Neuropsychological Consequences of COVID-19: Long COVID and the Relationship with Acute Illness

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June 2022

Submitted to the University of Hertfordshire in partial fulfilment of the requirements of the degree of Doctor of Clinical Psychology

Word count: 30704
Excluding abstract, acknowledgements, table of contents, list of tables and figures, list of appendices, tables, figures, references, and appendices.

Abstract

Rationale and aims: Long COVID has a substantial impact on quality of life for many, with international prevalence related to the worldwide COVID-19 pandemic. However, acute illness severity may not always predict the neuropsychological consequences in long COVID. This may be due to unique neurotropic mechanisms of the virus. Research to date has explored up to 12 months post infection but assessment is largely limited to screening and relies on cognitive testing alone to draw conclusions. Therefore, this research project aimed to answer two research questions: 'what are the objectively measured cognitive and emotional consequences of COVID-19/ long COVID at 20-24 months?' and 'how does this relate to the subjective experience of illness from COVID-19 and illness severity?'

Methodology: A two-part sequential explanatory mixed-methods design was used, firstly with inferential statistics to analyse data from cognitive testing and self-report mood measures. Participants (n=19) were assessed 20-24 months post infection. Results were compared between two groups: those that accessed a virtual hospital service (n=9) during the acute stages and those that accessed a long COVID service (n=10) at some stage after. Thematic analysis captured information from questionnaire responses to enhance findings.

Discussion: Many appear to recover cognitive function toward the 2-year mark, but some specific deficit in visuospatial, psychomotor and executive function was observed, which appears to be irrespective of illness severity. These concerns, often in combination with pandemic related concerns, had a substantial impact on quality of life for participants.

Implications: Due to the varied cognitive profile and substantial impact of long COVID, future research should utilise comprehensive cognitive testing in combination with accounts of participants' experiences of symptoms. Long COVID services could consider neuropsychological expertise for individualised assessment and therapy intervention.

Acknowledgements

With thanks to those that took part in this research, without you this would not have been possible. Thank you for committing to lengthy testing sessions and for your effort, which was evident throughout these. The information you have provided is invaluable. It has been a personal privilege to have met you and heard your stories.

To the research team: Dr. Gaby Parker, Dr. Keith Sullivan and Dr. Huw Williams, thank you for your support and guidance in making this research as impactful as possible. Your constant encouragement enabled me to continue at times when the project felt colossal, and I have learnt so much from our many warm research meetings.

I wish to extend my special thanks to Dr Paresh Patel who joined the research team as an expert by experience. You helped assure that the research maintained a position grounded in understanding the perspectives of those affected by offering valuable insights into the experience of COVID-19.

I would like to thank Cohort-19 whom I shared this journey with. Since presenting our research to each other at the very beginning I've been constantly inspired by the success we've shared at each stage. Your support has made the process that much more enjoyable.

To my friends and family, to mum and dad especially, I wish to show my appreciation for all that you have done, big and small, in supporting me throughout the past few years from the project's inception to completion. I'm continually grateful and inspired by your kindness and compassion.

Finally, a huge thank you to my wonderful partner, Charlotte, for keeping me on track and pushing me to keep going. You've helped in many ways, too many to list, and probably more than you know! You've always been willing to help in any way you can without hesitance, and I couldn't have done this without you.

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Introduction

1.1 Key Terms

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): SARS-CoV-2 is a strain of virus first identified in Wuhan, China in late 2019. It is responsible for the current ongoing pandemic as it causes the respiratory illness, COVID-19.

Coronavirus Disease 2019 (COVID-19): COVID-19 is the respiratory illness resulting from the virus SARS-CoV-2.

Long COVID: Long COVID is a condition related to persistent and/ or novel symptoms resulting from illness from COVID-19 and is typically defined by symptoms which persist beyond 12 weeks.

Neuropsychological: Neuropsychological refers to the branch of psychological understanding concerned with a person's cognition and behaviour in relation to the brain and nervous system.

1.2 Overview of Introduction

This research explored the long-term neuropsychological consequences of the COVID-19 illness caused by SARS-CoV-2, typically referred to as 'long COVID'. It compared patients referred to two National Health Service (NHS) COVID-19 services: an acute virtual hospital pathway and a long COVID pathway. In this chapter I situate myself within the context of the research, including my relationship to the topic as well as my ontological, epistemological, and philosophical position toward the research methodology. The chapter then reviews the current (and rapidly developing) literature on COVID-19, focused on aspects relevant to clinical neuropsychology and wider professions. It concludes by outlining the rationale for the subsequent systematic literature review.

1.3 Situating Myself and the Research

Before accepting a place on the Doctorate in Clinical Psychology (DClinPsy) course at University of Hertfordshire I completed a Masters in Applied Neuropsychology where I developed my interest within the field. My first placement whilst training for the DClinPsy was within neurorehabilitation and it was here that I began considering options for a neuropsychologically-informed final year thesis. I wanted to complete research within this field as it was familiar to me and because I aim to complete a postgraduate Qualification in Clinical Neuropsychology, which requires relevant research experience.

