)	−0.135 (0.129)	−0.091 (0.394)	−0.398 **(<0.001)**	−0.165 (0.119)	0.160 (0.071)	−0.033 (0.757)	−0.152 (0.088)	−0.027 (0.801)
Stress	−0.065 (0.482)	−0.129 (0.223)	−0.005 (0.959)	−0.116 (0.271)	0.008 (0.933)	0.108 (0.307)	−0.088 (0.350)	−0.048 (0.655)	−0.013 (0.888)	−0.114 (0.289)	−0.173 **(0.052)**	−0.023 (0.826)	−0.221 **(0.012)**	−0.264 **(0.012)**	0.012 (0.896)	0.138 (0.195)	0.009 (0.917)	−0.072 (0.490)
Sleep quality (PSQI)																		
Sleep quality	−0.172 (0.062)	−0.024 (0.823)	0.098 (0.289)	−0.087 (0.412)	0.167 (0.069)	0.019 (0.854)	−0.102 (0.274)	0.145 (0.175)	0.072 (0.440)	−0.037 (0.729)	−0.081 (0.363)	−0.034 (0.747)	−0.059 (0.506)	0.009 (0.930)	−0.078 (0.377)	0.019 (0.856)	0.039 (0.663)	0.192 (0.065)
Sleep latency	−0.080 (0.390)	0.033 (0.757)	0.133 (0.149)	−0.071 (0.504)	0.121 (0.190)	−0.049 (0.641)	−0.109 (0.242)	0.193 (0.069)	0.049 (0.601)	−0.147 (0.169)	−0.089 (0.319)	0.009 (0.931)	−0.051 (0.566)	−0.174 (0.100)	0.010 (0.908)	0.076 (0.477)	−0.064 (0.472)	0.141 (0.178)
Sleep duration	−0.145 (0.118)[a]	−0.114 (0.284)	0.001 (0.990)[a]	−0.091 (0.389)	0.069 (0.458)[a]	0.118 (0.264)	−0.050 (0.598)[a]	−0.059 (0.584)	0.089 (0.343)[a]	0.014 (0.900)	−0.155 (0.083)[a]	0.035 (0.744)	−0.135 (0.128)[a]	−0.040 (0.705)	0.025 (0.776)[a]	0.001 (0.989)	−0.189 **(0.035)**[a]	0.011 (0.915)
Sleep efficiency	−0.108 (0.251)[d]	−0.018 (0.870)[c]	0.157 (0.095)[d]	−0.181 (0.092)[c]	0.132 (0.162)[d]	−0.020 (0.856)[c]	−0.064 (0.505)[d]	0.103 (0.346)[c]	0.212 **(0.025)**[d]	0.117 (0.285)[c]	−0.047 (0.611)[d]	0.181 (0.094)[c]	0.048 (0.596)[d]	−0.076 (0.486)[c]	−0.033 (0.713)[d]	0.017 (0.874)[c]	−0.142 (0.118)[d]	0.149 (0.162)[c]
Sleep disturbance	−0.188 **(0.041)**	−0.117 (0.268)	0.262 **(0.004)**	0.123 (0.246)	0.143 (0.120)	0.156 (0.139)	−0.161 (0.083)	0.158 (0.140)	0.236 **(0.011)**	0.081 (0.449)	−0.110 (0.218)	−0.028 (0.794)	−0.190 **(0.031)**	−0.152 (0.152)	0.198 **(0.024)**	0.147 (0.165)	−0.150 (0.092)	0.099 (0.347)
Sleep medication	0.094 (0.316)[c]	0.056 (0.596)	0.146 (0.116)[c]	−0.034 (0.746)	−0.063 (0.498)[c]	−0.044 (0.680)	−0.084 (0.376)[c]	0.113 (0.291)	0.164 (0.082)[c]	−0.005 (0.965)	0.079 (0.383)[c]	0.119 (0.265)	−0.011 (0.906)[c]	−0.093 (0.383)	0.053 (0.553)[c]	0.002 (0.985)	−0.163 (0.069)[c]	−0.038 (0.718)
Daytime dysfunction	−0.110 (0.232)	−0.052 (0.623)	0.021 (0.817)	−0.046 (0.662)	0.004 (0.963)	−0.043 (0.687)	−0.010 (0.917)	0.088 (0.411)	0.079 (0.396)	−0.035 (0.747)	0.005 (0.958)	−0.022 (0.836)	−0.174 **(0.048)**	−0.046 (0.670)	0.042 (0.633)	−0.067 (0.530)	−0.061 (0.493)	0.135 (0.197)
Global PSQI score	−0.154 (0.094)	−0.028 (0.794)	0.195 **(0.034)**	−0.083 (0.435)	0.126 (0.173)	0.027 (0.801)	−0.118 (0.209)	0.159 (0.137)	0.212 **(0.022)**	−0.052 (0.631)	−0.090 (0.312)	0.050 (0.638)	−0.128 (0.148)	−0.105 (0.326)	0.050 (0.573)	0.040 (0.707)	−0.194 **(0.029)**	0.137 (0.192)

Table 5. *Continued*

	Processing speed			Attention		Working memory	Executive function		Memory
	Response accuracy (%) *r* (*p*)	RT correct responses (ms) *r* (*p*)	RT variability (SD of RT) *r* (*p*)	Response accuracy (%) *r* (*p*)	RT correct responses (ms) *r* (*p*)	Accuracy (%) *r* (*p*)	Response accuracy (%) *r* (*p*)	Completion time (ms) *r* (*p*)	Recognition accuracy (%) *r* (*p*)
	All *N* = 210	All *N* = 210	All *N* = 210	All *N* = 205	All *N* = 205	All *N* = 217	All *N* = 219	All *N*= 219	All *N* = 220
Physical health status (SF-36)									
Physical functioning	0.130 (0.060)	−0.289 **(<0.001)**	−0.243 **(<0.001)**	0.190 **(0.006)**	−0.324 **(<0.001)**	0.247 **(<0.001)**	0.152 **(0.024)**	−0.246 **(<0.001)**	0.189 **(0.005)**
Physical health	0.135 **(0.051)**	−0.166 **(0.016)**	−0.156 **(0.024)**	0.117 (0.096)	−0.260 **(<0.001)**	0.160 **(0.018)**	0.119 (0.079)	−0.120 (0.076)	0.088 (0.194)
Emotional problems	0.095 (0.170)	0.056 (0.417)	−0.013 (0.853)	0.017 (0.807)	−0.007 (0.920)	0.076 (0.267)	0.101 (0.138)	−0.014 (0.841)	0.023 (0.732)
Energy/fatigue	0.137 **(0.047)**	−0.180 **(0.009)**	−0.153 **(0.027)**	0.150 **(0.032)**	−0.216 **(0.002)**	0.135 **(0.047)**	0.092 (0.175)	−0.096 (0.158)	0.057 (0.403)
Emotional well-being	0.140 **(0.043)**	0.016 (0.820)	−0.099 (0.152)	0.042 (0.546)	−0.022 (0.757)	0.100 (0.140)	0.190 **(0.005)**	−0.029 (0.674)	0.090 (0.183)
Social functioning	0.156 **(0.024)**	−0.065 (0.350)	−0.137 **(0.048)**	0.118 (0.093)	−0.112 (0.110)	0.240 **(<0.001)**	0.196 **(0.004)**	−0.135 **(0.046)**	0.091 (0.181)
Pain	0.181 **(0.009)**	−0.277 **(<0.001)**	−0.300 **(<0.001)**	0.146 **(0.037)**	−0.255 **(<0.001)**	0.211 **(0.002)**	0.154 **(0.022)**	−0.169 **(0.012)**	0.129 (0.057)
General health	0.117 (0.092)	−0.266 **(<0.001)**	−0.211 **(0.002)**	0.144 **(0.039)**	−0.295 **(<0.001)**	0.093 (0.173)	0.128 (0.058)	−0.119 (0.079)	0.128 (0.058)
Mental health (DASS-21)									
Depression	−0.093 (0.177)	−0.020 (0.774)	0.053 (0.4434)	−0.038 (0.590)	0.003 (0.965)	−0.136 **(0.046)**	−0.207 **(0.002)**	0.020 (0.771)	−0.026 (0.698)
Anxiety	−0.190 **(0.006)**	0.017 (0.808)	0.093 (0.182)	−0.112 (0.110)	0.015 (0.834)	−0.142 **(0.036)**	−0.291 **(<0.001)**	0.116 (0.088)	−0.121 (0.073)
Stress	−0.095 (0.170)	−0.043 (0.533)	0.060 (0.385)	−0.082 (0.240)	−0.045 (0.520)	−0.123 (0.071)	−0.241 **(<0.001)**	0.057 (0.402)	−0.033 (0.624)
Sleep quality (PSQI)									
Sleep quality	−0.123 (0.076)	0.054 (0.436)	0.143 **(0.038)**	−0.069 (0.328)	0.068 (0.334)	−0.094 (0.167)	−0.029 (0.668)	−0.023 (0.741)	0.071 (0.296)
Sleep latency	−0.048 (0.486)	0.082 (0.234)	0.094 (0.175)	−0.064 (0.360)	0.015 (0.830)	−0.082 (0.226)	−0.109 (0.107)	0.054 (0.427)	−0.006 (0.934)
Sleep duration	−0.140 **(0.043)**[a]	−0.015 (0.827)[a]	0.112 (0.107)[a]	−0.069 (0.328)[a]	0.075 (0.286)[a]	−0.103 (0.133)[a]	−0.093 (0.170)[a]	0.028 (0.679)[a]	−0.120 (0.077)[a]
Sleep efficiency	−0.085 (0.226)[b]	0.077 (0.274)[b]	0.115 (0.101)[b]	−0.067 (0.345)[b]	0.134 (0.061)[b]	−0.020 (0.771)[b]	−0.011 (0.872)[b]	0.011 (0.868)[b]	−0.061 (0.376)[b]
Sleep disturbance	−0.171 **(0.013)**	0.233 **(0.001)**	0.183 **(0.008)**	−0.108 (0.124)	0.206 **(0.003)**	−0.113 (0.097)	−0.170 **(0.012)**	0.197 **(0.003)**	−0.081 (0.230)
Sleep medication	0.072 (0.304)[c]	0.104 (0.136)[c]	−0.029 (0.677)[c]	−0.062 (0.381)[c]	0.124 (0.077)[c]	0.065 (0.344)[c]	−0.040 (0.560)[c]	0.055 (0.417)[c]	−0.139 **(0.041)**[c]
Daytime dysfunction	−0.099 (0.151)	0.025 (0.719)	0.024 (0.731)	−0.025 (0.719)	0.074 (0.290)	−0.036 (0.595)	−0.118 (0.082)	0.030 (0.656)	−0.012 (0.862)
Global PSQI score	−0.118 (0.089)	0.123 (0.074)	0.141 **(0.041)**	−0.094 (0.181)	0.154 **(0.028)**	−0.085 (0.211)	−0.113 (0.095)	0.075 (0.267)	−0.093 (0.169)

Abbreviations: COV+, COVID group; COV−, Non-COVID group; DASS-21, The Depression, Anxiety and Stress Scale-21; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form Health Survey-36.

[a]Sample size reduced by 1.

[b]Sample size reduced by 7.

[c]Sample size reduced by 2.

[d]Sample size reduced by 5.

Table 6. Descriptive statistics and changes from pre-pandemic assessment (ANOVA results) in cognitive measures for the longitudinal investigation (sub-sample with pre-pandemic cognitive data)

		Time 1: Pre-COVID-19 pandemic Mean (SD)			Time 2: During COVID-19 pandemic Mean (SD)			ANOVA F(1,61) (*p*) η_p^2		
		COVID (*n* = 30)	Non-COVID (*n* = 33)	Total (*N* = 63)	COVID (*n* = 30)	Non-COVID (*n* = 33)	Total (*N* = 63)	Group effect	Time	Group × Time
Processing speed[a]	Response accuracy (%)	97.10	96.79	96.94	96.50	95.84	96.16	0.17 (0.681)	0.74 (0.393)	0.04 (0.846)
		(7.21)	(4.45)	(5.92)	(5.07)	(5.67)	(5.35)	*0.003*	*0.01*	*0.001*
	RT (correct responses, ms)	331.86	353.17	342.69	338.72	342.70	340.75	0.87 (0.354)	0.10 (0.748)	2.41 (0.126)
		(48.16)	(59.57)	(54.86)	(52.71)	(62.79)	(57.59)	*0.02*	*0.002*	*0.04*
	RT variability (SD of RT)	61.86	77.70	69.92	80.41	71.77	76.02	0.19 (0.667)	1.14 (0.291)	4.29 **(0.043)**
		(40.49)	(35.54)	(38.56)	(45.01)	(35.05)	(40.14)	*0.003*	*0.02*	*0.07*
Attention[b]	Response accuracy (%)	97.18	98.14	97.67	97.96	96.32	97.13	0.13 (0.722)	0.28 (0.599)	1.76 (0.190)
		(4.46)	(4.40)	(4.42)	(3.71)	(7.20)	(5.76)	*0.002*	*0.01*	*0.03*
	RT (correct responses, ms)	471.57	495.17	483.58	442.18	462.69	452.61	1.03 (0.314)	12.41 **(0.001)**	0.03 (0.861)
		(86.39)	(108.56)	(98.15)	(64.53)	(87.93)	(77.33)	*0.02*	*0.18*	*0.001*
Working memory[c]	Response accuracy (%)	92.81	94.35	93.58	95.66	95.80	95.73	0.361 (0.550)	4.78 **(0.033)**	0.51 (0.480)
		(9.22)	(6.28)	(7.86)	(4.47)	(5.05)	(4.73)	*0.01*	*0.08*	*0.01*
Executive function[d]	Accuracy (%)	97.00	96.03	96.50	97.20	94.78	95.95	2.09 (0.154)	0.33 (0.568)	0.62 (0.434)
		(4.64)	(6.30)	(5.53)	(4.06)	(7.57)	(6.20)	*0.03*	*0.01*	*0.01*
	Completion time (ms)	27173.43	32866.81	30111.95	26701.10	28917.69	27845.15	2.38 (0.128)	1.94 (0.168)	1.20 (0.277)
		(11,845.29)	(13,489.15)	(12,938.44)	(11,223.29)	(10,631.37)	(10,889.00)	*0.04*	*0.03*	*0.02*
Memory	Recognition accuracy (%)	90.38	90.16	90.27	90.57	91.23	90.92	0.02 (0.904)	0.37 (0.545)	0.18 (0.672)
		(7.92)	(6.83)	(7.31)	(7.54)	(10.25)	(9.00)	*0.0*	*0.01*	*0.003*

[a]Sample size reduced by 4 (1 COVID, 3 non-COVID).
[b]Sample size reduced by 6 (2 COVID, 4 non-COVID).
[c]Sample size reduced by 5 (1 COVID, 4 non-COVID).
[d]Sample size reduced by 1 (non-COVID).

symptoms in the longitudinal sample. Further noteworthy findings were: poorer physical and mental health in the COVID relative to non-COVID group; generally reduced psychological well-being in females, relative to males; and longer RTs with increasing age.

Concerning the cognitive impact of COVID-19, our findings indicated only a limited negative impact of COVID-19 history on cognitive function in UK adults <70 years, with only processing speed variability being impacted (with a small effect size) out of nine cognitive function indices examined in both the cross-sectional and longitudinal investigations. This is consistent with the findings of the UK Biobank data-based study [10] which found significant effects of COVID-19 on only 2 (Trails A and B completion time) out of 10 cognitive function indices examined. We did not detect the impact of COVID-19 as "slower speed" (including Trails B completion time) but rather a "more variable speed" on a task where speed was emphasised. Given that Douaud et al. [10] did not examine/report intra-individual variability in processing speed, the findings of their and our study combined suggest that intra-individual variability in speed might be relatively more sensitive to COVID-19 in people aged ≤69 years, since our sample had a wider age range of younger adults (18–69) compared to Douaud et al. [10] study's age range (51–81 years). Elevated intra-individual variability in RTs, reflecting momentary lapses in attention and/or task-irrelevant cognitions and a neural dysfunction involving multiple networks [25, 26], has also been shown to be a particularly sensitive measure in the context of ageing [27, 28], prediction of future cognitive outcomes [29], and various neurodegenerative diseases [30, 31]. A positive consideration here is that there may be scope for improving/reducing variability in processing speed using continuous cognitive training [32] or mindfulness-based approaches [33], given findings of a more stable performance in long-term meditators compared to meditation-naïve individuals [34], as well as other reports of improved processing speed following mindfulness practice [35, 36].

Against the backdrop of a limited general cognitive impact of COVID-19, our findings suggest reduced cognitive function across multiple domains in people who needed hospitalisation due to COVID-19. This is consistent with recent literature suggesting that brain and cognitive impairment may be more salient in people with a severe infection [37] or hospitalisation [38], highlighting the need for longitudinal cognitive monitoring and improvement efforts in such cohorts [39], for example using non-invasive brain stimulation [40, 41]. Furthermore, we found sizable associations between overall long-COVID symptom load and cognitive function across all domains, suggesting that affected individuals may also benefit from longitudinal cognitive monitoring and rehabilitation efforts. Interestingly, further to previous literature linking poorer cognitive function to greater acute COVID-19 severity and hospitalisation [9], our finding suggests that poorer cognitive function (executive function, memory) may also be a precursor of long-COVID symptoms. Taken together, our findings indicate that at least a part of COVID-19-related cognitive impairment in cross-sectional studies may reflect reduced pre-infection cognitive level (for various other reasons); and that the most robust short-to-medium impact of COVID-19 may be limited to a more variable processing speed. Follow-up assessments of our and other samples are crucially needed to fully chart the cognitive trajectory of COVID-19 and long-COVID.

Our further findings confirmed poorer mental health and well-being in COVID-19 survivors [3, 42] and suggest that this may continue for some time post-infection. In addition, sex differences (across groups) were observed with women reporting poorer mental health and well-being, which is also in line with previous literature on sex differences in affective disorders [43]. Lastly, our finding of longer RTs with increasing age is consistent with previous literature [44].

The limitations of the present study include: (i) most participants being White-British, limiting generalisability of the findings; (ii) significantly older participants, on average, in the COVID than non-COVID groups (due to the open recruitment strategy), though all COVID-related effects were sustained when covarying for age; and (iii) a reliance on self-report for COVID-19 diagnosis, which cannot rule out that at least some non-COVID group participants may have been pre-symptomatic when assessed. Future research should include more ethnically-diverse samples with consideration to the impact of socio-economic factors and, importantly, assess cognitive function at numerous times post-infection to understand the potential long-term cognitive recovery, especially in association with varying levels of long-COVID symptoms [45, 46].

Conclusions

We observed a limited cognitive impact of COVID-19 with only intra-individual variability in processing speed being significantly affected (becoming less stable) in an adult UK sample. However, those who required COVID-19-related hospitalisation, did display multifaceted cognitive impairment. Furthermore, long-COVID symptoms were associated with reduced cognitive function (assessed post-COVID-19 diagnosis) but also with poorer executive function and memory prior to the COVID-19 pandemic, suggesting that poorer cognitive function may be a precursor of long-COVID symptoms. Further research is required to understand whether COVID-19 and long-COVID continue to impede cognitive function over a longer period of time.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1192/j.eurpsy.2023.25.

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Cognitive and mental health trajectories of COVID-19: Role of hospitalisation and long-COVID symptoms

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Abstract

Background. There is considerable evidence of cognitive impairment post COVID-19, especially in individuals with long-COVID symptoms, but limited research objectively evaluating whether such impairment attenuates or resolves over time, especially in young and middle-aged adults.

Methods. Follow-up assessments (T2) of cognitive function (processing speed, attention, working memory, executive function, memory) and mental health were conducted in 138 adults (18–69 years) who had been assessed 6 months earlier (T1). Of these, 88 had a confirmed history of COVID-19 at T1 assessment (≥20 days post-diagnosis) and were also followed-up on COVID-19-related symptoms (acute and long-COVID); 50 adults had no known COVID-19 history at any point up to their T2 assessment.

Results. From T1 to T2, a trend-level improvement occurred in intra-individual variability in processing speed in the COVID, relative to the non-COVID group. However, longer response/task completion times persisted in participants with COVID-19-related hospitalisation relative to those without COVID-19-related hospitalisation and non-COVID controls. There was a significant reduction in long-COVID symptom load, which correlated with improved executive function in non-hospitalised COVID-19 participants. The COVID group continued to self-report poorer mental health, irrespective of hospitalisation history, relative to non-COVID group.

Conclusions. Although some cognitive improvement has occurred over a 6-month period in young and middle-aged COVID-19 survivors, cognitive impairment persists in those with a history of COVID-19-related hospitalisation and/or long-COVID symptoms. Continuous follow-up assessments are required to determine whether cognitive function improves or possibly worsens, over time in hospitalised and long-COVID participants.

Introduction

Since the start of the coronavirus disease 2019 (COVID-19) pandemic, a vast amount of literature has acknowledged the psychological issues and cognitive disruption experienced by survivors [1–6]. Living with COVID-19 has become the new normal, yet there is still uncertainty around the longer-term effects of COVID-19 on physical and mental well-being, given marked between-study variability in the proportion of survivors reporting cognitive and mental health impairments post-acute infection [7]. In a recent review [8], 21–65% of adults with long-COVID symptoms (≥12 weeks) were found to have some level of cognitive impairment, while another review [9] reported poor mental health for up to 6 months post a COVID-19 diagnosis. It is unclear at present whether COVID-19-related cognitive impairment and psychological symptoms attenuate or resolve over time and, if so, how long after a COVID-19 diagnosis an improvement can be seen, especially in young and middle-aged adults.

Previous studies have suggested some improvement in cognitive function [10–15] and psychological well-being [16], especially at longer (≥6 months) follow-ups, but these mostly examined older adults (mean age >50 years) [10, 11, 15, 16] and focused on severely ill or hospitalised COVID-19 patients [12–15]. As these groups are likely to need longer to recover from COVID-19 and its adverse cognitive and mental health impacts, with possible co-morbidities exacerbating and/or complicating post-COVID recovery, their findings may not generalise to working-age adults in the general population. A recent study [17] involving a large sample, though again with an over-representation of middle age adults (≥50 years), showed persistent cognitive deficits at about 2 years post-infection, especially in individuals who had experienced the symptoms for ≥12 weeks and/or a severe infection, or were experiencing ongoing symptoms. Encouragingly, the sub-group of adults who self-reported a full recovery showed no

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such deficits [17]. There is clearly a need for further work to fully characterise the cognitive trajectory of COVID-19 in survivors with varying levels of symptoms and younger age groups.

In our recent study [18] investigating the impact of COVID-19 on cognitive function and mental health in a working-age sample (mean age: 38.70 ± 12.08), we had found a limited cognitive impact of COVID-19 diagnosis, with only intra-individual variability in processing speed being significantly increased in COVID-19 survivors, compared to non-COVID controls. There was, however, multifaceted cognitive impairment in association with long-COVID symptoms. Mental health and sleep quality were also worse in COVID-19 survivors, relative to non-COVID controls. Here, with a further assessment (6-month follow-up) of this previously assessed sample [18], we aimed to examine: (i) the longitudinal impact of COVID-19 on cognitive function, mental health, and sleep, first, on average, and then classified by COVID-19-related hospitalisation; and (ii) changes in long-COVID symptom load and their association with cognitive function, mental health and well-being at 6 months post the initial assessment. Based on previous findings [10–12, 14, 16, 19], we predicted: (i) a change towards normalisation of cognitive function, mental health, and sleep from study entry (T1) [18] to the 6-month follow-up (T2) assessments, on average, in the COVID group, relative to non-COVID group, and (ii) persistently impaired cognitive function, mental health, and sleep in participants with a history of COVID-19-related hospitalisation and/or ongoing long-COVID symptoms.

Methods

Participants and design

The sample consists of 138 of 222 adults who had been assessed 6 months earlier (T1; March 2021–March 2022) for our previous study investigating the cognitive impact of COVID-19 in working-age UK adults [18]. Of 222 participants (129 with and 93 without a history of COVID diagnosis) assessed at T1 [18], 71 (41 COVID, 30 non-COVID) were lost to the follow-up, and 13 non-COVID (at T1) participants were excluded due to them having tested COVID-19 positive between T1 and T2, leaving 138 participants (mean age: 39.72 ± 11.81) for this investigation (re-assessed at T2; September 2021–October 2022) (see Figure 1). Of these 138 participants (current sample), 88 had a history of COVID-19 diagnosis (14 males, 74 females; mean days since diagnosis: 459 ± 180.84; range: 163–895) (to be referred to as the "COVID group") and 50 had no known history of COVID-19 (11 males, 39 females; to be referred to as the "non-COVID group").

The study was approved by the College of Health, Medicine and Life Sciences Research Ethics Committee, Brunel University London (26518-A-Sep/2021-34167-1). All participants provided informed written consent and received £10 (Amazon voucher) for their time.

Measures and procedures

As described in Vakani et al. [18], data on demographics, mental health, and sleep were collected using self-report measures administered via Qualtrics (an online survey tool), taking ˜45 minutes in total to complete. Additionally, the COVID groups were asked to detail their COVID-19 diagnosis, acute symptoms at the time of infection, subjective psychological well-being and cognitive impairment, and chronic long-COVID symptoms at both T1 and T2. Cognitive data (T1 and T2) were collected using the self-administered MyCognition [20] (MyCQ) PRO mobile application, taking ˜15 minutes to complete.

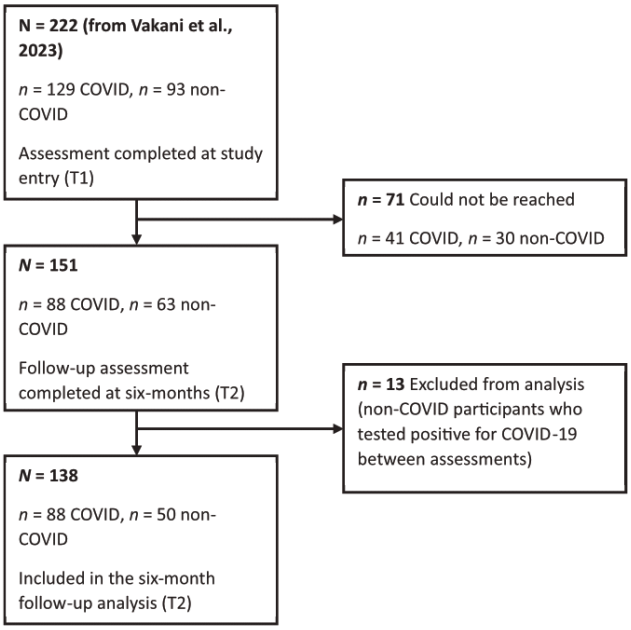

Figure 1. Study flowchart.

Assessments

Cognitive function

The MyCQ mobile application tool (approved by the National Health Service in the UK) assesses processing speed, attention, working memory, executive function, and memory domains, using digital versions of commonly utilised neuropsychological tests validated against the Cambridge Neuropsychological Automated Test Battery [21–23]. As described previously [18], *Processing Speed* was assessed using a simple reaction time (RT) task, *Attention* using a choice RT task, *Working Memory* using the 2-back task, *Executive Function* using the Trail-Making B task, and memory was assessed using a visual recognition memory task (for further details, see Table 1).

Mental health and sleep

The following two self-report scales were used:

The Depression, Anxiety and Stress Scale-21 [24] assessed depression, anxiety, and stress with corresponding seven-item sub-scales. Each item is rated by participants on a four-point scale according to how often in the past week it applied to them. Higher scores indicate higher levels (severity) of symptoms. Internal consistency for all sub-scales was good-to-excellent (Cronbach's $a \geq 0.82$) in this sample.

Pittsburgh Sleep Quality Index (PSQI) [25] assessed daytime dysfunction, use of sleeping medication, sleep disturbances, habitual sleep efficiency, sleep duration, sleep latency, and subjective sleep score (scores are derived for component, plus a global score). Participants respond to the PSQI items by relating them to their past month. Higher scores indicate lower sleep quality. The PSQI had an acceptable internal consistency (global score, Cronbach's $a = 0.76$) in this sample.

Statistical analysis

We first examined the demographic and other characteristics of study participants who provided both T1 and T2 data ($n = 138$) versus those with only T1 data ($n = 84$; not included in any further analysis), out of 222 participants from Vakani et al. [18], to

Table 1. Cognitive domains, tests, and indices examined through MyCognition's mobile application

Cognitive domains	Cognitive test	Cognitive performance indices
Processing speed	Simple reaction time (RT)	RA (% correct), average RT (ms), RT variability
Attention	Choice RT	RA (% correct), average RT (ms)
Working memory	2-Back	RA (% correct)
Executive function	Trail-making B	RA (% correct moves), total completion time (ms)
Memory	Visual recognition memory	RA (% correct)

Abbreviations: ms, milliseconds; RA, response accuracy; RT, reaction time.

determine if there were any factors associated with non-volunteering (especially in the COVID group) for T2 assessment.

Next, to examine possible changes from T1 to T2 in the COVID group ($n = 88$), relative to those in the non-COVID group ($n = 50$), we used a 2 (Group: COVID, non-COVID) × 2 (Time: T1, T2) repeated-measures analysis of variance (ANOVA), separately for each cognitive variable, with Group as a between-subjects factor and Time as a within-subjects factor. To examine possible differences in cognitive and mental health changes of hospitalised versus non-hospitalised COVID participants, we conducted 3 (Group$^{\text{Hospitalisation: Hospitalised}}$COVID, $^{\text{Non-hospitalised}}$COVID, non-COVID) × 2 (Time: T1, T2) repeated-measures ANOVAs; and confirmed any significant main or interaction effects after co-varying for age, given a trend-level age difference between hospitalised and non-hospitalised participants (see Results). To examine a change from T1 to T2 in total long-COVID symptom load (a sum of all symptom ratings), we ran a 2 (Hospitalisation: $^{\text{Hospitalised}}$COVID, $^{\text{Non-hospitalised}}$COVID) × 2 (Time: T1, T2) ANOVA with Hospitalisation as a between-subjects factor and Time as a within-subjects factor, co-varying for age. All ANOVAs were initially conducted with Sex entered as another between-subjects factor but Sex was then removed, as there were no main or interactive effects involving Sex, and the current sample has a relatively smaller number of males. Significant main effects and interactions from ANOVAs were followed up with the analysis of simple main effects and post hoc comparisons, as appropriate. Effect sizes, where reported, are partial eta squared (η_p^2; the proportion of variance associated with a factor). Finally, the relationship between changes (T1 to T2) in total long-COVID symptom load and cognitive function was examined using Pearson correlations.

All analyses were performed using the Statistical Package for Social Sciences (version 28; IBM, New York, USA). The data distribution on all variables met the assumptions of parametric statistical procedures. Alpha level for testing the significance of effects was maintained at $p \leq 0.05$.

Results

Sample characteristics

About two-thirds (62%) of the sample with T1 assessments ($n = 222$) [18] provided T2 data ($n = 138$) (Figure 1). Fifteen (75%) of 20 participants with a history of hospitalisation at T1 also provided T2 data. There was no age difference [$t(206) = 0.36$, $p = 0.72$] between the groups with both T1 and T2 assessments and only T1 assessment. Other characteristics were also comparable for these (T1 and T2, T1 only) groups (Supplementary Table S1). COVID participants who completed both assessments versus those with only T1 assessment also had comparable demographics, COVID-related symptoms (Supplementary Tables S1 and S2), as well as cognitive and mental health characteristics (Supplementary Table S3).

For the current sample, there was no significant difference in age [$t(136) = 1.66$, $p = 0.10$] or BMI [$t(136) = 1.66$, $p = 0.10$] between the COVID ($n = 88$) and non-COVID groups ($n = 50$) (Table 2; for demographics, see Supplementary Table S4). $^{\text{Hospitalised}}$COVID participants ($n = 15$) had a higher prevalence of most long-COVID symptoms (Supplementary Table S2) and were also non-significantly older compared to $^{\text{Non-hospitalised}}$COVID participants ($n = 73$) [$t(86) = 1.75$, $p = 0.08$] (Supplementary Table S5).

Cognitive function: Changes from T1 to T2

COVID versus non-COVID participants

For processing speed, we observed a significant Group × Time interaction in intra-individual RT variability [$F(1,126) = 3.77$, $p = 0.05$, $\eta_p^2 = 0.03$] (Table 3). Follow-up analysis showed significantly larger RT variability in the COVID group compared to the non-COVID group at T1 [$t(126) = 2.63$, $p = 0.01$], but not at T2 [$t(126) = 0.44$, $p = 0.67$]. From T1 to T2, there was a trend-level improvement in the COVID group [$t(78) = 1.92$, $p = 0.06$], with comparable T1 and T2 scores (i.e., no change) in the non-COVID group [$t(48) = 0.99$, $p = 0.33$] (Table 3; Figure 2).

For attention, there was only a main effect of Group in RTs [$F(1,123) = 4.67$, $p = 0.03$, $\eta_p^2 = 0.04$], showing slower RTs on both occasions in the COVID group, relative to the non-COVID group (Table 3).

For working memory, executive function, and memory tasks, no significant main effects or interactions were found.

The influence of COVID-19-related hospitalisation history

For processing speed, there were main effects of Group$^{\text{Hospitalisation}}$ for both average RTs [$F(2,125 = 3.71$, $p = 0.03$, $\eta_p^2 = 0.06$] and RT variability [$F(2,125 = 3.33$, $p = 0.04$, $\eta_p^2 = 0.05$]. Follow-up analysis of RTs showed significantly larger RTs in the $^{\text{Hospitalised}}$COVID group relative to the $^{\text{Non-hospitalised}}$COVID group [$F(1,77) = 3.87$, $p = 0.05$, $\eta_p^2 = 0.05$; age co-varied: $F(1,76) = 3.36$, $p = 0.07$, $\eta_p^2 = 0.04$], as well as the non-COVID group [$F(1,60 = 8.44$, $p = 0.005$, $\eta_p^2 = 0.12$; age co-varied: $F(1,59 = 6.76$, $p = 0.01$, $\eta_p^2 = 0.10$]. The $^{\text{Non-hospitalised}}$COVID and non-COVID groups did not differ from each other [$F(1,113 = 1.24$, $p = 0.27$, $\eta_p^2 = 0.01$] (Table 4). Follow-up analysis of processing speed RT variability showed that the $^{\text{Hospitalised}}$COVID group had larger RT variability compared to the non-COVID group [$F(1,60 = 8.62$, $p = 0.005$, $\eta_p^2 = 0.01$; age co-varied: $F(1,59 = 6.83$, $p = 0.01$, $\eta_p^2 = 0.10$] but not the $^{\text{Non-hospitalised}}$COVID group [$F(1,77) = 2.63$, $p = 0.11$, $\eta_p^2 = 0.03$; age co-varied: $F(1,76) = 2.46$, $p = 0.12$, $\eta_p^2 = 0.03$] (Table 4). There was no significant difference between the $^{\text{Non-hospitalised}}$COVID and non-COVID groups [$F(1,113 = 1.80$, $p = 0.18$, $\eta_p^2 = 0.02$].

Table 2. Comparison of T1 and T2 characteristics for the current sample (*N* = 138), classified by group

		COVID group (*n* = 88; 14 M, 74 F)		Non-COVID group (*n* = 50; 11 M, 39 F)	
		T1	T2	T1	T2
		Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Age (years)		40.47 (10.55)	40.97 (10.42)	37.04 (13.71)	37.52 (13.76)
BMI		28.94 (9.98)	30.13 (12.26)	26.58 (7.03)	26.99 (7.00)
		n (% of Total)	*n* (% of Total)	*n* (% of Total)	*n* (% of Total)
Physical health conditions	Cancer	3 (3.4%)	3 (3.4%)	0 (0%)	0 (0%)
	Diabetes	7 (8.0%)	6 (6.8%)	5 (10.0%)	3 (6.0%)
	Heart condition	4 (4.5%)	8 (9.1%)	2 (4.0%)	2 (4.0%)
	Immunosuppressed	7 (8.0%)	8 (9.1%)	0 (0%)	0 (0%)
	Kidney disease	1 (1.1%)	1 (1.1%)	0 (0%)	0 (0%)
	Liver disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Lung condition	18 (20.5%)	20 (22.7%)	4 (8.0%)	5 (10.0%)
	Neurological condition	5 (5.7%)	10 (11.4%)	0 (0%)	0 (0%)
	Obesity	12 (13.6%)	10 (11.4%)	5 (10.0%)	3 (6.0%)
	Organ transplantation	1 (1.1%)	1 (1.1%)	0 (0%)	0 (0%)
Mental health conditions	Anorexia nervosa	1 (1.1%)	1 (1.1%)	1 (2.0%)	1 (2.0%)
	Anxiety	38 (43.2%)	38 (43.2%)	19 (38.0%)	18 (36.0%)
	ADHD	3 (3.4%)	3 (3.4%)	1 (2.0%)	2 (4.0%)
	Depression	33 (37.5%)	32 (36.4%)	14 (28.0%)	14 (28.0%)
	Eating disorder(s)	7 (8.0%)	6 (6.8%)	2 (4.0%)	1 (2.0%)
	Insomnia	21 (23.9%)	24 (27.3%)	5 (10.0%)	6 (12.0%)
	OCD	4 (4.5%)	6 (6.8%)	2 (4.0%)	2 (4.0%)
	Panic disorder	7 (8.0%)	8 (9.1%)	5 (10.0%)	5 (10.0%)
	Personality disorder	3 (3.4%)	3 (3.4%)	1 (2.0%)	1 (2.0%)
	Phobias	6 (6.8%)	9 (10.2%)	6 (12.0%)	3 (6.0%)
	PTSD	12 (13.6%)	10 (11.4%)	3 (6.0%)	3 (6.0%)
	Psychosis	1 (1.1%)	1 (1.1%)	1 (2.0%)	1 (2.0%)
	Schizophrenia	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)
	Other	2 (2.3%)	3 (3.4%)	0 (0%)	1 (2.0%)

Abbreviations: ADHD, attention–deficit hyperactivity disorder; BMI, body mass index; F, females; M, males; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder.

For attention task RTs, there was a main effect of Group$^{\text{Hospitalisation}}$ [$F(2,122 = 7.54$, $p = 0.001$, $\eta_p^2 = 0.11$], with larger RTs in the $^{\text{Hospitalised}}$COVID group relative to the $^{\text{Non-hospitalised}}$COVID group [$F(1,75) = 9.60$, $p = 0.003$, $\eta_p^2 = 0.11$; age co-varied: $F(1,74) = 10.01$, $p = 0.002$, $\eta_p^2 = 0.12$] as well as the non-COVID group [$F(1,58 = 15.95$, $p < 0.001$, $\eta_p^2 = 0.22$; age co-varied: $F(1,57 = 14.23$, $p < 0.001$, $\eta_p^2 = 0.20$]. There was no difference between the $^{\text{Non-hospitalised}}$COVID and non-COVID groups [$F(1,111 = 1.82$, $p = 0.18$, $\eta^{p2} = 0.02$] (Table 4).

For working memory (RA, %), there was only a marginally significant main effect of Time [$F(1,131) = 3.98$, $p = 0.05$, $\eta_p^2 = 0.03$; higher RA at T2 than T1], which became non-significant after co-varying for age [$F(1,130) = 3.09$, $p = 0.08$, $\eta_p^2 = 0.02$] (Table 4).

For executive function, there was a main effect of Group$^{\text{Hospitalisation}}$ in task completion time (ms) [$F(2,133 = 3.91$, $p = 0.02$, $\eta_p^2 = 0.06$], explained by longer completion time (across T1 and T2) in $^{\text{Hospitalised}}$COVID group relative to both the $^{\text{Non-hospitalised}}$COVID [$F(1,85) = 6.72$, $p = 0.011$, $\eta_p^2 = 0.07$; age co-varied: $F(1,84) = 6.11$, $p = 0.02$, $\eta_p^2 = 0.07$] and non-COVID [$F(1,62 = 4.15$, $p = 0.046$, $\eta_p^2 = 0.06$; age co-varied: $F(1,61 = 2.30$, $p = 0.14$, $\eta_p^2 = 0.04$] groups. There was no difference between the $^{\text{Non-hospitalised}}$COVID and non-COVID groups [$F(1,119 = 0.61$, $p = 0.69$, $\eta_p^2 = 0.001$].

For memory tasks, no significant main effects or interactions were found (Table 4).