Toward the end of my first placement, COVID-19 spread through to the United Kingdom (UK) and in March 2020 I was involved in supporting the service prepare for an expected increase in hospital discharges in order to prepare for the influx of COVID-19 cases. Like many others, I had not expected the pandemic to evolve into the chronic issue that it has since become and a short time later, after many of my family and friends had fallen ill with COVID-19, I was due to select a topic for my thesis. Upon meeting in July 2020 with the external supervisor, Dr Gaby Parker, to discuss potential projects, she invited me to meet with a COVID-19 specialist interest group comprised of senior neuropsychologists in clinical and academic practice. It was at one of their meetings in August 2020 that I first learned about the complexity and persistence of neurological concerns associated with COVID-19. At the time this seemed an area which was still in its infancy in terms of research, and I felt that there was clear potential for developments to have a substantial impact on the wellbeing of those affected.

Specifically, many early reports in the media about persistent symptomatology from COVID-19 described how many individuals felt misunderstood or dismissed by medical professionals as cognitive impairments were felt to be “invisible” (Volpe & Diamond, 2021). These descriptions seemed to mirror how some of my clients had felt in clinical practice

within neuropsychology services, and had a personal resonance too, as my mother often reports experiencing her diagnosis of Multiple Sclerosis in a similar way. These concerns are commonly observed within neuropsychological contexts when client difficulties relate to cognitive impairment and/or fatigue (Goldstein & McNeil, 2013). Because of these connections to the topic, conducting research to illustrate the neuropsychological consequences of COVID-19 felt like an important and worthy research contribution. Doing so would hopefully raise awareness of the specific concerns experienced by this cohort to the professionals in a position to support them, and guide service developments that could enable effective support.

With these initial ideas in mind, the project developed further in April 2021 following meetings with local respiratory service leads across two NHS services. These services were involved with COVID-19 throughout the pandemic, working collaboratively across both acute and community services, and included a 'virtual hospital' team (who worked with all patients attending hospital with COVID-19) and a long COVID pathway (who worked with patients experiencing long COVID symptoms) (see 1.5 for more information). When discussing possible research options, it appeared that there was an important, seemingly unexplained, discrepancy being observed between those with more severe symptoms in the acute stages who had been seen by the virtual hospital, and those with initially less severe symptoms who had not been seen in acute hospitals, but had later gone on to be referred to the long COVID pathway. At the time it seemed that exploring this discrepancy in some way within the research would be beneficial in providing initial hypotheses as to why it might be present. Based on the rapidly developing literature at the time, it seemed that neuropsychological consequences across cognition and emotion would be central in understanding this. However, I was also aware of being drawn to many different ideas from different stakeholders in the research, and the practicalities of seeking to answer multiple

complex research questions within the confines of this thesis. In the end, the final IRAS form submitted in September 2021 proposed research that would explore the neuropsychological consequences more broadly, as well as specifically focus on comparing two groups from the two service pathways.

1.3.1 Ontological, epistemological, and philosophical position.

"The 3 fundamental elements of research are ontology, what exists in the human world that researchers can acquire knowledge about; epistemology, how knowledge is created; and philosophical perspective, the philosophical orientation of the researcher that guides her or his action." (Moon & Blackman, 2014, p. 1167). Defining my position on each of these elements can help situate the research and aid other researchers in interpreting how meaning is drawn from the research. Moon and Blackman (2014) provide a useful framework for positioning oneself across these elements (see Appendix A).

Using this guide, I suggest that this research takes an ontological position of "Critical Realist". Critical Realism suggests one reality that cannot be observed by humans but that has unobservable structures causing observable events. It is often viewed as a middle ground between Naïve Realist and Relativist positions. As a result of this position, the present research attempts to acquire knowledge about participants' experiences of cognitive and emotional difficulties by enquiring about perceptions of findings from neuropsychological assessment. The epistemological position is best described as "constructionism" as this research aims to generate data from objective neuropsychological assessment that it will then contrast with participants' reports of subjective reality. Finally, the philosophical position is best described as "pragmatic", recognising that multiple professional disciplines and research methodologies might be required to understand the extent of difficulties experienced in COVID-19, given the literature is only gradually emerging over time.

1.4 Background Literature

1.4.1 Coronaviruses and COVID-19.

Coronaviruses (CoVs) are a group of zoonotic viruses thought to be particularly efficient at mutation and adaptation, causing them to spread quickly amongst and across different species (NIAID, 2022). In humans, a total of seven CoV strains have been identified, four of which have caused relatively mild symptomatology involving respiratory tract infections. More severe respiratory symptoms were observed with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012. These both led to localised epidemics with high morbidity rates and large economic losses. SARS-CoV had registered 8096 confirmed cases and 774 deaths whilst MERS-CoV registered 2494 confirmed cases and 858 deaths (WHO, 2022). SARS-CoV-2, the strain of the virus causing the illness COVID-19, was officially classified as a pandemic in March 2020 by the World Health Organization (WHO, 2020) as the severe illness spread further from the initial outbreak focus in Wuhan, China, affecting many people in countries across the world. In contrast to previous coronavirus epidemics, as of the sixth May 20222, SARS-CoV-2 has registered 535,513,054 confirmed cases and 6,321,701 deaths (Worldometer, 2022) . This illustrates the severity of the current pandemic in comparison to similar viruses, which is thought to be due, at least in part, to increasing globalisation (Yacoub & El-Zomer, 2020).