Mental health and sleep: Changes from T1 to T2

COVID versus non-COVID participants

There were significant main effects of Group in depression [$F(1,136) = 5.09$, $p = 0.03$, $\eta_p^2 = 0.04$], anxiety [$F(1,136) = 5.89$, $p = 0.02$, $\eta_p^2 = 0.04$], and overall sleep quality [$F(1,136) = 26.49$, $p < 0.001$, $\eta_p^2 = 0.16$]. The COVID group had significantly higher depression and anxiety and lower sleep quality (PSQI) compared to

Table 3. Descriptive statistics and results of the repeated-measures Group (COVID, non-COVID) × Time (T1, T2) analysis of variance (ANOVA) on cognitive measures

		COVID group (n = 88)		Non-COVID group (n = 50)		Group (COVID, non-COVID) × Time (T1, T2) ANOVA results											
		T1: Study entry	T2: 6-month follow-up	T1: Study entry	T2: 6-month follow-up	Group				Time				Group × Time			
		Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2
Processing speed[a]	Response accuracy (%)	95.76 (6.30)	96.71 (4.47)	95.78 (7.60)	96.41 (4.31)	0.03	1,126	0.87	*0.0*	1.65	1,126	0.20	*0.01*	0.07	1,126	0.80	*0.001*
	RT (correct responses, ms)	376.51 (80.83)	367.54 (86.94)	354.71 (79.94)	345.90 (50.58)	2.84	1,126	0.09	*0.02*	2.29	1,126	0.13	*0.02*	0.0	1,126	0.99	*0.0*
	RT variability (SD of RT)	88.54 (40.89)	78.27 (42.53)	70.04 (34.67)	75.24 (29.97)	3.51	1,126	0.06	*0.03*	0.41	1,126	0.53	*0.003*	3.77	1,126	**0.05**	*0.03*
Attention[b]	Response accuracy (%)	95.36 (8.79)	95.02 (9.42)	97.71 (4.48)	95.64 (6.38)	1.55	1,123	0.22	*0.01*	2.06	1,123	0.15	*0.02*	1.05	1,123	0.31	*0.01*
	RT (correct responses, ms)	490.53 (92.15)	494.69 (114.00)	463.52 (92.97)	450.40 (87.67)	4.67	1,123	**0.03**	*0.04*	0.35	1,123	0.56	*0.003*	1.29	1,123	0.26	*0.01*
Working memory[c]	Response accuracy (%)	92.44 (8.48)	93.53 (7.03)	92.98 (7.83)	94.31(6.14)	0.33	1,132	0.57	*0.002*	2.79	1,132	0.10	*0.02*	0.03	1,132	0.87	*0.0*
Executive function[d]	Accuracy (%)	94.48 (7.48)	94.32 (9.02)	95.11 (8.50)	92.56 (12.74)	0.19	1,134	0.66	*0.001*	1.72	1,134	0.19	*0.01*	1.34	1,134	0.25	*0.01*
	Completion time (ms)	33692.22 (22321.50)	32263.90 (23740.74)	29556.16 (9761.48)	33450.29 (31759.02)	0.17	1,134	0.68	*0.001*	0.37	1,134	0.54	*0.003*	1.74	1,134	0.19	*0.01*
Memory[e]	Recognition accuracy (%)	89.95 (9.11)	92.05 (6.38)	92.30 (7.50)	92.56 (6.17)	1.60	1,135	0.21	*0.01*	2.78	1,135	0.10	*0.02*	1.71	1,135	0.19	*0.01*

Abbreviations: ms, milliseconds; RT, reaction time.
Sample size reduced [a]by 10 (9 COVID, 1 non-COVID), [b]by 13 (11 COVID, 2 non-COVID), [c]by 4 (1 COVID, 3 non-COVID), [d]by 2 (1 COVID, 1 non-COVID), [e]by 1 (COVID).

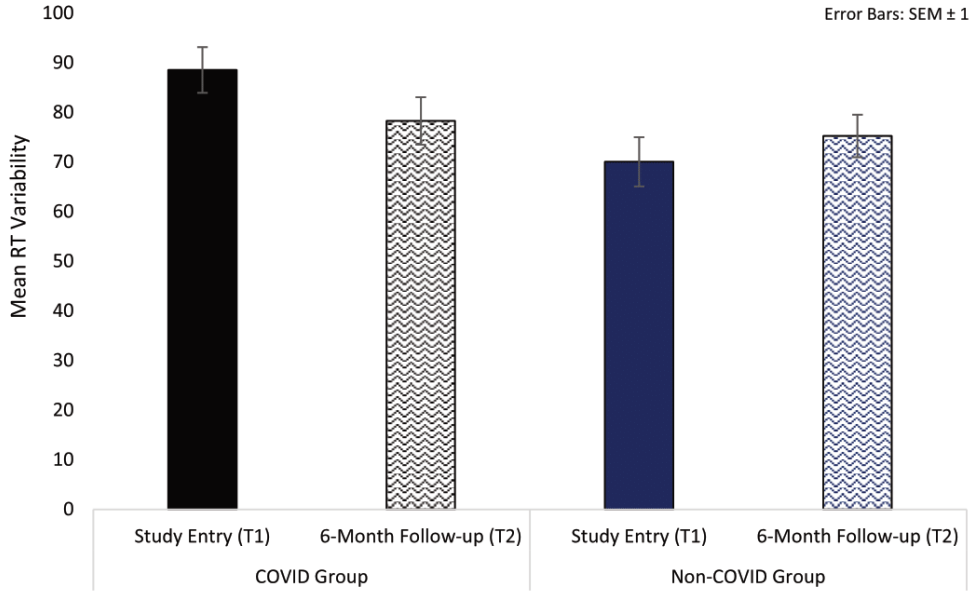

Figure 2. Processing speed reaction time (RT) variability in COVID and non-COVID groups at study entry (T1) and 6-month follow-up (T2).

the non-COVID group. Additionally, there was a main effect of Time for depression [$F(1,136) = 4.73, p = 0.03, \eta_p^2 = 0.03$] explained by lower depression at T2 relative to T1 in both groups (Table 5). No significant effects (only trends) were found for stress.

The influence of COVID-19-related hospitalisation history

For depression, there was a main effect of Group$^{\text{Hospitalisation}}$ [$F(2,134) = 2.99, p = 0.05, \eta_p^2 = 0.04$], with no difference between the $^{\text{Non-hospitalised}}$COVID and $^{\text{Hospitalised}}$COVID groups [$F(1,86) = 0.19, p = 0.67, \eta_p^2 = 0.002$] but a trend for higher depression in both $^{\text{Non-hospitalised}}$COVID [$F(1,121) = 3.99, p = 0.05, \eta_p^2 = 0.03$; age co-varied: $F(1,120) = 4.35, p = 0.04, \eta_p^2 = 0.04$] and $^{\text{Hospitalised}}$COVID [$F(1,63) = 3.69, p = 0.06, \eta_p^2 = 0.06$; age co-varied: $F(1,62) = 3.65, p = 0.06, \eta_p^2 = 0.06$] COVID groups, relative to the non-COVID group (Table 6). There was also a trend-level Group$^{\text{Hospitalisation}}$ × Time interaction [$F(2,134) = 2.67, p = 0.07, \eta_p^2 = 0.04$], explained by a significant reduction (T1 to T2) in depression in the $^{\text{Non-hospitalised}}$COVID group [$t(72) = 3.31, p = 0.001$], but no significant change in the $^{\text{Hospitalised}}$COVID [$t(14) = 0.68, p = 0.51$] or non-COVID [$t(49) = 0.54, p = 0.59$] groups (Table 6).

For anxiety, there was a main effect of Group$^{\text{Hospitalisation}}$ [$F(2,134) = 4.13, p = 0.02, \eta_p^2 = 0.06$], with both $^{\text{Hospitalised}}$COVID [$F(1,63) = 3.93, p = 0.05, \eta_p^2 = 0.06$; age co-varied: $F(1,62) = 3.89, p = 0.05, \eta_p^2 = 0.06$] and $^{\text{Non-hospitalised}}$COVID [$F(1,121) = 4.85, p = 0.03, \eta_p^2 = 0.04$; age co-varied: $F(1,120) = 6.23, p = 0.01, \eta_p^2 = 0.05$] groups showing higher anxiety relative to the non-COVID group (Table 6). No difference was found between the $^{\text{Non-hospitalised}}$COVID and $^{\text{Hospitalised}}$COVID groups [$F(1,86) = 0.12, p = 0.73, \eta_p^2 = 0.001$].

Finally, there was a main effect of Group$^{\text{Hospitalisation}}$ in sleep quality [$F(2,134 = 13.28, p < 0.001, \eta_p^2 = 0.17$], with a lower sleep quality in both $^{\text{Non-hospitalised}}$COVID [$F(1,121 = 21.69, p < 0.001, \eta_p^2 = 0.15$; age co-varied: $F(1,120 = 21.05, p < 0.001, \eta_p^2 = 0.15$] and $^{\text{Hospitalised}}$COVID [$F(1,63 = 18.60, p < 0.001, \eta_p^2 = 0.23$; age co-varied: $F(1,62 = 15.29, p < 0.001, \eta_p^2 = 0.20$] groups, relative to the non-COVID group. The $^{\text{Non-hospitalised}}$COVID and $^{\text{Hospitalised}}$COVID groups did not differ from each other [$F(1,86 = 1.64, p = 0.20, \eta_p^2 = 0.02$] (Table 6).

Long-COVID symptoms: Change from T1 to T2 in COVID participants

A similar pattern of self-reported long-COVID symptoms, with exhaustion and mild cognitive problems being the most prevalent, was seen at T1 and T2 (Figure 3), especially in the $^{\text{Hospitalised}}$COVID group (Supplementary Table S2).

Total long-COVID symptom load showed a main effect of Time [$F(1,79) = 4.86, p = 0.03, \eta_p^2 = 0.06$) and, importantly, a Hospitalisation × Time interaction [$F(1,79) = 5.18, p = 0.03, \eta_p^2 = 0.06$], explained by a marked reduction (T1 to T2) in symptom load in $^{\text{Non-hospitalised}}$COVID [$t(67) = 5.25, p < 0.001$] but not in $^{\text{Hospitalised}}$COVID participants [$t(13) = 0.49, p = 0.63$] (Figure 4). Long-COVID symptom load did not correlate significantly with the number of days since diagnosis [$r(82) = 0.16, p = 0.15$].

Long-COVID symptoms, cognitive indices, and mental health: Inter-relationships

Higher long-COVID symptom load was associated with poorer performance on most cognitive indices (Table 7). The reduction in symptom load from T1 to T2 correlated significantly with an improvement in executive function RA (%) when examined across all COVID participants ($p = 0.03$), and in $^{\text{Non-hospitalised}}$COVID participants ($p = 0.003$) (Table 7).

Across all participants, the reduction in long-COVID symptom load also correlated with a reduction in depression ($p = 0.003$), anxiety ($p < 0.001$), stress ($p = 0.01$), and improved sleep quality ($p = 0.01$); these associations were generally stronger in $^{\text{Hospitalised}}$COVID (r values 0.36 to 0.66) relative to $^{\text{Non-hospitalised}}$COVID participants ($r$ values 0.20 to 0.42) (Table 7). Improved sleep quality correlated with an improvement in memory ($r = 0.19, p = 0.03$); other mental health/sleep and cognition changes associations, though in the expected direction, were non-significant (Supplementary Table S6).

Table 4. Descriptive statistics and results of the repeated-measures Group^{Hospitalisation} (^{Hospitalised}COVID, $^{Non\text{-}hospitalised}$COVID, non-COVID) × Time (T1, T2) analysis of variance (ANOVA) on cognitive measures

			^{Hospitalised}COVID group (n = 15)		$^{Non\text{-}hospitalised}$COVID group ($n$ = 73)		Group ^{Hospitalisation} (^{Hospitalised}COVID, $^{Non\text{-}hospitalised}$COVID, non-COVID) × Time (T1, T2) ANOVA results											
			T1: Study entry	T2: 6-month follow-up	T1: Study entry	T2: 6-month follow-up	Group^{Hospitalisation}				Time				Group^{Hospitalisation} × Time			
			Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2
Processing speed[a]	Response accuracy (%)	Non-COVID group presented in Table 3	94.99 (9.06)	95.45 (5.50)	95.92 (5.68)	96.96 (4.24)	0.38	2,125	0.68	*0.01*	0.88	1,125	0.35	*0.01*	0.07	2,125	0.93	*0.001*
	RT (correct responses, ms)		417.46 (94.65)	401.77 (94.16)	368.44 (76.06)	360.80 (84.58)	3.71	2,125	**0.03**	*0.06*	2.19	1,125	0.14	*0.02*	0.08	2,125	0.92	*0.001*
	RT variability (SD of RT)		99.92 (35.62)	94.77 (35.87)	86.30 (41.73)	75.02 (43.21)	3.33	2,125	**0.04**	*0.05*	0.58	1,125	0.45	*0.01*	1.98	2,125	0.14	*0.03*
Attention[b]	Response accuracy (%)		94.54 (7.03)	92.85 (11.01)	95.51 (9.12)	95.42 (9.15)	1.15	2,122	0.32	*0.02*	1.48	1,122	0.23	*0.01*	0.68	2,122	0.51	*0.01*
	RT (correct responses, ms)		554.17 (75.13)	576.67 (123.67)	478.78 (90.63)	479.55 (106.36)	7.54	2,122	**0.001**	*0.11*	0.13	1,122	0.72	*0.001*	0.99	2,122	0.38	*0.02*
Working memory[c]	Response accuracy (%)		90.94 (7.37)	94.03 (4.22)	92.75 (8.71)	93.43 (7.50)	0.22	2,131	0.81	*0.003*	3.98	1,131	**0.05**	*0.03*	0.58	2,131	0.56	*0.01*
Executive function[c]	Accuracy (%)		91.36 (11.78)	92.72 (12.54)	95.13 (6.16)	94.66 (8.17)	1.06	2,133	0.35	*0.02*	0.20	1,133	0.65	*0.002*	0.83	2,133	0.44	*0.01*
	Completion time (ms)		44595.93 (34257.70)	47056.93 (44537.02)	31420.61 (18486.50)	29182.01 (15352.91)	3.91	2,133	**0.02**	*0.06*	0.33	1,133	0.57	*0.002*	1.13	2,133	0.33	*0.02*
Memory[c]	Recognition accuracy (%)		88.06 (11.49)	90.63 (6.55)	90.34 (8.58)	92.35 (6.35)	1.42	2,134	0.25	*0.02*	3.63	1,134	0.06	*0.03*	0.88	2,134	0.42	*0.01*

Sample size reduced [a]by 9 (2 Hospitalised, 7 non-hospitalised), [b]by 11 (3 Hospitalised, 8 non-hospitalised), [c]by 1 (non-hospitalised).
Abbreviations: ms, milliseconds; RT, reaction time.

Table 5. Descriptive statistics and results of the repeated-measures Group (COVID, non-COVID) × Time (T1, T2) analysis of variance (ANOVA) on mental health and sleep measures

	COVID group (n = 88)		Non-COVID group (n = 50)		Group (COVID, non-COVID) × Time (T1, T2) ANOVA results											
					Group				Time				Group × Time			
	T1: Study entry Mean (*SD*)	T2: 6-month follow-up Mean (*SD*)	T1: Study entry Mean (*SD*)	T2: 6-month follow-up Mean (*SD*)	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2
Mental health (DASS-21)																
Depression	14.11 (10.50)	11.61 (10.78)	9.36 (9.69)	8.76 (9.84)	5.09	136	**0.03**	*0.04*	4.73	136	**0.03**	*0.03*	1.78	136	0.19	*0.01*
Anxiety	10.59 (8.75)	10.41 (9.25)	7.04 (7.56)	7.08 (8.13)	5.89	136	**0.02**	*0.04*	0.02	136	0.90	*0.0*	0.04	136	0.84	*0.0*
Stress	14.70 (9.26)	12.95 (9.83)	13.28 (10.19)	12.76 (10.15)	0.25	136	0.62	*0.002*	3.22	136	0.08	*0.02*	0.95	136	0.33	*0.01*
Sleep quality (PSQI)																
Global score[a]	9.95 (3.70)	9.64 (4.00)	6.54 (3.25)	6.76 (3.68)	26.49	136	**<0.001**	*0.16*	0.04	136	0.84	*0.0*	1.19	136	0.28	*0.01*

DASS-21, The Depression, Anxiety and Stress Scale-21; PSQI, Pittsburgh Sleep Quality Index.
Higher scores indicate higher levels of depression, anxiety and stress. Higher scores indicate poor sleep quality.
[a]The Group Effect was present on all PSQI sub-components, indicating poorer sleep quality in the COVID compared to the non-COVID group.

Table 6. Descriptive statistics (non-COVID group presented in Table 5) and results of the repeated-measures Group^{Hospitalisation} (^{Hospitalised}COVID, $^{Non\text{-}hospitalised}$COVID, non-COVID) × Time (T1, T2) analysis of variance (ANOVA) on mental health and sleep measures

		^{Hospitalised}COVID group ($n = 15$)		$^{Non\text{-}hospitalised}$COVID group ($n = 73$)		Group^{Hospitalisation} (Hospitalised COVID, $^{Non\text{-}hospitalised}$COVID, non-COVID) × Time (T1, T2) ANOVA results									
		T1: Study entry total	T2: 6-month follow-up total	T1: Study entry total	T2: 6-month follow-up total	Group^{Hospitalisation}			Time			Group × Time			
		Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2
Mental health (DASS-21)	Non-COVID group presented in Table 5																
Depression		13.33 (7.43)	14.40 (7.38)	14.27 (11.06)	11.04 (11.30)	2.99	2,134	**0.05**	*0.04*	1.37	1,134	0.24	*0.01*	2.67	2,134	0.07	*0.04*
Anxiety		11.60 (7.49)	10.80 (8.06)	10.38 (9.02)	10.33 (9.52)	4.13	2,134	**0.02**	*0.06*	0.02	1,134	0.88	*0.0*	0.10	2,134	0.90	*0.002*
Stress		17.20 (7.44)	18.27 (8.81)	14.19 (9.55)	11.86 (9.72)	2.79	2,134	0.07	*0.04*	1.90	1,134	0.17	*0.01*	1.84	2,134	0.16	*0.03*
Sleep quality (PSQI)																	
Global score		10.80 (4.06)	10.93 (3.85)	9.78 (3.63)	9.37 (4.00)	13.28	2,134	**<0.001**	*0.17*	0.74	1,134	0.39	*0.01*	0.79	2,134	0.46	*0.01*

DASS-21, The Depression, Anxiety and Stress Scale-21; PSQI, Pittsburgh Sleep Quality Index.
Higher scores indicate higher levels of depression, anxiety and stress. Higher scores indicate poor sleep quality.

Discussion

This investigation focused on charting the cognitive and mental health trajectories of COVID-19 in a UK adult sample (≤69 years) that had been assessed 6 months earlier (T1) [18]. The findings showed: (i) a trend-level improvement (from T1 to T2) in processing speed RT variability but a continued slowing on the attention task (longer RTs) in the COVID, relative to the non-COVID group; (ii) within the COVID group, poorer cognitive function (processing speed, attention, executive function) in previously hospitalised, relative to non-hospitalised, participants on both occasions of testing (T1, T2); (iii) higher depression and anxiety, and reduced sleep quality in the COVID group, relative to the non-COVID group, at both T1 and T2, though an improvement in depression was visible in non-hospitalised COVID participants; (iv) reduced overall long-COVID symptom load at T2 compared to T1, particularly in non-hospitalised COVID participants (only a non-significant reduction in hospitalised COVID participants); (v) association between higher long-COVID symptom load and poorer performance on most cognitive indices; (vi) an association between reduced long-COVID symptom load and improved executive function at T2, again observed only in non-hospitalised COVID participants; and (vii) medium-sized associations between reduced long-COVID symptom load and improved mental health and well-being.

Regarding the impact of COVID-19 on cognitive function, in our previous study involving this working-age sample [18] the only cognitive variable to show a robust adverse impact of COVID-19 (regardless of hospitalisation history) was intra-individual variability in processing speed RTs, with larger RT variability in COVID-19 survivors compared to both non-COVID controls and their own pre-pandemic level (sub-sample for whom such data were available). The present investigation, encouragingly, demonstrated a trend towards normalisation (from T1 to T2) in this measure and thus suggested, on average, only a limited and possibly reversible adverse cognitive effects of COVID-19 in a working-age population. However, participants who had required COVID-19 hospitalisation showed continued cognitive impairment, a finding which is well documented in the literature, with hospitalisation status significantly impacting cognitive function and the speed of any possible recovery months after initial infection and hospitalisation [13, 26–31]. Our findings are also consistent with earlier findings of Del Brutto et al. [11] who observed an improvement towards normalisation in Montreal Cognitive Assessment scores at 18 months post-infection in older adults (mean age: 62.7 years) who had a history of mild COVID-19 and no hospitalisation and had shown a significant impairment when assessed earlier at 6 months post-infection. Their findings, taken together with ours, suggest cognitive improvement towards normalisation in COVID-19 survivors, especially without COVID-19-related hospitalisation, and that this recovery may occur relatively earlier (6–12 months post-COVID-19) in younger/working-age samples. Hospitalised COVID participants in our and other samples may show persistent cognitive impairment as a consequence of COVID-19-related structural and/or functional changes in the brain [32, 33], which needs to be explored further.