COVID-19 is associated with a range of clinical presentations which are commonly grouped by severity (e.g., asymptomatic, mild, moderate, severe and critical illness; NIH, 2021). Severity is typically ranked primarily by presence of symptoms and respiratory disease; the latter being determined by blood oxygen saturation (SpO2). Table 1 displays commonly reported symptoms of COVID-19 (CDC, 2022) and long COVID (CDC, 2021), described in more detail in the next section. Importantly, in the UK, there have been several

major virus variants of concern: Alpha, Delta, Omicron BA1, and the current sub-variant Omicron BA2 (UKHSA, 2022). There are identifiable differences in the severity and transmissibility of these. The Alpha and Delta variants are more fatal than Omicron, whilst Omicron is more transmissible. This is thought to be because the earlier variants, Alpha and Delta, were more invasive through the deeper sections of the lungs whereas Omicron infects faster in the bronchus (Dyer, 2021). It is worth noting that much of the earlier research, contributing the bulk of literature in this introduction, focuses on the first variants. Because of the severity and prevalence differences, the initial stages of the pandemic from March as well as the beginning of the Delta variant surge led to substantial pressures on health services in the UK. As of March 2022, national social distancing restrictions have diminished, despite prevalence of the illness thought to be at an all-time high (ONS, 2022).

Table 1

Centre for Disease Control and Prevention (CDC) commonly reported symptoms

COVID-19 symptoms (CDC, 2022)	Long COVID symptoms (CDC, 2021)
Difficulty breathing or shortness of breath	Difficulty breathing or shortness of breath
Tiredness or fatigue	Tiredness or fatigue
Cough	Cough
New loss of taste or smell	New loss of taste or smell
Joint or muscle pain	Joint or muscle pain
Headache	Headache
Diarrhoea	Diarrhoea
Fever or chills	Chest or stomach pain
Sore throat	Mood changes
Congestion or runny nose	Dizziness on standing (lightheadedness)
Nausea or vomiting	Pins-and-needles feeling
	Sleep problems
	Fever
	Changes in menstrual cycles
	Rash
	Symptoms that get worse after physical or mental activities (also known as post-exertional malaise)
	Fast-beating or pounding heart (also known as heart palpitations)
	Difficulty thinking or concentrating (sometimes referred to as “brain fog”)

1.4.1.1 Health inequalities.

Despite narratives that we are "all in it together" and that the virus "does not discriminate" from politicians and mainstream media throughout the current pandemic (Sky News, 2020), several health inequalities have been highlighted because of COVID-19. As has been demonstrated historically with the Spanish influenza pandemic in 1918 and the H1N1 influenza pandemic in 2009, rates of infection and mortality are three times higher in the most deprived areas of the UK compared to the least (Bambra et al., 2020). Existing social inequalities between the least and most deprived areas of the UK are likely to influence which populations of people are most adversely affected by COVID-19. For example, in England and Wales, people from Black, Asian or other minority ethnic groups accounted for 34.5% of critically ill COVID-19 patients, which is higher than the 11.5% usually seen with viral pneumonia (Intensive Care National Audit Research Centre; ICNARC, 2020) . In a systematic review of mortality-related risk factors, Dessie and Zewotir (2021) observed that older age was the most significant risk factor, followed by male gender and cigarette smokers. Bai et al. (2022) conversly suggest that females may be more likely to be adversly affected in the long-term. Long term health conditions such as Chronic Obstructive Pulmonary Disease (COPD), cardiovascular disease, diabetes, hypertension, obesity, cancer, and acute kidney injury (AKI) were also significant risk factors (Dessie & Zewotir, 2021). A full review of the interaction between social-health inequalities and health is beyond the scope of this thesis. However, to appreciate the context of the research and position of the researcher, Merrill Singer's term "syndemic" is helpful to consider: this means "a set of closely intertwined and mutual enhancing health problems that significantly affect the overall health status of a population within the context of a perpetuating configuration of noxious social conditions." (Singer, 2000, p. 24).

1.4.2 Long COVID.

Although most that fall ill with COVID-19 will go on to fully recover, many will experience symptoms beyond the acute stages of infection. If these symptoms remain past 12 weeks, then a diagnosis of long COVID may be considered. Long COVID is a patient-created term that has since been adopted and is typically used to describe both ongoing symptomatic COVID-19 as well as post-COVID-19 syndrome (NHS England and NHS Improvement, 2021). This captures symptoms that persist from initial infection and/or new novel symptoms considered to be a direct result of COVID-19 illness. The prevalence of long COVID is expected to be as high as 10% of all COVID-19 illnesses (ONS, 2022) with broad symptoms (see Table 1) impacting on multiple systems within the body (CDC, 2021). Health inequalities are likely somewhat similar to those seen with the initial illness of COVID-19. For example, an audit of long COVID referrals to an NHS Trust recently found a 2:1 ratio of male to female patients and a higher incidence of patients from Black, Asian and Minority Ethnic groups when compared to local area census data (Wilson, 2021).

A recent study conducted via an online survey explored the multi-system impact of long COVID in a large international sample of 3762 participants (Davis, et al., 2021). They explored the prevalence of symptoms across 10 organ systems and found that fatigue, post-exertional malaise and cognitive dysfunction were the most frequently reported. Secondary to this, they describe how relapses in symptoms across all organ systems were often triggered by physical exertion and stress. 45% of the participants in the study were required to work a reduced schedule and 22% were not working at all. This points to a substantial impact of symptoms on quality of life and ability to carry out activities of daily living. Although a multi-system impact is evident in long COVID, the nature and impact of many common symptoms highlights the need for neuropsychological expertise. A more detailed review of the psychological and neurological impact is described below.

1.4.3 Psychological consequences of COVID-19.

Cenat et al. (2021) conducted a systematic review and meta-analysis of the literature exploring the prevalence and type of psychological consequences of COVID-19, predominantly with self-reported outcome measures. Symptoms of depression and anxiety were observed in 15%, insomnia in 24%, PTSD in 22% and psychological distress in 13% of the populations studied. These were the five most commonly researched areas and were reported in this study for this reason. The findings represent a three to five times higher prevalence than seen in the general population, based on a previous World Health Organization study (WHO, 2017). No definition of psychological distress was provided, but the articles reviewed included outcome measures relating to general psychological wellbeing and coping. The utility of self-reported outcome measures in assessing complex psychological processes is often critiqued (Wright, 2011), however the study is useful in highlighting the prevalence of these issues. When reviewing differences across countries, gender and in healthcare workers, they found similar prevalence between groups except that healthcare workers were significantly more likely to report insomnia. Importantly, 33 out of the 55 studies included were conducted in China and none of the studies included reported on UK prevalence. However, Butler et al. (2020) as part of the comprehensive CoroNerve study, reported similar initial findings in the UK and observed similarities to findings following SARS-CoV and MERS-CoV. The authors point to a need for further research to guide our understanding of the psychological processes, especially in relation to long COVID.

Briefly, psychological consequences of COVID-19 are usefully described as a complex interplay between biological, psychological and sociological factors (Hussan, 2022). This section will explore these factors with a focus on the literature on psychological consequences of long COVID, as opposed to those symptoms and factors relevant at the acute phase.

1.4.3.1 Biological.

As mentioned, COVID-19 and long COVID symptoms (see Table 1) are numerous and varied. Poor physical health is often related to poor mental health, especially as severity increases the need for medical intervention (Marks, Murray, Evans, & Estacio, 2011). Some symptoms of long COVID overlap with difficulties experienced by many with various long-term health conditions. People with long COVID tend to relate to the subjective experience of 'brain fog' and cognitive impairment, which will be reviewed separately in the next chapter (see 1.4.4). A related concern is increased fatigue, which appears to be one of the most debilitating symptoms. Finally, all of the physical symptoms experienced can be substantially exacerbated in many after even minor physical or mental exertion, known as post-exertional malaise (Davis, et al., 2021).

1.4.3.2 Psychological.

Psychological consequences of COVID-19 in part relate to trauma processes. This could be as a result of being required to attend hospital and perhaps specifically Intensive Care Units (ICU) which would have been accommodated with patients experiencing similar difficulties, many of which would have sadly lost their lives (Dutheil, Mondillon, & Navel, 2020). Additionally, the lack of information and understanding of virus mechanisms would have led to an experience of trauma for many and may describe the increase in reported symptoms of anxiety (Cenat et al., 2021). The Y-Shaped process model is useful in describing how psychological consequences may arise in those with long COVID. The model depicts a process in which discrepancies in pre-morbid relationships, abilities and goals conflict with the self in the current context (Gracey, Malley, & Evans, 2009). In light of these difficulties, there is some evidence to suggest a mediating influence on poor psychological consequences with high self-efficacy and resilience (Paredes et al., 2021). Feeling in control

and able to cope with the physical, psychological and social outcomes of long COVID is likely, in turn, to improve outcomes.

1.4.3.3 Sociological.

Psychological consequences of illness from long COVID can only be fully understood within the unprecedented context of this pandemic. As the most severe pandemic that humanity has seen (WHO, 2020; Worldometer, 2022) there is still much to learn about the mechanisms of the illness as well as how the world responded to it. In the UK and many other parts of the world, national lockdowns meant that many experienced a sudden limited social life, less exercise, changes to work and complete restructuring of daily routine. For many this caused high levels of uncertainty, loss of jobs and an inability to be with loved ones whilst ill with COVID-19. This had and still has a catastrophic effect on people's quality of life. Media reports of mortality associated with COVID-19 would have also exacerbated fears of dying or of substantial changes to national economy and politics (The Health Foundation, 2020). For those with long COVID, this is exacerbated further by illness variables (such as fatigue and cognitive impairment) which have, in many cases, meant further loss of jobs and disruption to quality of life (Davis, et al., 2021). Accordingly, a systematic review (Macpherson, et al., 2022) conducted on the qualitative literature published on long COVID concluded that, when asked about their experience, participants often commented on self-management, varied emotional experiences and challenges with healthcare services.