Regarding total long-COVID symptom load, a significant reduction was observed from T1 to T2, which significantly correlated with improved executive function only in non-hospitalised COVID participants, again suggesting a stronger/faster recovery in those without a hospitalisation history. However, for the majority of the sample, regardless of hospitalisation history, various self-

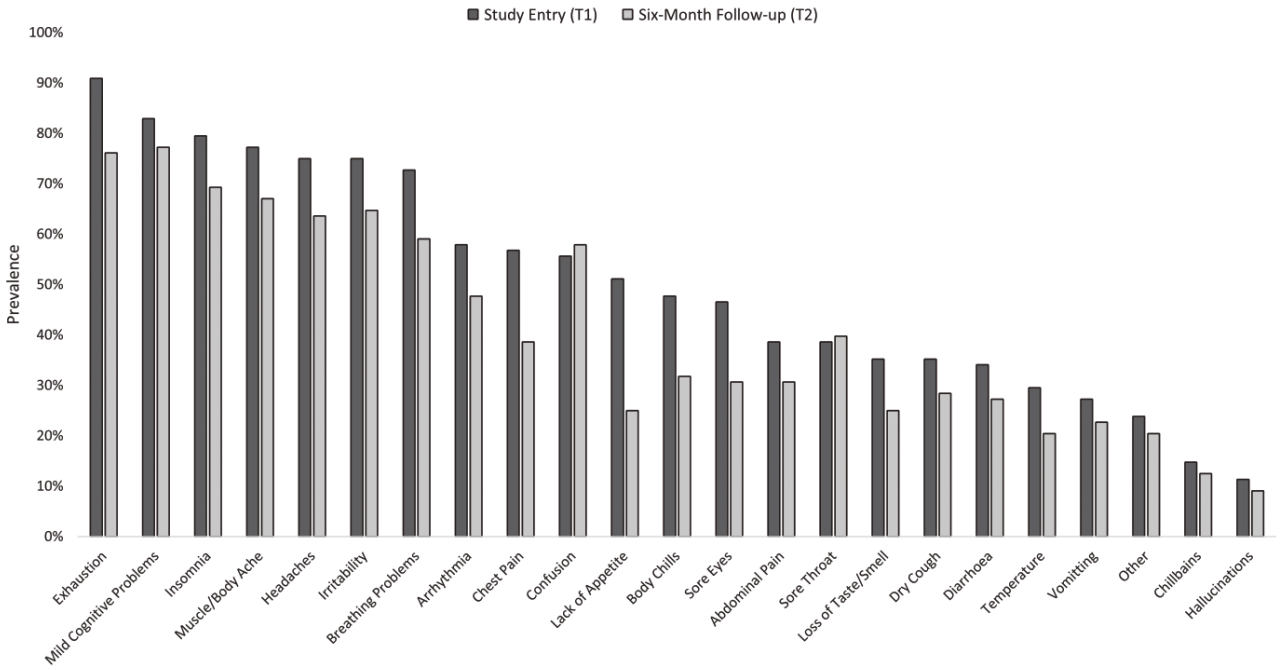

Figure 3. Prevalence of self-reported chronic COVID-19 (long-COVID) symptoms in the current sample (n = 82 of 88 provided data) at study entry (T1) and the 6-month follow-up (T2).

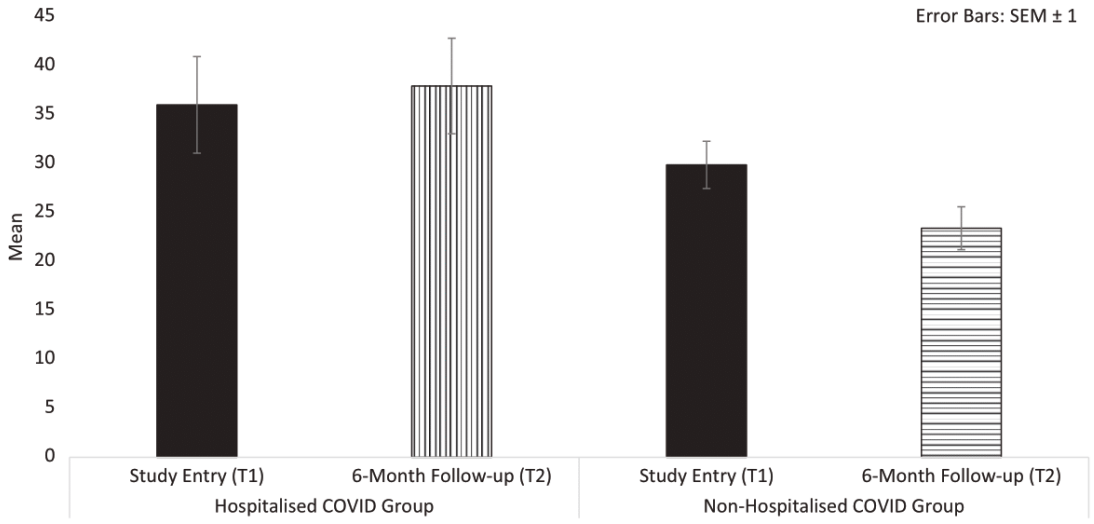

Figure 4. Total long-COVID symptom load in COVID participants, classified by hospitalisation history.

reported long-COVID symptoms were still present at T2, with sizeable associations between long-COVID symptom load and cognitive function, in line with previous findings [34, 35].

Mental health and sleep were still impacted at T2 in COVID-19 survivors, irrespective of hospitalisation history, though depression was lower at T2 than T1 in those without COVID-19-related hospitalisation. Notably, sleep appeared to be the most impacted. Interestingly, recent findings show that people with a COVID-19 history are more likely to be a late/evening chronotype, compared to those with no known history of COVID-19 [36], and late chronotype itself has been associated with poor quality of sleep [37–39]. There are also suggestions that the lockdowns resulted in delayed chronotype due to the altered social schedule, such as, reduced exposure to sunlight coupled together with longer and later sleeping patterns, which can all contribute to reduced quality of sleep [37, 40, 41]. It is possible that those with a history of COVID-19 were more impacted by subsequent lockdowns and shifted more towards eveningness and consequently poor sleep quality.

The strengths of this follow-up study include: (i) the response rate was reasonable with about two-thirds of the original sample [18] available for this investigation, and (ii) the current sample was representative of the original sample. Nonetheless, the limitation of relying on self-report for COVID-19-related information inherent to our earlier study [18] also applies to this study. Despite this limitation, the findings may have important implications. For example, consistently poor(er) performance observed in hospitalised COVID participants on tasks which emphasise speed could

Table 7. Associations (Pearson's *r*) of total long-COVID symptom load (at T1 and T2, and the change from T1 to T2) with cognitive function and mental health (at T1 and T2, and the change from T1 to T2)

		Correlations of total long-COVID symptom load with cognitive function, mental health, and sleep						Correlations between decrease in total long-COVID symptom load from T1 to T2[a] and improvement in cognitive function and mental health							
		At T1			At T2[a]			All COVID participants			Hospitalised group			Non-Hospitalised group		
		r	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*
Processing speed	Response accuracy %	−0.21	0.06	80	−0.10	0.40	78	0.06	0.59	73	0.26	0.41	12	0.002	0.99	61
	RT correct responses, ms	0.29	**0.01**	80	0.44	**<0.001**	78	−0.11	0.34	73	0.07	0.82	12	−0.16	0.22	61
	RT variability SD of RT	0.19	0.09	80	0.42	**<0.001**	78	−0.07	0.53	73	0.14	0.67	12	−0.13	0.31	61
Attention	Response accuracy %	−0.21	0.07	80	−0.32	**0.01**	77	0.21	0.08	71	0.39	0.23	11	0.18	0.18	60
	RT correct responses, ms	0.31	**0.01**	80	0.53	**<0.001**	77	0.00	1.00	71	0.16	0.64	11	−0.06	0.64	60
Working memory	Response accuracy %	−0.17	0.11	87	−0.23	**0.04**	82	−0.11	0.32	81	0.01	0.99	14	−0.12	0.34	67
Executive function	Accuracy %	−0.27	**0.01**	88	−0.21	0.06	81	0.24	**0.03**	81	−0.001	1.00	14	0.36	**0.003**	67
	Completion time, ms	0.31	**0.003**	88	0.37	**0.001**	81	0.09	0.41	81	−0.31	0.29	14	0.20	0.11	67
Memory	Recognition accuracy %	−0.30	**0.01**	87	−0.45	**<0.001**	81	0.18	0.12	81	0.40	0.16	14	0.10	0.42	67
Mental health (DASS-21)	Depression	0.28	**0.01**	88	0.41	**<0.001**	82	0.32	**0.003**	82	0.66	**0.01**	14	0.21	0.08	68
	Anxiety	0.54	**<0.001**	88	0.56	**<0.001**	82	0.42	**<0.001**	82	0.62	**0.02**	14	0.42	**<0.001**	68
	Stress	0.33	**0.002**	88	0.36	**0.001**	82	0.30	**0.01**	82	0.50	0.07	14	0.20	0.11	68
Sleep quality (PSQI)	Global score	0.39	**<0.001**	88	0.46	**<0.001**	82	0.30	**0.01**	82	0.36	0.20	14	0.28	**0.02**	68

Abbreviations: ms, milliseconds; RT, reaction time.
[a]Long-COVID data not available for 6 participants (1 hospitalised, 5 non-hospitalised).

negatively impact daily activities such as driving [42] and may present as a bio-marker for accelerated aging [13]. Given this, frequent follow-ups of COVID-19 survivors, especially those with COVID-19-related hospitalisation and/or long-COVID symptoms, are needed to assess any potential worsening and/or improvement in cognitive function over time. Moreover, remedial interventions, such as mindfulness training, may help reduce cognitive slowing [43] in diverse samples impacted by COVID-19.

Conclusions

The findings of this follow-up study indicate some cognitive normalisation over a 6-month period in young and middle-aged COVID-19 survivors. However, those participants who had required hospitalisation due to COVID-19, compared to those who did not, continued to display multifaceted cognitive impairment. Continuous follow-up assessments are required to determine whether cognitive improvement continues over time in COVID-19 survivors, particularly in hospitalised/long-COVID participants or whether cognitive function in this sub-group worsens further unless addressed by suitable interventions.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1192/j.eurpsy.2024.7.

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Competing interest. Martina Ratto was working for Beingwell Group, Sheffield, United Kingdom at the time of data collection for this study (now at I.S. Giancardi-Galilei-Aicardi Alassio). No conflicts of interest are reported by other authors.

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Research article

Cognitive function and brain structure in COVID-19 survivors: The role of persistent symptoms

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ABSTRACT

Persistent COVID-19 symptoms post-acute state have been shown to have a significant negative impact on brain structure and function. In this study, we conducted magnetic resonance imaging (MRI) of the whole brain in 43 working-age adults (mean age: 44.79±10.80; range: 24–65 years) with a history of COVID-19 (731.17±312.41 days post-diagnosis), and also assessed their cognitive function (processing speed, attention, working memory, executive function, and recognition memory), mental health, and sleep quality. MRI data were processed using FSL to derive regional volumes for bilateral nucleus accumbens, caudate, pallidum, putamen, thalamus, amygdala, and hippocampus, and total grey matter, white matter, and cerebral spinal fluid volume, and analysed in relation to persistent COVID-19 symptom load, mental health, and sleep quality. Higher persistent COVID-19 symptom load was significantly associated with smaller putamen volume, lower response accuracy on working memory, executive function, and recognition memory tasks, as well as a longer time to complete the executive function task, and poorer mental health and sleep quality. Smaller putamen fully mediated the relationship between persistent COVID-19 symptom load and lower executive function. Further research is required to confirm whether reduced putamen volume and its association with poor executive function persists in COVID-19 survivors in the long term.

1. Introduction

Post-acute sequelae of COVID-19 (PASC) is a highly debilitating condition, broadly defined as symptoms that develop during an infection of coronavirus disease 2019 (COVID-19), are continuously experienced ≥12 weeks post-infection, and cannot be attributed to any other plausible condition [7,73,87]. PASC is often used interchangeably with long COVID, which is a term coined by COVID-19 survivors experiencing persistent COVID-19 symptoms (PCS) [2,62]. The prevalence of PASC varies amongst the literature and has been difficult to measure given its novelty and the large array of symptoms [44]. Approximately 10–20 % of COVID-19 survivors are believed to be experiencing PCS ([25,44]; World Health Organization [99], although the Office for National Statistics estimated that only 3.3 % of the UK population (2 million people) were self-reporting PCS [76] O'Mahoney and colleagues [75], in their meta-analysis of 194 studies (from 2019 to 2022) estimated that 45 % of COVID-19 survivors experienced at least one PCS [75]. Similarly, a meta-analysis of 31 studies examining the prevalence of PCS reported a regional prevalence of 51 % in Asia, 44 % in Europe, and 31 % in the USA, with a pooled prevalence of 43 % in COVID-19 survivors [21]. Regional variations in the prevalence of PCS may be explained by differences in the severity of acute illness, population age, and other co-morbidities [25].

Many PCS have been self-reported by survivors, and recently these have been categorised into four different phenotypes [36]: (i) chronic fatigue-like syndrome (fatigue, memory loss, headaches), (ii) respiratory syndrome (dyspnoea and cough), (iii) chronic pain syndrome (myalgia and arthralgia), and (iv) neurosensorial syndrome (change in taste and smell). Females are generally more likely to report PCS [6,91,93] with fatigue being the most commonly reported symptom [20,46,88]. PCS

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post-acute infection have also been associated with substantial impairment in multiple cognitive domains, including but not limited to attention [39,81], working memory [39,55,65], recognition memory [42], and executive function [55,65,81]. Taquet and colleagues [90] in their large retrospective study (n=856,588, aged 18–64 years) reported cognitive deficits, as captured by relevant codes of the International Statistical Classification of Diseases and Related Health Problems - 10th Revision (ICD-10) [98], in survivors at six months post-diagnosis and this remained true even at the two-year mark, relative to non-COVID controls. Similarly, Zhao et al. [102] observed a cognitive slowing in long-COVID patients, particularly in the processing speed domain, compared to patients who had previously had a diagnosis of COVID-19 but not developed long COVID, a finding which has also been echoed by Vakani et al. [95].

The prominent cognitive impairment observed across multiple domains in COVID-19 survivors experiencing PCS may be indicative of abnormalities in the brain's structure [58] and/or function [55,58]. A number of studies that assessed participants both with and without PASC point towards alterations in the brain, including lower whole-brain [30], total grey matter (GM) ([10,28,31,53]; but see [32]) and white matter (WM) volumes [40], along with lower volumes of the amygdala [82], hippocampus [82,105], putamen [10,27,47,82,92], pallidum [27,47], and thalamus [10,27,47]. There is also evidence of dynamic brain changes in long-COVID patients with neuropsychiatric symptoms [11] and larger cerebral spinal fluid (CSF) volume in association with a COVID-19 history [30,40].

The neural impact of COVID-19 and its association with cognitive function is an ongoing area of research. Many studies, utilising MRI or electroencephalogram (EEG), have found a correlation between brain abnormalities and reduced cognitive performance post a COVID-19 infection [3,12,13,19,28,47], although, only a handful focus solely on PASC. Andriuta and colleagues [3] found right-sided WM hypersensitivies, especially in the superior frontal region, to be associated with cognitive slowing and executive dysfunction in patients with post-acute COVID-19 cognitive complains. More recently, Díez-Cirarda and colleagues [28] found lower GM volume in people with long-COVID symptoms (n=86, mean age: 50.71 years), compared to controls (n=36, mean age: 49.33), and that lower GM volume in patients was correlated with poorer processing speed, attention, and working memory. Heine et al. [47] observed reduced left thalamus, putamen, and pallidum volumes in adults with long-COVID symptoms who also had moderate to severe fatigue, approximately seven months post COVID-19 diagnosis (n=50, mean age: 43.40 years), compared to healthy controls (n=47, mean age: 44.5), and also found lower thalamus volume to be significantly associated with poorer short-term memory in the long-COVID group.

The present study aimed to examine the association of any persistent COVID-19 symptoms (overall load as well as specific symptoms) in COVID-19 survivors, with total GM, WM, and CSF volumes as well subcortical brain volumes and cognitive function in a working-age, non-clinical population of COVID-19 survivors (none acutely unwell at the time of investigation). Furthermore, we examined the mediating role of brain structures (that associated with PCS in this sample) in the relationship of PCS with cognitive variables. We expected multifaceted cognitive impairment [55,81,95,102] and reduced GM volumes across the brain [10,47,82,105] in association with PCS, and expected the volumes of the brain areas associated with PCS to mediate the relationship between PCS and cognitive function [28,47].

2. Materials and methods

2.1. Participants and design

The study initially involved 50 adults recruited from the general population. All recruited participants were required to (i) be able to communicate in English and be in reasonably good health, (ii) have no potential magnetic resonance imaging (MRI) contraindications (e.g., metal in the body, claustrophobia, pregnancy), and (iii) have no past or current diagnosis of a brain injury and/or psychosis. The study recruitment was open to both individuals with and without a history of COVID-19. However, only seven people without a COVID-19 history volunteered which was insufficient to provide a meaningful non-COVID comparison group (thus not reported hereafter).

The final study sample consists of 43 adults (14 male, 29 female), aged between 24 and 65 years (mean age: 44.79±10.80), with a previous diagnosis of COVID-19 (65.1 % confirmed via polymerase chain reaction test; see Supplementary Table 1 for demographic characteristics), who underwent whole-brain MRI, followed by a cognitive assessment via a mobile application tool, and a psychometric test online, via Qualtrics, on a single occasion, on average, 731.17 ± 312.41 days post a COVID-19 diagnosis (range: 183–1160).

The study was approved by the College of Health, Medicine and Life Sciences Research Ethics Committee, Brunel University London (34033-A-Sep/2022–41521–1). All participants provided informed written consent and received £25 voucher for their time.

2.2. Measures and procedure

2.2.1. Sample characterisation and self-report measures

A Qualtrics survey, taking ~30 minutes to complete, was used to acquire data relating to the participant's COVID-19 diagnosis (date, acute and chronic symptoms, hospitalisation status, subjective cognitive impairment), in addition to demographic data (age, sex, ethnicity, education, occupation, existing mental and physical illnesses), as in our previous studies [94,95].

The Qualtrics survey also included two self-report measures assessing mental health and sleep quality. Mental health was assessed using the Depression, Anxiety and Stress Scale-21 (DASS-21) [56], a 21-item scale measuring depression, anxiety, and stress. Each DASS-21 item is rated by participants on a four-point Likert scale with higher scores indicating higher levels (severity) of symptoms. Internal consistency for all DASS-21 sub-scales (Depression: Cronbach's α=0.92; Anxiety: Cronbach's α=0.75; Stress: Cronbach's α=0.88) was acceptable-to-excellent in this sample. Quality of sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) [17], which is a 19-item, four-point Likert scale assessing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Higher PSQI scores indicate poorer sleep quality. The PSQI had an acceptable internal consistency in this sample (global score, Cronbach's α=0.75).

Data relating to acute and chronic COVID-19 symptoms were acquired through a self-report scale (Supplementary Table 2) designed specifically for this study. The scale is broadly based upon symptoms that were mentioned on the UK's National Health Service (NHS) website [72]. The scale required the participant to rate four acute symptoms (temperature, dry cough, loss of taste/smell, and other), and 26 chronic symptoms (Supplementary Table 2) on a seven-point Likert scale (Not at all/not applicable to Very Severe). Total PCS load was calculated by tallying together the sum of individual symptom ratings (with each symptom rated 0–7 as already mentioned).

2.2.2. MRI: data acquisition and processing

The imaging data were acquired using a 3 Tesla (3 T) Magnetom TIM Trio whole-body MRI scanner (Siemens Medical Solutions, Erlangen, Germany), fitted with a 32-channel head coil. For each participant, high-resolution T_1-weighted images were acquired, with the following parameters: inversion time (TI) = 1100 ms, repetition time (TR) = 1830 ms, echo time (TE) = 3.03 ms, flip angle (FA) = 11°, field of view (FOV) = 256 ×256 x 160 mm^3, voxel size = 1 ×1×1 mm^3, and a total of 160 images per participant.

All pre-processing and analysis of the T_1-weighted images were performed using FSL [Functional Magnetic Resonance Imaging of the

Brain (FMRIB) Software Library, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/, version 6.0.3] [50,86,97]. Prior to the analysis, removal of non-brain areas was performed on all T_1-weighted images utilising the Brain Extraction Tool (BET) in FSL. This tool uses a set of locally adaptive model forces which adapt to fit the brain's surface [85]. Hereafter, grey matter (GM), white matter (WM), cerebral spinal fluid (CSF), and subcortical brain structures (bilateral accumbens, caudate, pallidum, putamen, thalamus, amygdala, hippocampus) were outlined using FMRIB's Integration Registration and Segmentation Tool (FIRST) [77]. FIRST is a model-based segmentation tool that utilises both shape and appearance models constructed from an atlas of manually segmented images from the Centre for Morphometric Analysis. These manual segmentations are parameterised as surface meshes from which a point distribution is modelled. Utilising the observed intensities from each individual's T_1-weighted image, FIRST finds the most probable shape by searching through linear combinations of shape variation modes, resulting in segmentation for each tissue and subcortical structure per participant. Finally, intracranial volume (ICV) was estimated through the summation of GM, WM, and CSF volumes for each participant. During each step, processed images were carefully inspected by one of the authors (RN) to ensure accuracy of results.

2.2.3. Cognitive function

Participants completed a cognitive function assessment via the MyCQ mobile application tool [71]. The MyCQ mobile application tool has been validated against the Cambridge Neuropsychological Automated Test Battery [9,29]. It assesses five domains: processing speed, attention, working memory, executive function, and recognition memory, through digital versions of commonly utilised neuropsychological tests, taking ~15 min to complete [71].

Processing speed was assessed using a Simple Reaction Time (RT) task, with response accuracy (RA; % correct), average RT (ms), and RT variability examined. For this task, participants were required to tap the circle button as quickly as possible when a red circle was shown on the screen.

Attention was assessed using a Choice Reaction Time task, with RA (% correct) and average RT (ms) examined. Participants had to tap either the triangle or circle button based on the shape that was presented to them on the screen.

Working memory was assessed using the 2-Back task, with RA (% correct) used to examine task performance. In this task, participants were asked to tap 'yes' or 'no' based on whether the picture presented to them on the screen matched the picture presented to them two screens back.

Executive function was assessed using the Trail-Making B task, with RA (%, correct moves) and total task completion time (ms) examined. Participants had to produce an alternating sequence consisting of 13 numbers and 12 letters by tapping a number and a letter in ascending and alphabetical order, respectively, (e.g., 1, A, 2, B).

Recognition memory was assessed using a Visual Recognition Memory task, with RA (% correct) used to examine task performance. Participants were presented with a set of 24 images and were instructed to memorise them. They were then presented with another set of 96 images (including the 24 images presented to them earlier), and were asked to select either 'yes' or 'no' based on whether they remembered seeing the image.

2.3. Statistical analysis

Normality checks were performed on total PCS load, MRI data, cognitive indices, DASS-21, and PSQI (global) scores using the Shapiro-Wilk test [63,84]. All of the MRI variables, total PCS load, and sleep quality data met the assumption for normality, but some cognitive indices [processing speed RA (%), RT; attention RA (%); working memory RA (%); executive function RA (%), mean completion time; recognition memory RA (%)] and the DASS-21 variables were non-normally distributed. Given the correlational nature of this study, no data transformation was applied to the non-normally distributed data and instead, non-parametric correlations (Spearman's *rho*) were conducted for the non-normally distributed data.

Pearson's (r) correlations were used to examine whether total PCS load and age correlated with brain volumetric data (see Supplementary Table 3 for intercorrelations between subcortical structures), followed by partial correlations controlling for age and ICV. Non-parametric Spearman's (*rho*) correlations were conducted to examine the relationship of total PCS load with cognitive function and then mental health and sleep quality measures (see Supplementary Table 4 for associations between variables), followed by non-parametric partial correlations controlling for age. Spearman's (*rho*) correlations were also conducted to explore the relationship between specific subcortical structures and individual PCS.

Finally, mediation analyses (co-varying for age and ICV) were performed using 'PROCESS' toolbox to examine whether the putamen volume (the only subcortical structure that was significantly associated with total PCS load) mediated the association of total PCS load (independent variable) with executive function (RA, completion time) and recognition memory (RA) (outcome variables) (see Fig. 1); these cognitive variables had significant correlations with both PCS load and putamen volume, and a significant correlation was also present between PCS load and putamen volume (see Section 3.2). Given the non-normal distribution of some outcome variables and multiple model testing, the p values and 95 % confidence intervals were estimated using 10,000 bootstraps, equivalent to $p \leq 0.01$ [51] (the same pattern of results was obtained when using 5000 bootstraps; Supplementary Table 5). The simple PROCESS mediation model centred the mean for all variables to 0, with all p values $\pm$ 1 *SD* from the mean. Mediating effects were tested following [104]) method: (1) X and M should be correlated, (2) M and Y should be correlated, and (3) the direct effect of X on Y should be attenuated when M is accounted for, and the confidence intervals for the indirect effect should not include zero. For the sake of completion, we also examined the mediating role of putamen in PCS association with poor sleep (since sleep correlated with both PCS and putamen volume; see Section 3.4), using the same model parameters as described for the cognitive variables.

Analyses were performed using the Statistical Package for Social Sciences (SPSS) software (for Windows, version 28; IBM, New York, USA) and the 'PROCESS' toolbox (v4.1) add-on for SPSS [45]. Alpha level for testing the significance of effects was maintained at $p \leq 0.05$, unless stated otherwise.

3. Results

3.1. Sample characteristics

The majority of the participants were White British, held a Bachelor's degree or above and were in some form of employment, with 51.2 % being in the healthcare profession (e.g., doctor, nurse, dentist). In subjective reports, their most common health problem related to lung function (39.5 %), and the most common mental health problem was depression (44.2 %), closely followed by anxiety (32.6 %), and insomnia (25.6 %) (Supplementary Table 1). All but two participants (95.3 %) had at least one dose of the COVID-19 vaccine (Supplementary Table 1). Further characteristics of the sample, including MRI volumes, cognitive performance, mental health and sleep are provided in Table 1.

The most prevalent persistent COVID-19 symptoms reported in the entire sample, were mild cognitive problems, muscle/body ache, and exhaustion (Fig. 2). Total PCS load (total sum of individual symptom ratings) correlated significantly with increasing age [$r(43)=0.32$, $p=0.04$], but not with the number of days since diagnosis, controlling for age [$r(40)=-0.10$, $p=0.55$].

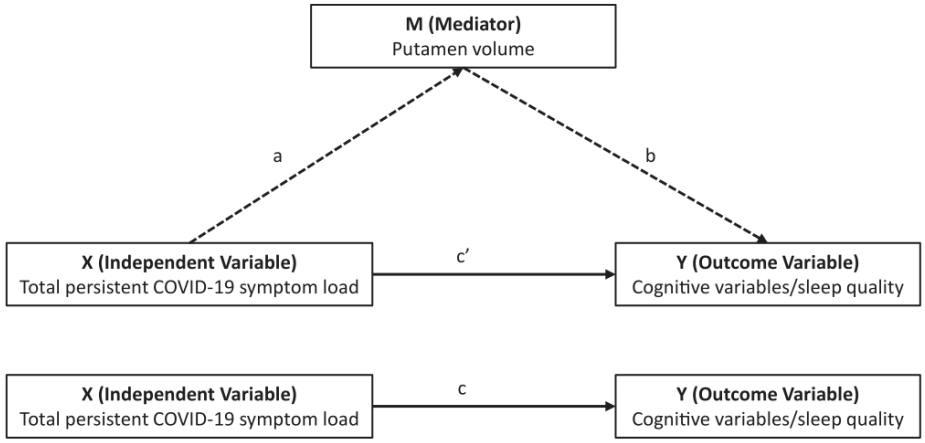

Fig. 1. The simple mediation model illustration.

Table 1
Characteristics of the sample (N = 43), classified by hospitalisation history.

		Entire Sample (N = 43)		Hospitalised Participants (*n* = 7)		Non-hospitalised Participants (*n* = 36)	
		Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***
Age (years)		44.79	10.80	51.71	8.48	43.44	10.78
Brain Volumes (Total, mm^3)	Cerebral Spinal Fluid	254958.33	43424.58	261415.29	65021.50	253702.81	39091.03
	Grey Matter	607893.86	61178.09	561499.00	53461.39	616915.08	59052.03
	White Matter	587816.65	57884.76	557449.43	60563.40	593721.39	56317.77
	Intracranial Volume	1450668.84	133168.14	1380363.71	137781.56	1464339.28	129789.69
	Accumbens	943.84	192.95	888.00	262.08	954.69	179.32
	Caudate	7144.84	829.09	7072.29	613.32	7158.94	871.28
	Pallidum	3655.42	353.85	3638.86	482.89	3658.64	331.98
	Putamen	10061.23	920.91	9698.71	701.40	10131.72	949.72
	Thalamus	16652.21	1656.14	15578.86	2075.85	16860.92	1509.11
	Amygdala	3084.79	333.17	2958.00	278.64	3109.44	340.67
	Hippocampus	7880.00	860.85	7401.29	977.82	7973.08	818.91
Cognitive, Mental Health and Well-being Measures							
Processing Speed[a]	Response accuracy (%)	96.52	6.44	98.16	2.54	96.17	6.97
	RT (correct responses, ms)	405.80	112.57	431.14	140.10	400.42	107.68
	RT variability (SD of RT)	87.45	43.09	85.29	27.40	87.91	46.06
Attention[b]	Response accuracy (%)	93.21	12.41	85.12	20.40	94.97	9.50
	RT (correct responses, ms)	529.28	113.50	587.00	145.51	516.66	103.81
Working Memory[b]	Response accuracy (%)	88.83	12.15	87.43	10.50	89.13	12.61
Executive Function[a]	Response accuracy (%)	93.02	9.96	93.08	7.13	93.01	10.55
	Completion time (ms)	45878.60	48309.41	51214.86	29663.94	44746.67	51689.24
Recognition Memory[c]	Recognition accuracy (%)	90.35	8.12	93.61	3.58	89.68	8.66
Mental Health (DASS−21)	Depression	12.14	10.65	16.57	13.10	11.28	10.10
	Anxiety	6.60	7.06	8.57	6.71	6.22	7.15
	Stress	11.53	9.40	16.29	9.90	10.61	9.16
Sleep Quality (PSQI)	Global Score	9.47	4.34	10.43	4.20	9.28	4.41
Total Persistent COVID−19 Symptom Load		35.16	24.14	47.86	23.08	32.69	23.87

Note: This table is differentiated by hospitalisation status for information purposes only. Participants who required hospitalisation, relative to those who did not, generally were older, had lower subcortical brain volumes, poorer cognitive performance, poorer mental health and sleep quality, as well as higher total persistent COVID-19 symptom load.
Sample size reduced [a] by 3 (non-hospitalised), [b] by 4 (non-hospitalised), [c] by 2 (non-hospitalised).
Abbreviations: mm^3, cubic millimetre; ms, milliseconds; RT, Reaction Time; SD, Standard Deviation.
DASS-21: The Depression, Anxiety and Stress Scale-21. Higher scores indicate higher levels of depression, anxiety and stress.
PSQI: Pittsburgh Sleep Quality Index. Higher scores indicate poor sleep quality.

3.2. Associations between total persistent COVID-19 symptom load and brain volumes

Higher total PCS load was significantly associated with lower putamen volume (r=-0.44, p=0.003), and this association remained significant after controlling for age and ICV (r=-0.33, p=0.03) (Table 2). Of the 26 individual PCS that had been assessed, lack of appetite (*rho*=-0.50, p=0.001), muscle/body ache (*rho*=-0.48, p=0.001), and mild cognitive problems (*rho*=-0.44, p=0.003) correlated most strongly with putamen volume.

The total GM, total WM and total volumes of all subcortical structures generally had non-significant negative correlations with PCS load [r values −0.12 (for amygdala) to −0.44 (for putamen), and became negligible when controlling for age and ICV (Table 2).

3.3. Associations of persistent COVID-19 symptoms with cognitive function and the mediating role of putamen

Higher total PCS load, controlling for age, was associated with lower working memory RA (%) (*rho*=-0.33, p=0.05), lower executive function

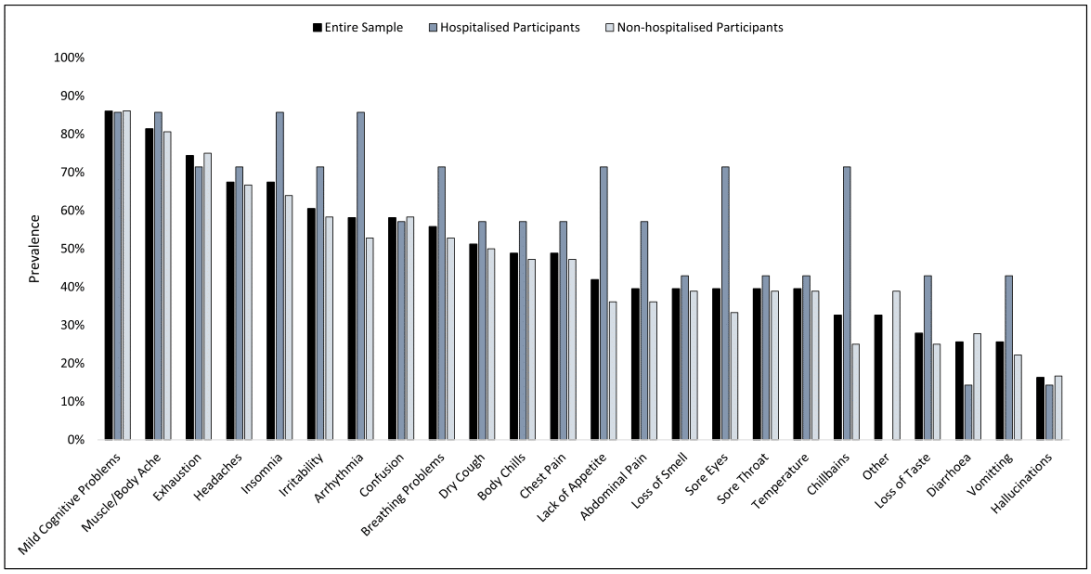

Fig. 2. Prevalence of self-reported chronic COVID-19 (persistent) symptoms, classified by hospitalisation history.

Table 2
Associations (Pearson's *r*) between brain volumes, age, and total persistent COVID-19 symptom load.

Brain Volumes (Total, mm^3)		**Age**		**Total persistent COVID-19 symptom load**		**Persistent COVID-19 symptom load controlling for age and ICV**	
		r (*df* = 43)	*p*	*r* (*df* = 43)	*p*	*r* (*df* = 39)	*p*
Cerebral Spinal Fluid		0.33	**0.03**	−0.03	0.83	−0.03	0.86
Grey Matter		−0.46	**0.002**	−0.24	0.12	0.13	0.42
White Matter		−0.21	0.18	−0.27	0.09	−0.11	0.48
Accumbens	Total	−0.36	**0.02**	−0.17	0.27	0.05	0.76
	Left	−0.43	**0.004**	−0.22	0.16	0.01	0.93
	Right	−0.20	0.19	−0.08	0.62	0.07	0.65
Caudate	Total	−0.24	0.12	−0.13	0.39	0.04	0.81
	Left	−0.21	0.19	−0.14	0.39	0.04	0.79
	Right	−0.26	0.09	−0.12	0.43	0.03	0.85
Pallidum	Total	0.18	0.25	−0.20	0.20	−0.21	0.19
	Left	0.11	0.48	−0.17	0.29	−0.11	0.50
	Right	0.23	0.15	−0.22	0.16	−0.25	0.11
Putamen	Total	−0.35	**0.02**	−0.44	**0.003**	−0.33	**0.03**
	Left	−0.26	0.10	−0.39	**0.01**	−0.28	0.08
	Right	−0.42	**0.01**	−0.47	**0.002**	−0.35	**0.02**
Thalamus	Total	−0.23	0.15	−0.24	0.12	−0.04	0.82
	Left	−0.24	0.12	−0.25	0.11	−0.05	0.76
	Right	−0.21	0.19	−0.23	0.15	−0.02	0.89
Amygdala	Total	0.15	0.33	−0.12	0.45	−0.10	0.52
	Left	0.08	0.60	−0.18	0.25	−0.16	0.32
	Right	0.17	0.29	−0.03	0.87	−0.02	0.93
Hippocampus	Total	−0.23	0.13	−0.19	0.23	0.03	0.88
	Left	−0.28	0.07	−0.13	0.39	0.09	0.59
	Right	−0.15	0.35	−0.21	0.17	−0.06	0.72

Note: Bold font indicates statistical significance ($p \leq 0.05$).
Abbreviations: ICV, Intracranial Volume; mm^3, cubic millimetre.

RA (%) (*rho*=-0.41, *p*=0.009), longer completion time (ms) in the executive function task (*rho*=0.39, *p*=0.01), and lower recognition memory RA (%) (*rho*=-0.51, *p*<0.001) (Table 3). Of these cognitive variables, lower RA (%) (*rho*=0.34, *p*=0.03) and longer completion time (ms) (*rho*=-0.44, *p*=0.005) in the executive function task and reduced RA (%) in the recognition memory (*rho*=0.38, *p*=0.01) were significantly correlated with smaller putamen volume (Table 4); and all of these remained significant when controlling for age [executive function RA (%) (*rho*=0.33, *p*=0.04); executive function completion time (*rho*=-0.37, *p*=0.02); recognition memory RA (%) (*rho*=0.42, *p*=0.007)].

The significant association of higher total PCS load with poorer executive function RA (%) was significantly mediated by putamen volume [Model Summary: R^2=0.22, $F_{(4,35)}$=3.78, *p*=0.012], with a significant indirect effect of total PCS load (i.e., mediated by the putamen volume) on executive function RA (%) (β=-0.06, SE=0.03, 95 % CI: −0.125, −0.002) and a non-significant direct effect (β=-0.07, SE=0.06, *p*=0.29, 95 % CI: −0.196, 0.059) (Fig. 3a). The mediation model with executive function completion time as an outcome variable yielded no significant direct or indirect effects. For recognition memory RA (%), the overall model was significant [Model Summary: R^2=0.26, $F_{(4,36)}$=5.35, *p*=0.002]; however, the confidence interval for the indirect effect of the total PCS load on recognition memory RA (%) contained zero, indicating that the mediating effect of putamen volume was insignificant (β=-0.02, SE=0.02, 95 % CI: −0.063, 0.020). Taken together, these findings suggest that putamen volume robustly mediated the association of total PCS load with executive function RA (%) but not recognition memory RA (%)

Table 3
Associations (Spearman's *rho*) of cognitive, mental health and sleep measures with age and total persistent COVID-19 symptom load.

		Age			Total persistent COVID-19 symptom load			Persistent COVID-19 symptom load controlling for age		
		rho	*df*	*p*	*rho*	*df*	*p*	*rho*	*df*	*p*
Cognitive Measures										
Processing Speed	Response accuracy (%)	0.06	40	0.71	−0.06	40	0.72	−0.08	37	0.64
	RT (correct responses, ms)	0.35	40	**0.03**	0.19	40	0.24	0.11	37	0.51
	RT variability (SD of RT)	−0.05	40	0.76	0.25	40	0.12	0.27	37	0.09
Attention	Response accuracy (%)	−0.37	39	**0.02**	−0.28	39	0.09	−0.19	36	0.24
	RT (correct responses, ms)	0.53	39	**<0.001**	0.33	39	**0.04**	0.22	36	0.19
Working Memory	Response accuracy (%)	−0.10	39	0.53	−0.34	39	**0.03**	−0.33	36	**0.05**
Executive Function	Response accuracy (%)	−0.07	40	0.65	−0.42	40	**0.008**	−0.41	37	**0.009**
	Completion time (ms)	0.31	40	**0.05**	0.45	40	**0.003**	0.39	37	**0.01**
Recognition Memory	Recognition accuracy (%)	0.02	41	0.92	−0.49	41	**0.001**	−0.51	38	**<0.001**
Mental Health and Sleep Quality Measures										
Mental Health (DASS−21)	Depression	0.05	43	0.75	0.38	43	**0.01**	0.38	40	**0.01**
	Anxiety	0.09	43	0.58	0.40	43	**0.009**	0.39	40	**0.01**
	Stress	0.08	43	0.59	0.32	43	**0.02**	0.34	40	**0.03**
Sleep Quality (PSQI)	Global Score	0.10	43	0.54	0.65	43	**<0.001**	0.65	40	**<0.001**

Note: Bold font indicates statistical significance ($p \leq 0.05$).
Abbreviations: DASS-21, The Depression, Anxiety and Stress Scale-21; ms, milliseconds; PSQI, Pittsburgh Sleep Quality Index; RT, Reaction Time; SD, Standard Deviation.

(Fig. 3b).

3.4. Persistent COVID-19 symptoms and mental health

Higher total PCS load was significantly associated with higher levels of depression (*rho*=0.38, *p*=0.01), anxiety (*rho*=0.40, *p*=0.009), stress (*rho*=0.32, *p*=0.02), and sleep quality (*rho*=0.65, *p*<0.001). All of these associations remained significant when co-varying for age (Table 3). Smaller putamen volume also correlated with poorer sleep quality (*rho*=-0.37, *p*=0.01) (Table 5), and this association too remained significant when co-varying for age (*rho*=-0.37, *p*=0.02). The mediation analysis revealed total PCS load to be a significant predictor of sleep quality [Model Summary: R^2=0.45, $F_{(4,38)}$=8.20, *p*<0.001], with a significant direct effect (β=0.11, SE=0.02, 95 % CI: 0.062, 0.160), but insignificant indirect effect with putamen volume as a mediator (β=0.01, SE=0.008, 95 % CI: −0.003, 0.030) (Fig. 4).