1.4.4 Neurological consequences of COVID-19.

Understanding the mechanisms of COVID-19's effect on the nervous system is of crucial importance to neuropsychologists if it is expected that this results in cognitive, emotional or behavioural difficulties for those affected (Sozzi et al., 2020; Wilson,

Betteridge, & Fish, 2020). Of the most commonly reported persisting symptoms of COVID-19 listed by the CDC (2021) (see Table 1), symptoms such as fatigue, headache and light headedness are suggestive of potential neurological involvement. Additionally, anosmia (loss of smell) and ageusia (loss of taste) are often reported as initial indicators of COVID-19 which suggests that this may manifest early in some cases (Leichen, et al., 2020). In a systematic review conducted by Misra et al. (2021), one third of COVID-19 patients experienced at least one neurological symptom. Because of these observations, researchers set out to explore the potential neurological involvement and SARS-CoV-2 is now thought of as a neurotropic virus, which means it is capable of infecting nerve tissue (White, 2012). Aghagoli et al. (2021, p. 1063) state 'The reported neurologic effects of COVID-19 infection are myriad and may include complications related to viral infection, immune response, critical illness, related therapies and recovery'. In their recent review, they categorise findings under three main mechanisms: cytokine storm, Angiotensin-converting enzyme 2 (ACE2) enzyme pathways, and secondary effects. Although research efforts are currently ongoing and often incongruent in their appreciation of these mechanisms (Maiese, et al., 2021), a brief description is provided here based on Aghagoli, et al. (2021).

1.4.4.1 Indirect via cytokine storm.

In what has been referred to as COVID-19 cytokine storm syndrome (Chen & Quach, 2021), maladaptive immune response is thought to lead to increase in cytokines that have been identified in those suffering from the illness. These are proteins that are responsible for activation and growth of cells in the immune system and, when released, affect inflammation responses (Murphy & Weaver, 2016). They are able to cross the blood-brain barrier, which is made up of endothelial cells that's role it is to protect the brain by regulating exchange of substances (like SARS-CoV-2) between blood and tissue. The blood-brain barrier is compromised by the crossing of cytokines, with the secondary consequence of inflammation

in the central nervous system (CNS; Chen & Quach, 2021). This may explain why some post-mortem neuroimaging studies observe limited direct impact of SARS-CoV-2 infection within the brain, due to lower-than-expected levels of the virus itself (Solomon, et al., 2020).

1.4.4.2 Direct via angiotensin-converting enzyme 2 (ACE2).

SARS-CoV-2 might also directly impact on the brain by attaching to ACE2. Attaching to this enzyme allows the virus to infiltrate the associated cell and then multiply inside it, impairing its capabilities. It was initially thought that ACE2 was only found in cells of the lungs, kidneys, heart and gut, but research has since shown that it is also present in the supporting cells of the olfactory epithelium (Fodoulian, et al., 2020). It has been suggested that the high levels of ACE2 in these supporting cells, found near the mouth and nose, may explain the initial anosmia and ageusia experienced by many with COVID-19 (Ellul, et al., 2020). Conversely, Cui et al. (2021) found evidence for neuronal cell ACE2 expression across all brain regions in post-mortem studies of COVID-19, with high levels found in the pons, visual cortex, and amygdala. The authors suggest this indicates greater virus-provoked damage to these specific regions but point to the need for further research to identify the relationship with clinical symptoms.

1.4.4.3 Secondary effects.

Finally, COVID-19 can have several secondary neurological consequences. Aghagoli et al. (2021) describe how it might increase the likelihood of thrombosis in the blood. Helms et al. (2020) suggest this is above what would be expected in similar non-COVID conditions (e.g., ARDS or influenza) and that it may cause deep vein thrombosis, pulmonary embolism and acute ischemic stroke. In the UK, the national CoroNerve Studies Group (2021) carefully catalogued cases of patients presenting to hospitals nationally with neurological symptoms. They found that, from 125 COVID-19 patients studied, 74% had an ischaemic stroke, 12% an

intracerebral haemorrhage and 1% had CNS vasculitis (Varatharaj et al., 2020). Hypoxia is also common, especially in those with more severe respiratory symptoms, and may occur in the acute or post-acute stages (Rahman, et al., 2021) consistent with the severity of acute illness often being ascertained by SpO2 levels (NIH, 2021).

1.4.4.4 Brain areas affected.

It seems clear from the neurological literature that SARS-CoV-2 can have a varied and substantial impact on the brain and CNS in a subset of patients with COVID-19 illness. As Cui et al. (2021) indicate in their observation of ACE2 expression across the brain, it is plausible that COVID-19 may affect certain brain regions more than others. Identifying potential patterns of lesioning may add to a biopsychosocial approach to formulating research and generating clinical hypotheses in practice. Wilson and Betteridge (2019) describe this in terms of a triangulation process between the evidence from neuroanatomical findings, cognitive assessment and function/ behaviour, which informs clinical practice. Professionals working early in the pandemic anecdotally reported frontal and temporal lobe lesion were more likely although others have observed posterior damage (Wilson, 2021). Neuroimaging studies have since attempted to confirm these observations and have evidenced abnormalities in areas such as the hippocampus (Lu, et al., 2020), fronto-parietal network (Butowt & Bilinska, 2020), thalamus (Griffanti, et al., 2021) and orbital gyrus rectus/ right medial temporal lobe (Guedj, et al., 2021). Poyiadji et al. (2020) also report similar findings across these specific areas. However, none of these studies were able to indicate whether the broad range of abnormalities observed predated COVID-19 infection.