4. Discussion

4.1. Main findings

This study investigated the association between persistent COVID-19 symptoms and brain structural volumes, and examined how PCS load, brain volumes and their intercorrelations might relate to widely reported cognitive impairment in a working-age population. The findings revealed that higher total PCS load (especially lack of appetite, muscle/body ache, and mild cognitive problems) was associated, controlling for age, with lower putamen volume, as well as with poorer cognitive function (working memory, executive function, and recognition memory), mental health, and sleep quality. Lower putamen volume was also associated with poorer executive function and recognition memory performance, and sleep quality, and fully mediated the association of higher PCS load with poorer executive function.

Before discussing these findings in relation to previous research, it is important to consider the COVID-19-related characteristics of our sample. Approximately 88 % of the present sample reported at least one PCS, a rate that seems much higher than the predicted incidence rate for long COVID. This could be attributed to the fact that the vast majority of the present sample happened to be frontline medical workers, who in the UK have been severely impacted by long COVID [14]. For example, in a UK-based study, approximately 76 % of medical doctors were experiencing one or more long COVID complications [14]. The British Medical Association also found that 60 % of frontline medical workers were impacted in their day-to-day lives due to long COVID, and 18 % were no longer able to work [14,16]. Based upon this recent evidence and the occupation of our participants (Supplementary Table 1), the high incidence rate of PCS in this sample is not a deviation from the norm. On the other hand, it could also be argued that PCS observed in this particular sample are attributed to post-exertional malaise, in which symptoms worsen post any physically and mentally demanding activity [41], such as that experienced by healthcare workers in their highly demanding role.

The most frequently self-reported PCS in the present sample was mild cognitive problems (86 %), often referred to as 'brain fog'. With an incidence rate of >50 %, this has been one of the most prevalent long-COVID symptom in many previous studies [33,48,61,64,74]. Based on the symptom categorisation by Gentilotti et al. [36] that was explored earlier and on the observed symptom profile (Fig. 2), the current sample appears to have mainly either 'chronic fatigue-like syndrome' or 'chronic pain syndrome' [36]. The continuous experience of mild cognitive problems, or, in other words, 'chronic fatigue-like syndrome', post a COVID-19 diagnosis can have numerous psychosocial consequences [18], reflecting a relatively greater impact of the virus on the brain [25,74].

We found lower putamen volume to be associated with a higher PCS load, most strongly with muscle/body ache and mild cognitive problems. Both of these PCS have been associated with delayed clearance of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) viral particles from the upper respiratory tract in the acute stage of the infection [4]. Prolonged expression of viral particles can cause tissue damage and induce a proinflammatory response [4], which may impact the striatum, particularly the putamen [15]. Our finding of PCS and lower putamen volume association is consistent with the current literature indicating that a reduction in putamen volume occurs post a SARS-CoV-2 infection [10,27,47,82,92]. Putamen volume loss has also been associated with other viruses, such as Human Immunodeficiency Virus (HIV) [67,100]. Although HIV (*Lentivurs*) and SARS-CoV-2 (*β-coronavirus*) are not from the same viral family [49], they both can infiltrate the central nervous system (CNS) [8], [22,37,54,83,100,101], and increase proinflammatory cytokines [49]. Cytokines in general aid in controlling infections and diseases. However, an excess of cytokines can lead to tissue damage [24,68] as well as exacerbate the release of proinflammatory cytokines [68]. This overproduction of a protective measure, such as proinflammatory cytokines, towards viruses can lead to further damage, for example, cell death and tissue damage, including those of vital organs [1,24,34,68]. The response can occur directly as a

Table 4
Associations (Spearman's *rho*) between brain volumes and cognitive variables.

Brain Volumes (Total, mm^3)		**Processing Speed ($n = 40$)**						**Attention ($n = 39$)**				**Working Memory ($n = 39$)**		**Executive Function ($n = 40$)**				**Recognition Memory ($n = 41$)**	
		Response accuracy (%)		**RT (correct responses, ms)**		**RT variability (SD of RT)**		**Response accuracy (%)**		**RT (correct responses, ms)**		**Response accuracy (%)**		**Response accuracy (%)**		**Completion time (ms)**		**Recognition accuracy (%)**	
		rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
Cerebral Spinal Fluid		−0.16	0.31	0.28	0.09	0.03	0.84	−0.08	0.64	−0.02	0.91	0.17	0.31	−0.13	0.42	0.05	0.75	0.23	0.16
Grey Matter		−0.06	0.73	−0.03	0.87	−0.22	0.18	0.31	**0.05**	−0.29	0.07	0.19	0.24	0.11	0.50	−0.31	0.06	0.18	0.25
White Matter		−0.02	0.93	−0.04	0.80	−0.30	0.06	0.19	0.26	−0.31	**0.05**	0.20	0.22	0.12	0.46	−0.20	0.21	0.32	**0.04**
Accumbens	Total	0.13	0.42	−0.20	0.22	−0.44	**0.005**	0.51	**0.001**	−0.50	**0.001**	0.12	0.46	0.07	0.67	−0.23	0.15	0.35	**0.02**
	Left	0.15	0.36	−0.19	0.25	−0.30	0.06	0.46	**0.003**	−0.52	**0.001**	0.17	0.30	0.11	0.49	−0.31	**0.05**	0.32	**0.04**
	Right	0.03	0.85	−0.18	0.28	−0.43	**0.005**	0.48	**0.002**	−0.32	**0.05**	0.01	0.97	−0.06	0.70	−0.03	0.88	0.29	0.07
Caudate	Total	0.14	0.40	−0.14	0.38	−0.18	0.26	0.12	0.46	−0.32	**0.05**	0.37	**0.02**	0.26	0.10	−0.39	**0.01**	0.13	0.41
	Left	0.15	0.35	−0.11	0.49	−0.19	0.24	0.12	0.49	−0.27	0.10	0.34	**0.04**	0.18	0.28	−0.33	**0.04**	0.16	0.33
	Right	0.13	0.41	−0.16	0.34	−0.11	0.49	0.09	0.57	−0.33	**0.04**	0.40	**0.01**	0.30	0.06	−0.40	**0.01**	0.07	0.67
Pallidum	Total	−0.04	0.81	−0.01	0.96	−0.31	**0.05**	−0.04	0.83	−0.35	**0.03**	0.17	0.31	0.32	**0.04**	−0.36	**0.02**	0.41	**0.009**
	Left	−0.01	0.96	−0.01	0.97	−0.26	0.10	−0.03	0.84	−0.32	**0.05**	0.24	0.13	0.26	0.10	−0.29	0.07	0.32	**0.04**
	Right	−0.09	0.60	−0.04	0.79	−0.30	0.06	−0.03	0.84	−0.33	**0.04**	0.06	0.72	0.29	0.07	−0.36	**0.03**	0.42	**0.007**
Putamen	Total	0.12	0.46	−0.23	0.16	−0.36	**0.02**	0.45	**0.004**	−0.52	**0.001**	0.003	0.98	0.34	**0.03**	−0.44	**0.005**	0.38	**0.01**
	Left	0.16	0.33	−0.25	0.12	−0.35	**0.03**	0.38	**0.02**	−0.42	**0.008**	−0.02	0.92	0.28	0.08	−0.31	**0.05**	0.37	**0.02**
	Right	0.09	0.58	−0.25	0.12	−0.35	**0.03**	0.46	**0.003**	−0.60	**<0.001**	0.02	0.92	0.30	0.06	−0.51	**0.001**	0.34	**0.03**
Thalamus	Total	−0.12	0.46	−0.05	0.75	−0.22	0.17	0.21	0.21	−0.39	**0.02**	0.20	0.23	0.02	0.90	−0.23	0.15	0.22	0.17
	Left	−0.15	0.35	−0.05	0.78	−0.23	0.15	0.25	0.13	−0.38	**0.02**	0.16	0.32	0.03	0.85	−0.23	0.15	0.22	0.17
	Right	−0.09	0.58	−0.03	0.86	−0.23	0.16	0.19	0.24	−0.38	**0.02**	0.20	0.22	0.01	0.96	−0.23	0.15	0.24	0.13
Amygdala	Total	−0.11	0.50	−0.12	0.48	−0.24	0.13	−0.08	0.63	−0.24	0.14	0.01	0.97	−0.07	0.67	−0.02	0.90	0.18	0.26
	Left	−0.18	0.28	−0.15	0.36	−0.22	0.18	−0.23	0.17	−0.19	0.26	−0.01	0.94	−0.07	0.69	−0.03	0.87	0.06	0.70
	Right	0.03	0.86	−0.02	0.91	−0.25	0.12	0.06	0.73	−0.25	0.13	0.01	0.96	0.01	0.95	−0.06	0.72	0.20	0.22
Hippocampus	Total	−0.03	0.84	−0.07	0.66	−0.21	0.20	0.37	**0.02**	−0.28	0.08	0.20	0.22	−0.16	0.33	−0.17	0.29	0.28	0.08
	Left	−0.13	0.44	−0.13	0.44	−0.17	0.29	0.33	**0.04**	−0.29	0.08	0.07	0.66	−0.25	0.11	−0.09	0.57	0.20	0.20
	Right	0.06	0.74	−0.02	0.90	−0.21	0.20	0.18	0.26	−0.22	0.19	0.26	0.11	−0.07	0.69	−0.19	0.25	0.30	**0.05**

Note: Bold font indicates statistical significance ($p \leq 0.05$).
Abbreviations: mm^3, cubic millimetre; ms, milliseconds; RT, Reaction Time; SD, Standard Deviation.

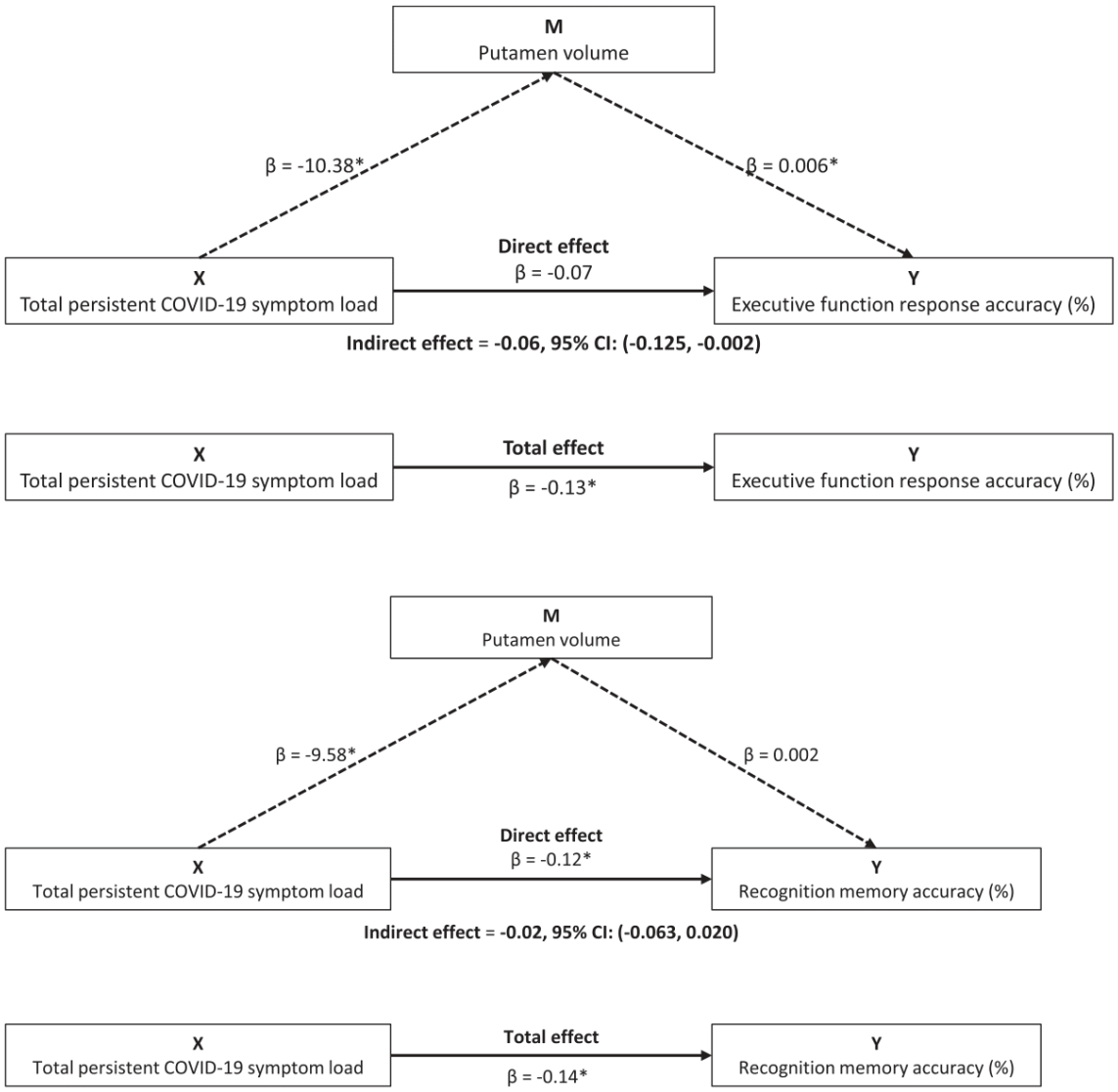

Fig. 3. a. The mediating role of putamen volume between total persistent COVID-19 symptom load and cognitive variables. b. The mediating role of putamen volume between total persistent COVID-19 symptom load and cognitive variables.

Table 5
Associations (Spearman's *rho*) of brain volumes with mental health measures.

Brain Volumes (Total, mm^3)	**Mental Health (DASS-21)**						**Sleep Quality (PSQI)**	
	Depression		**Anxiety**		**Stress**		**Global Score**	
	rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
Cerebral Spinal Fluid	0.28	0.07	0.43	**0.004**	0.24	0.13	0.17	0.27
Grey Matter	0.03	0.87	0.16	0.30	−0.05	0.74	−0.15	0.34
White Matter	0.13	0.41	0.19	0.21	0.11	0.48	−0.15	0.34
Accumbens	0.02	0.91	0.02	0.88	−0.07	0.67	−0.34	**0.03**
Caudate	−0.04	0.80	−0.09	0.58	−0.10	0.55	−0.19	0.22
Pallidum	0.07	0.64	0.15	0.34	0.04	0.78	−0.18	0.25
Putamen	−0.14	0.39	0.05	0.76	−0.15	0.33	−0.37	**0.01**
Thalamus	0.18	0.26	0.18	0.26	0.06	0.72	−0.10	0.53
Amygdala	0.05	0.78	0.09	0.55	−0.10	0.51	−0.17	0.29
Hippocampus	0.13	0.40	0.15	0.34	0.05	0.75	−0.10	0.52

Note: Bold font indicates statistical significance ($p \leq 0.05$).
Abbreviations: DASS-21, The Depression, Anxiety and Stress Scale-21; mm^3, cubic millimetre; PSQI, Pittsburgh Sleep Quality Index.

result of the virus or indirectly due to the overdrive of the immune system [24]. A previous study has shown that an increase in proinflammatory cytokines can affect the striatum in COVID-19 survivors [15, 57].

As expected, higher PCS load was negatively associated with performance in the attention, working memory, executive function, and

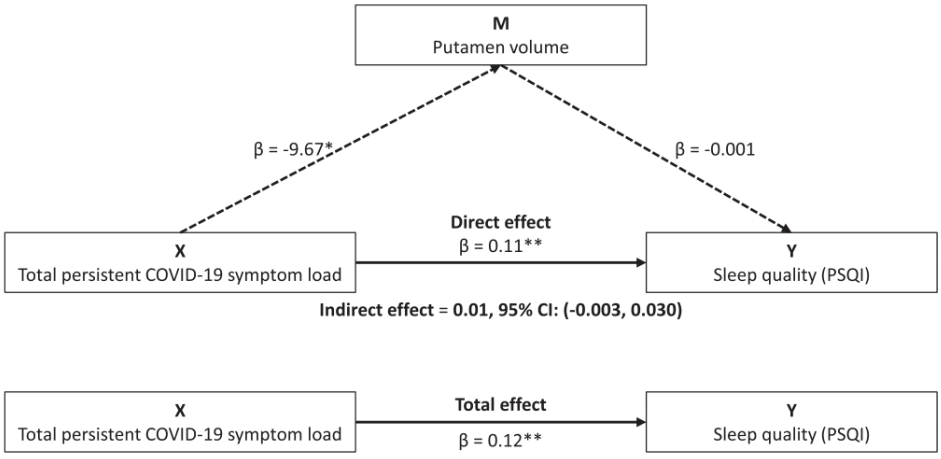

Fig. 4. The mediating role of putamen volume between total persistent COVID-19 symptom load and sleep quality.

recognition memory domains, replicating our findings in a different sample of working-age adults [94,95]. Importantly, the relationship between PCS and executive function was fully mediated by putamen volume. The putamen as part of the striatum [38], plays a vital role in learning, language, motor control, and other cognitive functions [35,38, 52,59,80]. Moreover, previous functional MRI (fMRI) research supports the role of putamen in executive function [5,66,89]. In our previous studies, we observed a multi-domain cognitive impairment in individuals with PCS [94,95], and a reduction in putamen volume has been associated with disrupted global cognitive performance [26,59].

We did not find a significant association between PCS and any other brain structural volumes (except putamen), for example, hippocampus [82,105]. The majority of our sample was highly educated and, given the protective effect of education on brain health and overall cognitive function [70], may have shown a rather limited neural impact of PCS. However, it is also possible that some brain changes associated with COVID-19 or PCS may be expressed more strongly in the presence of other comorbidities or advancing age [30]; and the extent and spread of neural changes may further depend on the expressed long COVID phenotype [36]. Furthermore, some of the PCS related cognitive effects may appear in neuronal function while not being detectable in, or not associating with, volumetric changes in individual brain structures after a COVID-19 infection [81,103].

Lastly, this study replicated previously reported associations of long COVID with poor mental health and sleep [23,43,60,69,96]. Our previous work has shown that sleep quality, relative to mental health, was more impacted due to long COVID and PCS [94,95]. Similarly, in this study, PCS load was associated with both poorer mental health and sleep quality, but with a stronger impact on sleep quality. Notably, changes in sleep quality were associated with total PCS load, and not with any brain volumes. Pellitteri et al. [79] have suggested that poor sleep may be associated with underlying neuroinflammation that occurs due to COVID-19, yet this association weakens overtime. However, to gauge the trajectory and timeline of this association, a follow-up study would be required.

5. Limitations

The design of this study lacks a control (comparison) group. The original study design included a group of non-COVID participants; however, following the lifting of the pandemic-related restrictions in the UK, it became difficult to recruit a sufficient number of participants with no exposure to COVID-19 (only seven non-COVID people were assessed; thus, not included). Moreover, the findings from this study are predominantly correlational, therefore further research and replication would be required to confirm these findings. Finally, the sample was predominately female, preventing a meaningful investigation of possible sex differences in the neurobiological impacts of persistent COVID-19 symptoms [78].

6. Conclusion

The present study revealed that persistent COVID-19 symptoms may be associated with volume loss in the putamen. PCS was also associated with poor performance in attention, working memory, and executive function, as has been reported consistently in recent studies. Importantly, the relationship between higher PCS load and poorer executive function was found to be fully mediated by lower putamen volume, suggesting a reduction in putamen volume due to persistent symptoms, which then affects executive function. Further research is required to understand whether putamen volume reduction is present in follow-up assessments and continues to mediate the association of PCS with poor executive function, in particular, relative to a control (comparison) group with no history of COVID-19.

CRediT authorship contribution statement

Elena Antonova: Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis. **Veena Kumari:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Martina Vanova:** Writing – review & editing, Formal analysis. **Martina Ratto:** Resources, Methodology. **Krupa Vakani:** Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ray Norbury:** Writing – review & editing, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andrew Parton:** Writing – review & editing.

Data Availability

Data will be made available on request.

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Conflicts of interest

Martina Ratto was working for Beingwell Group, Sheffield, United Kingdom at the time of data collection for this study (now at I.S. Giancardi-Galilei-Aicardi Alassio). No conflicts of interest are reported by other authors.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2024.115283.

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Camera-based visual feedback learning aid for recovering sense of smell and taste in COVID-19 survivors: a proof-of-concept study

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Introduction: A significant proportion of people report persistent COVID-19-related anosmia, hyposmia or parosmia, often accompanied with ageusia, hypogeusia or dysgeusia. Here, we present a proof-of-concept study that assessed the feasibility and acceptability of a new Camera-Based Visual Feedback Learning Aid (CVFLA) and explored its potential to restore or improve persistent COVID-19-related smell and/or taste impairment.

Methods: Fifteen adult participants with persistent smell and/or taste impairment were randomly allocated to 7-, 14-, or 21-days baseline of symptom monitoring before receiving the intervention in up to 10 sessions (length and frequency determined by participant's preference and progress) using a specialised CVFLA apparatus (patent no. 10186160). Smell and taste were assessed pre- and post-intervention subjectively, and also objectively using the ODOFIN Taste Strips and Sniffin Sticks. Participant feedback about their experience of receiving CVFLA was obtained via a semi-structured interview conducted by someone not involved in delivering the intervention.

Results: The intervention was extremely well received, with no dropouts related to the intervention. There was also a significant improvement in smell and taste from pre- to post-CVFLA intervention (mean number of sessions = 7.46, *SD* = 2.55; total duration = 389.96 min, *SD* = 150.93) both in subjective and objective measures. All participants, except one, reported experiencing some improvement from the 2nd or 3rd session.

Discussion: This new CVFLA intervention shows promise in improving COVID-19 related impairment in smell and taste with a very high level of acceptability. Further studies with larger samples are required to confirm its potential in restoring, improving or correcting smell and/or taste impairment in relevant clinical and non-clinical groups.

KEYWORDS

visual feedback, learning, smell, taste, COVID-19, impairment, intervention

1. Introduction

A new onset of smell or taste loss has been considered a clinical indicator of SARS-CoV-2 infection since the start of the pandemic (e.g., Borsetto et al., 2020; Costa and Carnauba, 2020; Giacomelli et al., 2020; Lechien et al., 2020; Spinato et al., 2020). About 1 in 5 people with COVID-19 report persistent (i.e., lasting more than 10 days) COVID-19-related anosmia (loss

of the sense of smell), hyposmia (reduced sense of smell) or parosmia (distorted sense of smell; e.g., Chary et al., 2020; Chiesa-Estomba et al., 2020; Antolín-Amérigo et al., 2021; Printza et al., 2021). A similar proportion of people with COVID-19 report ageusia (loss of the sense of taste), hypogeusia (reduced sense of taste) or dysgeusia (altered perception of taste), with many people reporting both smell and taste impairment (Wang et al., 2023). Even though the prevalence of COVID-19-associated smell and taste impairment decreased with later variants of the virus (Boscolo-Rizzo et al., 2022), it still appears significant for the Omicron variant at around 12% in people with European ancestry (von Bartheld and Wang, 2023). Furthermore, persistent qualitative disturbances of smell and/or taste have been reported in around one-third of patients who recover from COVID-19 (Ercoli et al., 2021).

An early longitudinal study (Boscolo-Rizzo et al., 2022) that followed up people with COVID-19 for eight weeks found that one in three people had smell or taste impairment at four weeks, and 1 in 5 still had smell and/or taste impairment when assessed at eight weeks, with that the loss of smell and taste being the most prevalent long-lasting symptom, followed by fatigue and breathing problems. Later studies (e.g., Jensen et al., 2022) also show impaired smell in about 20% of people at six-months post-COVID 19. Full recovery of smell and/or taste may occur by one year in about half of such cases (Nguyen et al., 2021; review, Peterson et al., 2021; Boscolo-Rizzo et al., 2023) but may still persist in a significant proportion even two years after the infection (Boscolo-Rizzo et al., 2023).

Impaired sense of smell and taste have implications for mood and daily activities of the affected individuals. Empirical evidence shows that pleasant and unpleasant smells are powerful manipulators of mood and emotions (e.g., Kaviani et al., 1998) and, perhaps not surprisingly, smell and/or taste impairment in the context of COVID-19 has been associated with low mood and anxiety (Dudine et al., 2021), unhealthy eating patterns (Javed et al., 2022), reduced quality of life and safety related issues (Coelho et al., 2021) as well as with brain fog (Garcia-Melendez et al., 2023). Even in non-COVID populations, impaired sense of smell is reported to occur in people with depression (Pause et al., 2001, 2005; Pollatos et al., 2007; Yuan and Slotnick, 2014) and has been linked with cognitive impairment and depression in the elderly, in certain types of dementias (Suzuki et al., 2004; Seo et al., 2009) and known to influence appetite and immunity (Schiffman and Graham, 2000). Thus, there is a need to find acceptable and scalable interventions that can aid recovering of smell and taste in the context of COVID-19 as well as in other disabling conditions that commonly present with impaired sense of smell and/or taste.

The present study was designed to assess the acceptability, feasibility and potential benefits of a specialized Camera-Based Visual Feedback Learning Aid (CVFLA) in restoring, improving and/or correcting the sense of smell and taste, along with possible changes in mental health and well-being, in people with persistent COVID-19-related smell and/or taste impairment. This CVFLA involves the use of a camera-based technology and a specialized collar technique for smell and taste training whereby real time video feedback about the individual is observed, while the direct view of the self is obscured (patent no. 10186160). During a session, the individual "learns" by observing their self through real time video feedback. In an early study by Ramachandran and Rogers-Ramachandran (1996), a series of patients were reported to recover phantom limb sensation using a technique involving a virtual reality mirror box (a mirror placed vertically on the table and reflected the patients' intact hand superimposed on the experienced position of the phantom limb). There is recent evidence that visual feedback training can help to restore accurate sensation of the self, change sensations within the self (from discomfort to comfort and *vice-versa* as required), improve mobility, balance and movement, reduce pain, retrain stress responses, improve breathing, and many other sensations and pertaining to the individual (e.g., Deconinck et al., 2015; Kim and Lee, 2020; Pak and Lee, 2020). The specialized CVFLA we report had shown promise in unpublished case studies. The present proof-of-concept study aimed to examine the feasibility of delivering this intervention, its acceptability and potential to facilitate recovery of smell and taste that was lost or distorted due to COVID-19.

2. Methods

2.1. Participants

The study initially involved 16 adults residing in different parts of the UK who self-reported experiencing persistent COVID-19-related loss of smell and/or taste. Of these, 15 participants (5 males, 10 females; age range: 20–62 years) completed the study (one person could not continue for personal reasons). The participants were recruited through social media and contacts with relevant charities as well as from our ongoing COVID-19-related projects (Vakani et al., 2023). The study inclusion criteria required all participants to be (i) aged ≥18 years, (ii) experiencing persistent (lasting >10 days) smell and taste impairment following COVID-19 infection, and (iii) able to provide written informed consent.

The study was approved by the University Research Ethics Committee (ref no. 18771-LR-Oct/2019–20,701-1). All participants provided written informed consent and were compensated for their time and travel expenses. All study procedures followed ethical standards set by the Helsinki declaration (1964).

2.2. Design and procedure

The study utilized a non-concurrent multiple baseline across participants design (Watson and Workman, 1981). This is a type of single-case design where each participant acts as their own control, and can be used to study the effect of an intervention across several participants. When using this design, the intervention for any given problem or behavior begins at different times for the different participants; and effects of the intervention are shown when changes in the target problem/behavior are observed that coincide with the intervention and do not systematically covary with the duration of the baseline. For this study, we opted for a non-concurrent type to allow more flexibility in recruiting participants, especially when the pandemic-related restrictions in the context of laboratory-based research studies at the university were continuously changing. The study involved three different pre-selected baselines (7 days, 14 days, and 21 days), with an equal number of participants in a pre-determined sequence allocated to each of the three baselines to avoid experimenter bias (Christ, 2007).

Of 15 participants in the study, five participants had been allocated to receive the CVFLA intervention after 7 days, five participants after

14 days, and five participants after 21 days of baseline periods of monitoring for changes in the sense of smell and/or taste (see Table 1). However, one of the participants who had been allocated to start receiving the intervention after a 14-day baseline, started receiving the intervention a week later than planned due to personal reasons, and hence a 14-day baseline became a 21-day baseline in this case. Therefore, there were only four participants with a 14-day baseline monitoring and six participants with a 21-day baseline period in the final sample; this, if anything, contributes to the robustness of the results as a 21-day baseline was sufficiently long for smell and taste to return (but it did not happen) spontaneously without the CVFLA intervention.

Prior to being allocated to 7/14/21 days of baseline (smell and taste monitoring), all participants were carefully screened to ensure they met our study inclusion criteria (see Table 1). In addition, information was obtained for any known allergies and medical history. The selected participants were asked to subjectively rate their sense of smell and taste during their allocated baseline period, and invited for the pre-intervention assessments if their smell and taste impairment persisted at the end of the allocated baseline period (found to persist in all cases) (Table 1).

For pre-intervention assessments, a trained researcher (SC or KV) administered a range of self-report measures to obtain information on participants' COVID history, mental health and well-being, interoceptive awareness, smell and taste impairment, and objectively assessed their smell and taste impairment using an ODOFIN taste strip and Sniffin stick test kit (Rumeau et al., 2016). They then received the intervention (see "CVFLA Intervention" CVFLA intervention) and were re-assessed one week after the last intervention session on the same measures as used for pre-intervention assessments. All 15 participants provided subjective ratings of smell and taste impairment after the last intervention session (audio-video recordings obtained and the videos subsequently rated by someone who was not involved in delivering the intervention for scoring purposes), but four (three with significant travel commitments, and one re-infected with COVID-19) of the 15 participants did not complete the remaining post-intervention assessments.

2.3. Pre- and post-intervention assessments

Smell and taste, mental health and well-being, and interoceptive awareness were assessed before and after the intervention. In addition, a semi-structured interview was conducted at the very end of study participation (post-intervention) by a researcher who was not involved in delivering the intervention (KV) to gather participant feedback about the acceptability of the current version of the CVFLA and possible future improvements.

2.3.1. Smell and taste

Smell and taste impairments were first assessed subjectively by asking the participants to rate their ability to smell (loss of smell and distorted sense of smell) and taste (loss of taste and distorted sense of taste) on a seven-point scale ["not at all" (0) to "very severe" (6)]. The ODOFIN *Taste and Sniffin Sticks* (Rumeau et al., 2016) were then used to measure smell and taste impairment objectively. The ODOFIN smell and taste identification test has 12 Sniffin sticks of different odors (orange oil, leather, cinnamaldehyde, peppermint oil, banana, lemon oil, anethole, coffee, clove oil, pineapple, rose, and fish) and four paper strips impregnated with salt, sugar, sour, and bitter taste. Each stick was presented with a gap of 5 s under three conditions (smelling with left, right, and both nostrils respectively). Each time, a cue card was presented with four options to sniff the stick and choose the option that matched their olfactory perception. They were asked to guess the smell if they could not smell anything. A total score was achieved for each condition by adding the individual response, with 0 indicating "no smell" and 12 indicating "maximum ability to smell". Four taste strips were given with a gap of 30 s, and a cue card was presented with four different options. They were asked to choose the option that matched their taste perception. A score of 0 was given if the response was wrong, and a score of 1 was given if it was correct. All information, including prompted/unprompted answers, whether guessed, known, or remembered from the previous trial, distorted or no smell/taste, were recorded on a separate scoring sheet.

2.3.2. Mental health and well-being

The levels of depression, anxiety and stress were assessed using the Depression Anxiety and Stress Scale (DASS-21; Lovibond and Lovibond, 1995). This 21-item self-report scale has three subscales (each with seven items): depression, anxiety and stress. Each item is rated on a four-point scale (0 to 3) based on how often in the past week it applied to them. Higher scores indicate higher levels (severity) of symptoms. Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest, anhedonia, and inertia. The anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect.

TABLE 1 Study design and phases.

Screening	Baseline	Pre-intervention Assessments	CVFLA Intervention	Post-intervention Assessments
1. Demographics 2. COVID history 3. Smell and Taste impairment 4. *If found to meet inclusion criteria – allocated to* 7, 14, or 21 days of smell and taste monitoring	7, 14, or 21 days of symptom (smell and taste) monitoring *If smell and taste impairment still present (self-reported) at the end of the allocated baseline period – invited for Pre-intervention Assessment*	1) Smell and Taste 2) Mental health and well-being 3) Interoceptive awareness	Up to 10 sessions over 5–10 weeks	1) Smell and Taste 2) Mental health and well-being 3) Interoceptive awareness 4) Semi-structured interview to obtain participant feedback about their experience of the CVFLA

Finally, the stress scale assesses difficulty relaxing, nervous arousal, easily upset, agitated, irritable, over-reactive, and impatient.

Overall quality of life was assessed using the five-item World Health Organization Well-being Index (WHO-5, Bech et al., 1996). Participants rate each item on a six-point Likert scale based on their feelings over the past two weeks. Higher scores indicate a higher quality of life or level of well-being.

2.3.3. Interoceptive awareness

The Multidimensional Assessment of Interoceptive Awareness-2 (MAIA-2; Mehling et al., 2018) was used to assess interoceptive bodily awareness. It has 37 items, belonging to one of the eight dimensions: noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening, and trust. Each item is rated on a six-point scale ["never" (0) to "always" (5)], with higher scores indicating greater bodily awareness. The main reason for including this scale was to explore whether those scoring higher on this scale may benefit more from the CVFLA intervention; or whether the CVFLA intervention increases interoceptive awareness.

2.4. CVFLA intervention

The intervention was delivered by a researcher (SC) following a predetermined protocol in up to 10 sessions over 5–10 weeks, depending on the participant's progress and preference, with each session lasting up to 60 min. Typically, sessions 1–3 focused on introducing and implementing the CVFLA techniques, sessions 4–6 aimed to consolidate previous learning, and sessions 7–9 focused on confirming the re-learning of smell and taste.

All CVFLA sessions were conducted with participants sitting on a comfortable chair. During the first CLFLA session, the participant was briefed about the CVFLA set up (Figure 1) with a practical demonstration. A collar was then placed around their neck, and they were asked to observe themselves in real time (with ~100-ms delay) on the computer screen from two different views: (i) a close-up view to help them focus on the task that they were performing (e.g., smelling or tasting a food item) and (ii) a wide-angle view which showed a broader view of themselves sitting on the chair (Figure 1). If they reported feeling aroused or stressed (or appeared stressed), the demonstration was immediately paused, the collar was removed, the cameras were moved away, and a relaxation exercise (breathing and/or muscle relaxation) was introduced to give them time to recover. Once the participants were comfortable with the practical demonstration and the collar, the session began.

Before each session, the participants were asked to indicate their ability to smell and taste on a scale of 0 to 10, with zero indicating "no smell or taste" and 10 indicating "maximum smell or taste". This was followed by a breathing and muscle relaxation exercise. Specific smell and taste experiences for any particular food item were then generated in three successive attempts, with each attempt lasting for about 15–25 s. If the participant showed a clear improvement in smell or taste, further attempts were made with another food item in the same category; if no improvement occurred, a different item from a different taste category was presented. Within five taste categories (sweet, sour, salty, umami, and bitter), different food items (e.g., salt, jam, dates, cream crackers, malted biscuits, watercress) were presented; and within each category, the items were clustered by intensity, going from the least to the most intense within the session (e.g., umami - seaweed, soy sauce, bovril, marmite; sour- goji berries, cherries, cranberries; bitter- broccoli, rocket, kale, coffee beans). For the sour category, flavored and plain yoghurt, citrus fruits (grapes, raspberry, satsumas, oranges), apple cider vinegar, candies, lemon, and lime were given depending upon individual's progress. The food items were presented in a different order for individual sessions and participants depending upon the progress and choice of the participant. However, we consistently started all sessions with a tiny amount of sugar for all participants, regardless of the stage of intervention and progress of the individual, to maintain some consistency. The participants were not blinded to any food item and had been asked in advance for any known allergies and food/smell preferences. Whenever participants reported an unpleasant response (e.g., disgust or stress) to any food items, relaxation exercises were re-introduced to reduce their emotional stress response and/or physical tension. All sessions ended with a breathing or muscle relaxation exercise, as per the participant's preference.

In addition, during the second and subsequent CVFLA sessions, the participant was also asked to describe any observable changes (from the previous session) in their smell and taste (in addition to indicating their ability to smell and taste on a scale of 0 to 10 as mentioned above for all sessions). These sessions proceeded with taste/flavors based on the participant's experience from the previous session/week and their comments from the current week, focusing on food and smell items that still needed to be accurately tasted. The number of actual sessions depended upon the individual's progress. Throughout the sessions, participants' responses were recorded for identification accuracy and pleasantness/unpleasantness of the item.

2.5. Data analysis

As this was a proof-of-concept study with only 15 participants, the data for each participant on all key measures are first presented and summarized descriptively and then analyzed across the entire sample using repeated-measures analysis of variance (ANOVA) to explore the impact of the CVFLA on the primary outcome variable/s (i.e., improvement in the sense of smell and/or taste); the effect sizes where reported are partial eta squared (η_p^2; the proportion of variance associated with a factor). Next, Pearson's correlations were used to examine whether the pre- to post-CVFLA changes seen in the primary outcome variables were correlated with any baseline sample characteristics, including age, the duration of smell and taste impairment, various measures of mental health and well-being, and interoceptive awareness. Following the observation of significant associations of post-intervention reduction (improvement) in smell and taste impairment with age, the duration of smell or taste impairment, and the "Noticing" subscale of the MAIA-2 (Interoceptive Awareness), a stepwise regression analysis was run to explore the most robust correlate of the CVFLA-led improvement. Various measures of mental health and well-being, and interoceptive awareness, were also explored for any pre- to post-intervention changes using repeated-measures ANOVAs. Prior to running these analyses, the data properties (skewness, kurtosis) of all variables, including the subjective ratings of smell and taste, were examined and found suitable for parametric statistical procedures. Alpha level for testing the significance of effects was maintained at $p \leq 0.05$.

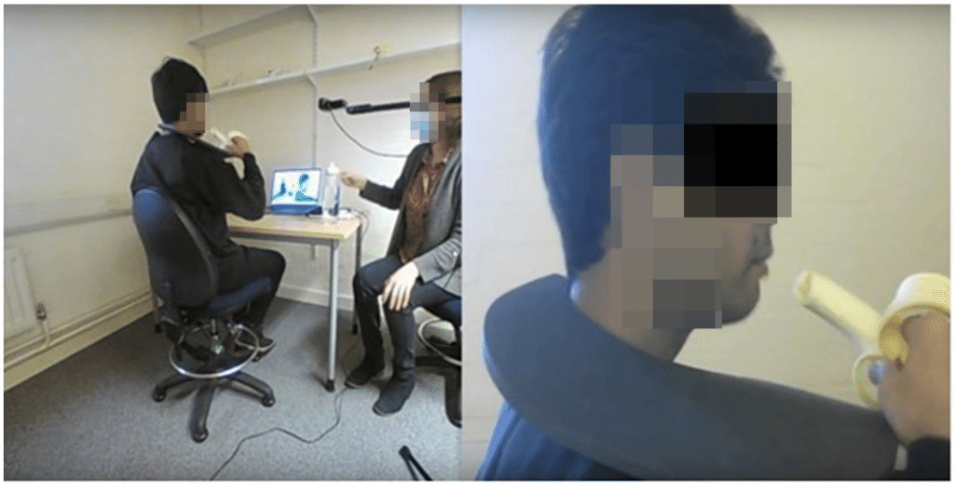

FIGURE 1
An illustration of the CVLFA set-up and intervention. This image is a screen shot from the computer screen that the participant is watching. The participant observes a real-time video of their actions, via the two webcams being streamed to the computer. The black collar, worn around the neck, blocks the individual's direct view of their self, meaning the visual information about their actions is now restricted to being **only** what they can see on the computer screen. In this illustration, as the banana is eaten, the taste of the banana may be re-learnt since the "taste" of the banana has been learnt previously, and most likely being predicted. The real-time video stream on the computer provides new/additional visual feedback for the participant to learn from.

All analyses were conducted using the Statistical Package for Social Sciences (for Windows, version 28; IBM, New York, United States).

3. Results

3.1. Sample characteristics

On average, the sample had moderate-to-severe smell and taste impairment, lasting for about 8 months prior to taking part in this study (see Tables 2, 3). None of the included participants had a neurodegenerative disorder, but one participant had rhinitis (no. 5), and one participant (no. 6) had asthma.

TABLE 2 Sample characteristics.