Recently, a large UK Biobank study explored multi-model serial neuroimaging of 785 participants (Douaud et al., 2022), including 401 participants who contracted COVID-19 between their first and second scans, plus 384 control participants. Having access to pre COVID-19 images and a control group increases the reliability and validity of findings as it

reduces the possibility of a type two error. Where previous neuroimaging research has mainly explored participants with severe COVID-19 symptoms, this study includes participants with mild-moderate symptoms. The authors suggest that those infected by COVID-19 show a 'greater reduction in grey matter thickness and tissue-contrast in the orbitofrontal cortex and parahippocampal gyrus, greater changes in markers of tissue damage in regions functionally-connected to the primary olfactory cortex, and greater reduction in global brain size.' (Douaud et al., 2022, p. 1). The study suggests that findings were still observed when data from the 15 hospitalised participants, with severe acute symptoms, were excluded.

1.4.5 Impact on cognition.

The impact of SARS-CoV-2 on cognition is complex, varied and often substantial, playing a key role in the difficulties experienced by those with COVID-19 and long COVID. Whilst hospitalised, patients might undergo cognitive testing as part of assessment protocols, offering the opportunity to detail the cognitive profiles in these more severe presentations. Ritchie, Chan and Watermeyer (2020) observed that 70% of COVID-19 patients on ICU needed ventilation, linking this to previous research on ARDS demonstrating 78% of patients experienced cognitive problems post-discharge. There is also a growing recognition that milder COVID-19 illness can also lead to cognitive difficulties; however, there are several barriers to researching this, including strains on healthcare services and restrictions on face-to-face assessment (NHS, 2022). Short batteries of tests typically used for screening impairment may not be sufficiently sensitive to identify nuanced difficulties in mildly affected cohorts (Lezak, et al., 2012), particularly when sample sizes are small (Pallant, 2016). Smaller studies are also likely to be unable to account for differences within populations such as across age, gender or racial-ethnic group. These issues present a substantial barrier for research exploring the full impact on cognition across different severities of illness from COVID-19 and, subsequently, long COVID.

One study in particular was able to negate many of these obstacles by exploring data from The Great British Intelligence Test. This was a TV show from BBC Two Horizon in collaboration with Imperial College London that, just before the pandemic, published an open invite for participants to complete a cognitive testing battery online (BBC, 2022). As a result of the pandemic, they subsequently included questions exploring COVID-19 exposure. Data from a sample of 12689 COVID-19 exposed participants were then compared with 68648 non-exposed controls (Hampshire et al., 2021). It is important to acknowledge the limitations of such online cognitive testing; the transferability of validated measures to virtual modalities (without re-norming) has rightly been criticised, and testing would have been unobserved, meaning (for example) there was no way to be sure that the individual has completed the testing alone. These challenges impact the reliability and validity of the results obtained. Despite these issues, the study justifies a battery of tests that covers some important areas of cognition and the large sample collected helps to reduces the chance of type one and type two errors substantially (Pallant, 2016). It appears that these tests were based on validated measures commonly used in clinical practice (Lezak et al., 2012) but with some appropriate adjustments made in order to make them feasible for virtual use. The large sample size also meant the authors could control for numerous confounding variables. A significant and substantial deficit in global cognitive score was observed across the COVID-19 participants, with greater deficit observed in tests of verbal reasoning, visual problem solving, visual planning, visual short-term memory and visual attention when compared to controls.

The Hampshire et al. (2021) study was conducted relatively early in the course of the pandemic and since then research in the field has developed rapidly. A recent systematic review and meta-analysis (Crivelli et al., 2022) summarised the literature exploring cognitive deficits in COVID-19 patients either during the acute stages or after recovery. Most of the studies incorporated focused on participants with more severe symptoms than the Hampshire

et al. (2021) study. Limited studies were identified that assessed cognitive function beyond 12 weeks post-infection (i.e., beyond the criterion for long COVID diagnosis). It was concluded that, up to three months, impairment was typically evident across executive functions, attention and memory. However, about half of the studies included only administered brief screens of cognitive ability, such as the Mini Mental State Exam (MMSE) or Montreal Cognitive Assessment (MoCA). Accordingly, elaborating which executive functions were impacted, or whether visual or verbal memory functions were more affected, was not possible. The authors acknowledge this lack of assessment across specific domains, but mention that in the few papers that did include detailed assessment, 'deficits were also seen in some studies for working memory, learning, delayed control, inhibitory control, set-shifting, phonological verbal fluency, and processing speed.' (Crivelli, et al., 2022, p. 17). Importantly, recommendations for future research were made that emphasised the need for longer follow ups (i.e., one year post infection) as well as ensuring the use of comprehensive cognitive test batteries.

1.4.5.1 Summary and correlation with neurological literature.

The cognitive deficits highlighted in this systematic review, as well as the large population study by Hampshire et al. (2021) are somewhat congruent with the wider literature on neurological consequences. However, it is difficult to completely integrate findings across these studies as the tests used were quite different. Above all else, it should be recognised that COVID-19 and long COVID have the potential to substantially impact a broad range of cognitive functions located across the brain. Specific concerns found in both of the studies may relate to deficits in some executive functions and in tasks of attention. Importantly, poor attention is likely to impact on the ability of participants to perform to the best of their abilities in tasks assessing other functions. With regard to the neurological literature, comparisons can be drawn between the studies on cognitive deficits, suspected vulnerable

brain areas and broader literature describing what functions specific brain regions may be responsible for. A full review of the latter is not possible here (but please see Goldstein & McNeil, 2013). A brief synthesis of and comparison of these areas of literature may be useful in highlighting potential correlations; however, these should not be taken as established facts.

Firstly, Hampshire et al. (2021) highlight visual deficits in four of the five functions highlighted to be of concern. This may be as a result of the high levels of ACE2 found in the pons, which is responsible for motor function and eye movement, and/or the visual cortex (Cui et al., 2021). Posterior lesions, including the occipital lobe, have also been reported in the UK (Wilson, 2021). Conversely, verbal functions appear relatively intact except for the suggestion of poorer phonemic verbal fluency (Crivelli, et al., 2022), which may be influenced by frontal lobe lesion (Butowt & Bilinska, 2020). Interestingly, previous research has found phonemic function correlates more with posterior-dorsal left inferior frontal gyrus, whilst semantic function correlates more with anterior-ventral inferior frontal gyrus (Costafred, et al., 2006), the latter located further away from viral entry points (Ellul, et al., 2020). Fronto-parietal lesions (Ellul, et al., 2020) along with evidence of hippocampal (Lu, et al., 2020), right medial temporal lobe (Guedj, et al., 2021) and parahippocampal gyrus lesions (Douaud, et al., 2022) may associate with the observed executive function deficit (Hampshire, et al., 2021; Crivelli, et al., 2022) and along with thalamic lesions (Griffanti, et al., 2021) may associate with attention and working memory deficits (Hampshire, et al., 2021; Crivelli, et al., 2022). Processing speed (Crivelli et al., 2022) may also be influenced by these. Finally, memory functions (Crivelli et al., 2022) and specifically visual short term memory (Hampshire et al., 2021) may be in influenced by temporal lobe (Wilson, 2021), hippocampus (Lu, et al., 2020), right medial temporal lobe (Guedj, et al., 2021) and parahippocampal gyrus lesions (Douaud, et al., 2022).

Psychological consequences of COVID-19 are also likely to influence cognition. For example, low mood (Snyder, 2013), anxiety (Castaneda et al., 2008) and trauma (Horner & Hamner, 2004) have all been linked to cognitive impairment in the absence of brain injury. The combination and potential interaction of cognitive and emotional sequelae of COVID-19 make it an important avenue of research and practice for neuropsychologists. The interplay of emotion and cognitive test results makes interpretation difficult.

1.5 Context of Services Involved in This Research

1.5.1 Virtual hospital pathway.

During the first wave of the pandemic, an NHS service set up a pilot for the first UK COVID-19 virtual hospital pathway that aimed to reduce pressure on NHS services by enabling easy referral and home monitoring of acute symptoms. The pilot was recognised in the Queen's Birthday 2020 Honours List after providing more than 10000 virtual consultations for over 1250 patients (Louis, 2020). The service was structured so that respiratory consultants reviewed refeerals into the service and provided different levels of support based on risk across age, comorbidities and symptomatology. When symptoms of concern were raised, these patients would quickly be transferred to hospital for early intervention. Initially patients were provided with pulse oximeters and reviewed virtually by healthcare workers to report on heart rate and blood oxygenation (Knight, et al., 2020). This developed to include the use of an app called Medopad, which allows patients to record their symptoms easily with their healthcare workers and includes measures of blood pressure and body temperature (Huma, 2021). Further to achieving its main goal in saving 1000 hospital beds, staff working at the service anecdotally report that their patients have commented feeling reassured and contained by the process. This is mirrored in formal feedback on the use of Medopad at the virtual hospital, with 93% of patients rating it as "good" or "very good", and patients commented on feeling reassured by these systems (NHSX, 2021).

1.5.2 Long COVID pathway.

In conjunction with the virtual hospital pathway service, another NHS service established a long COVID pathway in January 2021. This was set up to provide support for those experiencing long COVID either as ‘ongoing symptomatic COVID-19’ or ‘Post-COVID-19 syndrome’. This means where persistent or new symptoms, respectively, following infection with COVID-19 are apparent 12 weeks after acute illness. Following an initial national investment of £10 million in October 2020 and further investment of £24 million in March 2021 by NHS England and NHS improvement, similar services have since been set up across the country. Briefly, the specific aim of these services is to provide assessment for access to multidisciplinary team support that accounts for the multi-system impact of long COVID. Services should ensure access for groups who experience health inequalities and be directed by formal guidelines (NHS England and NHS Improvement, 2021). For example, the National Institute of Clinical Excellence (NICE) published guidelines in December 2020, updated in November 2021, that provide recommendations across assessment, planning care, service organisation and equality considerations as well as others (NICE, 2021).