Sample characteristics	Mean (*SD*)	Range
Age (in years)	43.53 (12.25)	20–62
Duration of smell/taste impairment prior to receiving CVFLA (in days)	236.66 (234.91)	28–817
Mental health and well-being		
Depression (DASS-21)	9.13 (7.97)	0–30
Anxiety (DASS-21)	10.80 (10.25)	0–32
Stress (DASS-21)	13.33 (9.96)	0–30
Well-being Index 9 (WHO-5)	13.00 (4.31)	7–21
Introspective awareness		
Noticing (MAIA-2)	3.75 (0.86)	1.75–5
Not-distracting ((MAIA-2)	2.14 (1.39)	1.60–4.85
Not-worrying (MAIA-2)	2.87 (0.68)	0.60–3.80
Attention-regulation (MAIA-2)	3.15 (1.24)	1.29–5
Emotional- awareness (MAIA-2)	4.03 (0.81)	2.20–5
Self-regulation (MAIA-2)	3.38 (1.08)	1.50–5
Body-listening (MAIA-2)	2.75 (1.32)	1–5
Trusting (MAIA-2)	3.53 (1.23)	1–5

DASS-21, Depression Anxiety Stress Scale (DASS-21; Lovibond and Lovibond, 1995); WHO-5, World Health Organization Well-being Index (WHO-5; Bech et al., 1996). MAIA-2: Multidimensional Awareness of Introspective Awareness-2 (MAIA-2; Mehling et al., 2018)

3.2. CVFLA intervention delivery and acceptability

On average, study participants attended about seven intervention sessions (mean = 7.47; SD = 2.56), taking on average about 7 h per person (mean = 389.96 min, SD = 150.93). The intervention was extremely well received, as evident from responses to the feedback interview questions presented in Table 4. All participants found the intervention training to be "generally" or "definitely" useful and enjoyable and believed that it helped them to recover their sense of taste and/or smell. Around one-third (36.37%) of the sample reported that they had practiced the methods and techniques learnt during the sessions outside the sessions (e.g., at home), and they all stated that they would recommend this intervention to other individuals with taste and smell impairment. One person reported concerns regarding body image issues once they began to enjoy food after the fourth CVFLA session. Several participants reported during the last interview that they were skeptical about the intervention and found watching them on camera somewhat uncomfortable initially but were pleasantly surprised with how it helped them to recover their smell and taste. There were no drop-outs due to the CVFLA intervention not being acceptable.

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TABLE 3 Duration of smell and taste impairment, and subjective ratings of impairment before and after CVFLA for individual participants.

Participant No.	Age (years)	Sex	Duration of smell/taste impairment prior to receiving CVFLA (in days)	Baseline (in days)	Subjective ratings of impairment [scale 0 (none)-to-6 (very severe)]								Pre- to post-CVFLA decrease in impairment across smell and taste (total pre- *minus* total post ratings)
					Smell				Taste				
					Loss		Distortion		Loss		Distortion		
					Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	31	Female	172*	7	5	2	5	2	5	2	5	2	12
2	36	Female	28	14	5	0	0	0	5	0	0	0	10
3	49	Female	177*	21	4	2	4	3	4	3	4	3	5
4	50	Male	208	7	5	3	5	5	5	1	5	5	6
5	38	Female	207*	14	2	1	5	1	0	0	4	1	8
6	37	Female	207*	21	3	0	3	1	4	0	4	1	12
7	39	Female	50	7	6	0	6	3	5	0	5	2	17
8	59	Female	220*	14	6	2	6	1	1	1	1	1	9
9	60	Male	817*	21	4	2	2	1	1	2	0	1	1
10	41	Male	32	7	4	0	0	0	0	0	6	0	10
11	62	Female	533*	14	5	3	5	3	5	3	2	2	6
12	37	Female	619*	21	2	0	2	0	2	0	2	0	8
13	20	Male	54	7	5	3	5	3	2	1	3	1	7
14	36	Female	172*	21	5	1	5	1	5	1	5	1	16
15	58	Male	54	21	4	1	1	1	4	1	1	1	6

*Participants with impairment for more than 24 weeks.

3.3. Pre- to post-intervention changes in smell and taste impairment

In post-intervention subjective ratings, relative to the pre-intervention ratings, all participants reported less severe impairment (or no loss) in their sense of smell, 11 participants (of 13 participants with a distorted sense of smell at pre-intervention) reported less severe or no distortion of smell, 11 participants (of 13 participants who had taste impairment) showed a reduction in the severity of taste impairment, and 11 (of 13 participants) showed a less distorted sense of taste (Table 3). All participants, except one, started to report experiencing a positive change in smell and/or taste from the second or third session (session-wise data not presented as the number of sessions varied for individual participants depending on their progress); and each of the 15 participants showed some reduction in total (smell and taste) impairment as assessed by subjective ratings (see Figure 2).

When explored across the entire sample using repeated-measures ANOVAs, there was a significant reduction in subjective ratings of both smell and taste impairment after, compared to before, the CVFLA intervention (all $p \leq 0.004$), with somewhat larger effect sizes for smell than taste, and for recovery (based on "loss of smell" or "loss of taste ratings") relative to correction of distorted smell or taste (Table 5). This improvement (total across smell and taste loss and distortion ratings) was correlated negatively with age [$r = -0.514$ (95% CI −0.812, −0.023), $p = 0.05$] and the duration of smell or taste impairment [$r = -0.529$ (95% CI −0.819, −0.002), $p = 0.04$] and positively with pre-intervention scores on the "Noticing" dimension of the MAIA-2 (Interoceptive Awareness) scale [$r = 0.544$ (95% CI 0.043, 0.826), $p = 0.036$]; there was also a trend-level positive association with the Emotional-Awareness dimension of MAIA-2 [$r = 0.47$ (95% CI −0.055, 0.792), $p = 0.07$]. The regression model with these variables as predictors and improvement in smell and taste as the dependent variable was significant ($F = 5.45$, $df = 1, 14$, $p = 0.036$), with a significant effect of the 'Noticing' dimension (standardized coefficient $\beta = 0.544$, $t = 2.335$, $p = 0.036$); age, the duration of smell or taste impairment, and Emotional-Awareness (MAIA-2) were not significant (all $p > 0.10$). No measure of mental health, well-being, or interoceptive awareness showed a significant difference between pre- and post-CVFLA assessments (all p values >0.10).

An improvement in taste and smell following the intervention was also visible in the smell and taste identification accuracy (ODOFIN test) scores (Figures 3, 4) of 8 participants for whom pre- and post-intervention data were available (unavailable for 7 participants due to late arrival of the test kit or no final in-person follow-up assessment). Exploratory analyses of these data across the entire sample using repeated-measures ANOVAs (Table 5) indicated significantly higher identification accuracy for smells at the post-intervention assessment compared to the pre-intervention assessment ($p \leq 0.004$) (see Table 5). There was a positive change also for taste identification accuracy, but only at the trend level. Improvements in smell identification correlated in the same direction as noted earlier for subjective ratings but

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TABLE 4 Post-CVFLA feedback from individual study participants.

Post-CVFLA Feedback (n-11)	Questions				
	Overall, how did you find the CVFLA?	Do you believe the CVFLA has aided in improving your loss and/or distorted sense of taste and/or smell?	Did you find the intervention enjoyable and helpful?	Did you practice the methods and techniques used during the sessions at home or any other place than the lab?	Will you recommend this to other individuals with Taste and Smell impairments?
	Response Options				
	1=not at all useful	1=not at all	1=not at all	1=not at all	1=not at all
	2=not really useful	2=not really	2=not really	2=not really	2=not really
	3=yes generally useful	3=yes generally	3=yes generally	3=yes generally	3=yes generally
	4=yes definitely useful	4=yes definitely	4=yes definitely	4=yes definitely	4=yes definitely
Participant no.	Participant responses				
01	4	4	4	1	4
03	3	4	4	1	4
04	4	4	4	4	4
05	3	3	4	1	4
09	4	4	4	2	4
10	3	4	3	4	4
11	4	4	4	4	4
12	4	4	4	4	4
13	3	4	4	2	4
14	4	4	4	2	4
15	4	4	4	2	4

non-significantly ($n = 8$) with symptom duration [$r = -0.688$ (95% CI -0.938, 0.032), $p = 0.059$] and Noticing dimension of the MAIA-2 (Interoceptive Awareness) scale [$r = 0.504$ (95% CI 0.311, 0.892), $p = 0.203$] (no correlation with age, $r = 0.016$).

4. Discussion

This was the first study to assess the feasibility and acceptability of a new Camera-Based Visual Feedback Learning Aid (CVFLA) and explore its potential to restore or improve persistent COVID-19-related smell and/or taste impairment. The findings demonstrated that this non-invasive intervention is highly acceptable and can be easily administered even in non-clinical settings, contributing to the accessibility and feasibility of the intervention. The findings also suggested that the intervention could be helpful to people who have COVID-19-related loss or distortion of smell and taste, with relatively stronger benefits in people who scored relatively higher on the "noticing" aspect of interoceptive awareness (assessed with items, such as "I notice changes in my breathing, such as whether it slows down or speeds up."). The effects of CVFLA seemed somewhat stronger for smell than taste; and for recovery of the lost smell or taste, relative to correction of distorted smell or taste though this might, at least partly, be explained by the sample characteristics (i.e., relatively more severe impairment of smell than taste; and relatively more participants with loss of the sense of smell/taste rather than the distorted sense of smell or taste).

The findings of this proof-of-concept study support the CVFLA as a novel and innovative approach to improving smell and taste that is scalable and may also be preferable to other treatments for taste and smell recovery, such as corticosteroids (Harless and Liang, 2016), which may cause dependency and side-effects in at least a proportion of the users. Furthermore, this approach to improving or correcting smell and taste may also be applied in many different clinical and non-clinical settings, for example, in the context of aging (Delgado-Lima et al., 2023) and neurodegenerative disorders (Hawkes, 2006) where smell and taste alterations are typical problems. However, this was the first study to have tested this intervention in a relatively small number of participants who appeared highly motivated to regain their sense of smell and taste (some people cried with happiness when first reporting improvement during the session). Further studies involving larger samples and appropriate control groups are needed to confirm

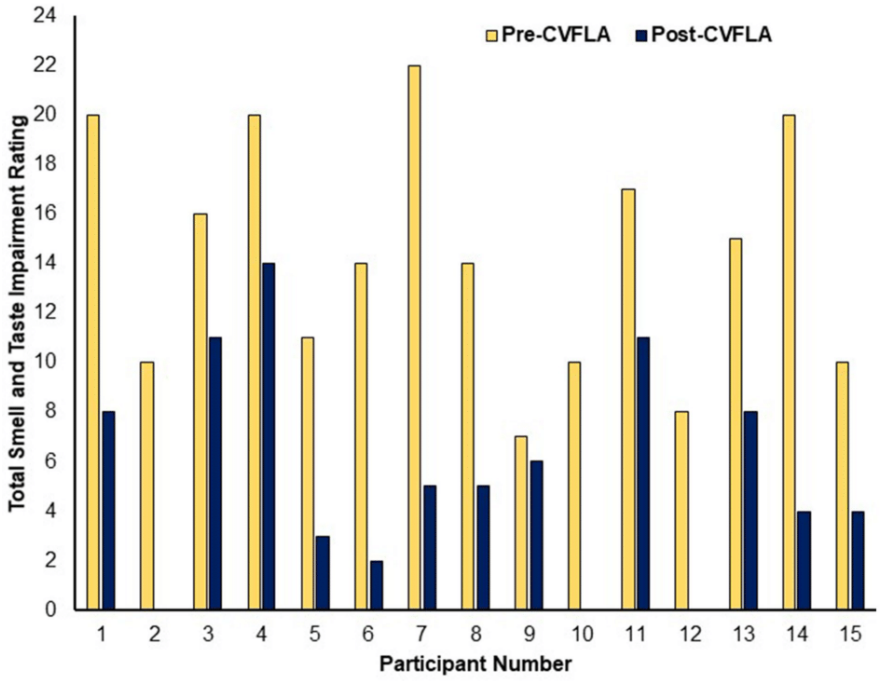

FIGURE 2
Subjective ratings of total smell and taste impairment before and after the CVFLA intervention.

TABLE 5 Descriptive statistics for subjective ratings of smell and taste impairment and objective (ODOFIN test) assessment of smell and taste identification accuracy before and after the CVFLA intervention and the results of the ANOVAs analyses.

Assessment	Pre-CVFLA (baseline)	Post-CVFLA	ANOVA: Pre- vs. Post-CVFLA comparison		
Subjective ratings of impairment	Mean (*SD*)	Mean (*SD*)	*F (df= 1.14)*	*p*	Effect size (η_p^2)
Loss of smell	4.33 (1.23)	1.33 (1.17)	72.69	**<0.001**	0.839
Distorted smell	3.60 (2.10)	1.67 (1.45)	21.25	**<0.001**	0.603
Loss of taste	3.20 (1.97)	1.00 (1.07)	18.68	**<0.001**	0.572
Distorted taste	3.13 (1.99)	1.40 (1.30)	11.92	**0.004**	0.460
Total (Smell and Taste) Impairment	14.27 (4.83)	5.40 (4.30)	67.19	**<0.001**	0.828
ODOFIN test for smell and taste identification accuracy[a]	Mean (*SD*)	Mean (*SD*)	$F\,(df = 1.7)$	*p*	Effect size (η_p^2)
Left nostrils	7.12 (2.36)	10.37 (1.40)	23.20	**0.002**	0.768
Right nostrils	7.37 (2.26)	10.37 (1.19)	12.60	**0.009**	0.643
Both nostrils	7.37 (2.39)	10.75 (1.03)	20.01	**0.003**	0.741
Taste test total[a]	3.12 (0.99)	3.87 (0.35)	4.20	0.08	0.375

[a]Sample size reduced to 8 due to late arrival of the test kit or missed final in-person follow-up assessment.

its potential for recovering or correcting smell and taste in relevant clinical and non-clinical populations.

Concerning the possible mechanisms that might be involved in smell or taste improvement following the CVFLA intervention, one possibility is that it facilitated re-learning of the smell or taste via their correct prediction by the brain (from previous episodic memories of the smell and food items) in response to the visual signals received during the intervention sessions (Clark, 2013; Hutchinson and Barrett, 2019). For example, as shown in Figure 1, the taste of a banana may be re-learnt with additional visual feedback provided to the participant to learn from, since the "taste" of the banana has been learnt previously and is most likely being predicted. Our finding showing a positive relationship between the 'noticing' aspect of interoceptive awareness and the degree of improvement suggests that attention and interoceptive awareness may facilitate this effect. There is recent evidence for COVID-19 related anosmia to be associated with higher functional connectivity between the left orbitofrontal cortex and visual association areas, along with greater cerebral blood flow in the hippocampus, insula, and posterior cingulate (Wingrove et al., 2023). Some of these areas may be involved in CVFLA-led benefits given

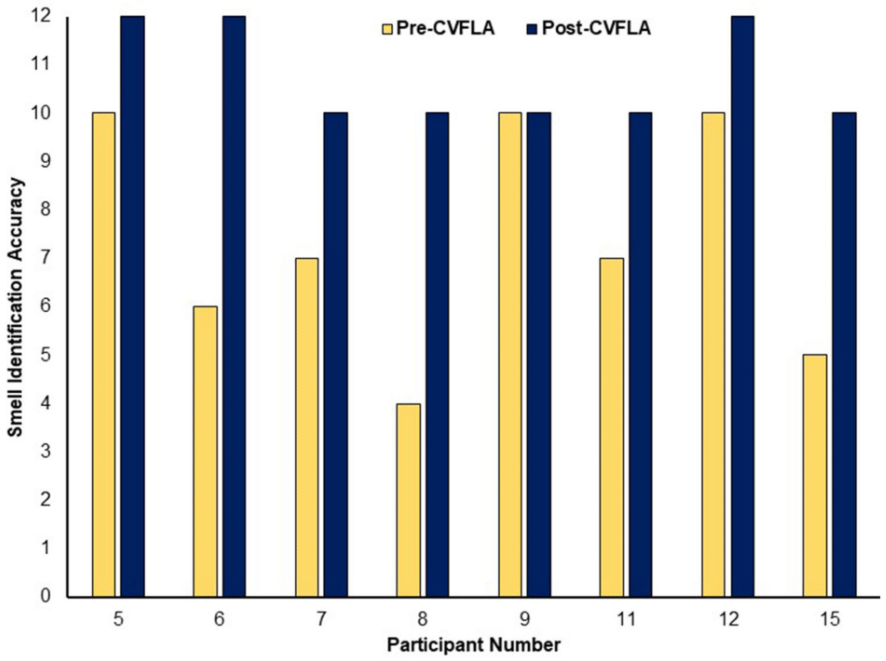

FIGURE 3
Objective (ODOFIN test) assessment of smell identification accuracy before and after the CVFLA intervention. With the 12 Sniffin' Sticks test, scores 0–6 indicate anosmia, scores 7–10 indicate hyposmia, and scores 11–12 indicate normosmia.

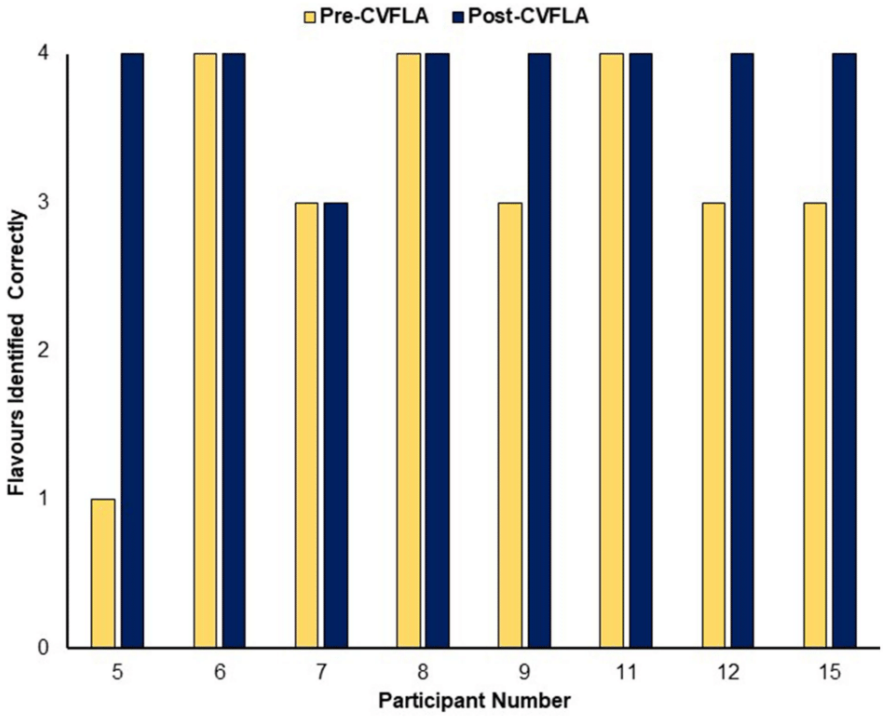

FIGURE 4
Objective (ODOFIN test) assessment of taste identification accuracy before and after the CVFLA intervention.

their known roles in episodic memory (hippocampus; Danieli et al., 2023), interoceptive awareness (insula; Craig, 2009; Evrard, 2019), and recall of self-related information (posterior cingulate; Morel et al., 2014). Another factor deserving some comment in the context of our study is the use of breathing exercises during the intervention sessions that may have contributed, at least partly, to the observed smell and

taste improvement, given recent evidence for respiration-driven normalization of the olfactory cortex (Gonzalez et al., 2023).

The present study had a number of limitations. First, the study involved only 15 participants and four of these participants did not complete their final in-person post-intervention assessments. Second, it cannot be ruled out that some improvement in taste and smell, especially in participants who had less than eight weeks of impairment, occurred simply with time (independent of 5–10 weeks of receiving CVFLA), although a noticeable improvement was also present in participants who had smell and taste impairment for more than six months, and all participants subjectively reported that the CVFLA intervention was helpful to them. Third, some participants reported practicing smelling and tasting in front of a mirror in between intervention sessions which may have potentially introduced a confound. Fourth, we did not use the complete Sniffin' Sticks Extended test which may have provided a more detailed assessment of the olfactory function and, in addition, complete pre- and post-CVFLA data on ODOFIN test assessment of smell and taste identification accuracy were available for only 8 of the 15 participants due to late arrival of the test kit or missed final in-person follow-up assessment for various reasons. Lastly, the intervention may be more beneficial for the recovery of smell than taste or, alternatively, the recovery of taste may follow smell recovery. A longer follow-up of the participants in further studies may help to clarify this as well as any secondary effects on mental health that may follow a different time course.

In conclusion, the new CVFLA intervention tested in this proof-of-concept study showed a very high level of acceptability and appeared to be a promising powerful tool to improve smell and taste. Further studies involving larger samples and appropriate control groups are required to confirm the effectiveness of this new intervention in improving smell and/or taste impairment in relevant non-clinical and clinical groups and to examine potential mediators and moderators of its effectiveness.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the College of Health, Medicine and Life Sciences Research Ethics Committee (DLS) Brunel University London. The patients/participants provided their written informed consent to participate in this study.

Author contributions

VK and JB contributed to conceptualization of the study and funding acquisition. SC contributed to research design, participant recruitment, intervention delivery, data acquisition, manuscript creation, and review and editing. KV contributed to data acquisition and scoring, and manuscript review and editing. EA contributed to project administration, and manuscript review and editing. VK contributed to project administration, research design, data analysis, manuscript creation, and review and editing. JB contributed to staff training for intervention delivery. All authors have reviewed the manuscript prior to submission.

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Conflict of interest

JB was employed by Learning JBE Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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