Having completed initial informal audit of long COVID referrals, professionals at the NHS services noted that very few patients had been referred to both services. This is despite those being referred through to the virtual hospital being considered more likely to have had more severe acute symptoms given that they sought support from services at the time. This points to a potential discrepancy between patients with more severe acute symptoms but less likelihood of long COVID and those with less severe acute symptoms but a higher likelihood of long COVID. However, the level of support available from services at the time of illness as well as increased fear of attending hospital (The Health Foundation, 2020) will likely have impacted on who was referred to and/or accessed each service, complicating interpretation.

1.6 Summary of the Current Understanding of COVID-19

In a subset of people infected with SARS-CoV-2, COVID-19 illness can be severe and is capable of substantially impacting on the brain and CNS (Wilson, 2021). Milder illness can also have an effect (Misra et al., 2021; Douaud et al., 2022). Psychological consequences of COVID-19 relate to the experience of national lockdown, acute illness severity, trauma and self-efficacy (Paredes et al., 2021) but also cognitive functioning. The mechanisms involved in neurological impairment are relatively unique in SARS-CoV-2 infection, including cytokine storm, ACE2 enzyme pathways and secondary effects (Aghagoli et al, 2021). This can result in cognitive deficits which can be broad and varied (Hampshire et al., 2021; Crivelli et al., 2022). Whilst research has developed rapidly to catalogue acute psychological and cognitive consequences of COVID-19, there is limited research on expected cognitive profiles, especially for long COVID. The research that has been conducted tends to use brief cognitive screening tools which fail to describe the nuance of cognitive profiles across specific functions (Crivelli et al., 2022). Also, a large focus of research to date has been conducted on severe illness during wave 1 of the pandemic and there remains some discrepancy as to the consequences for those with mild-moderate acute illness or with more recent strains of the virus, such as Omicron. Of the research that has been conducted, there is some level of coherence with the neurological literature, such as visuospatial difficulties associated with lesions in the occipital lobe and executive function difficulties associated with the frontal lobe (Goldstein & McNeil, 2013). As services across the country continue to restructure to accommodate support for those reporting symptoms of long COVID, evidence informing hypotheses about cognitive impairment will be invaluable.

1.6.1 Need for research.

Research so far has demonstrated that cognitive and emotional consequences of COVID-19 are frequent, varied and have a substantial impact on quality of life. This has been observed more frequently and reliably in patients with more severe initial COVID-19 illness but research on large samples has also shown mild-moderate, but consistent, cognitive deficits. Much of the research has been conducted on patients from wave one of the pandemic, using short cognitive screens assessed in the short to medium term after infection. There is potential for future research to describe a more nuanced cognitive deficit profile and to explore the longevity of any potential cognitive deficits, especially past the 12-week long COVID criterion. So far, there is limited research exploring differences across demographics with demonstrated health inequalities highlighted by COVID-19, particularly across racial-ethnic groups. Finally, no mixed methods research was identified exploring how participants make sense of their cognitive test results. This would be useful in exploring how objective psychometric test data compares with subjective experience, supporting validation of any observed findings. In order to assess the extent to which these research goals have been met, a systematic literature review exploring the objectively measured cognitive impairments in those affected by long-COVID is set out in the next chapter.

Systematic Literature Review

2.1 Overview of Systematic Literature Review

This systematic review explores the following question: “What is the objectively measured cognitive impairment profile of those affected by long-COVID?”. I will comment on the literature search strategy and summarise the identified relevant literature. Results will be synthesised primarily to compare cognitive profiles and secondarily to highlight unique contributions from each study. I will then provide a critical review of the quality of each study. Finally, I will present how this review partially informed the rationale for the current research. Terminology used throughout will generally reflect the terminology found in the studies presented, unless otherwise stated.

2.2 Rationale

Since the start of the pandemic there have been increasing accounts of subjective cognitive complaints during the acute stages of infection from COVID-19 and, eventually, long-COVID. Persistent “brain fog” is reported as one of the main symptoms of long COVID, defined on the NHS website as involving problems with memory and concentration (NHS, 2022). To guide services in supporting clients with long-COVID it would be important to understand exactly what cognitive profiles or deficits are associated with the subjective experience of brain fog. This allows neuropsychologists and other professionals to tailor assessment and intervention toward specific expected difficulties (Wilson & Betteridge, 2019). With this in mind, an initial scoping review was conducted in February 2021 which showed that literature on cognitive impairment in the acute stages of COVID-19 had developed rapidly following the first wave of the pandemic. A search for related systematic reviews was conducted in December 2021 using the International Database of Prospectively Registered Systematic Reviews in Health and Social Care (PROSPERO) database which

found four systematic reviews due for publication in the following months (NIHR, 2022). Despite this, research exploring beyond the 12-week long-COVID criterion appeared, at that time, much more limited and often only incidental. The PROSPERO search did not find any systematic reviews specifically looking at long-COVID. Only one systematic review was found via the Google search engine which explored "cognitive impairment after COVID-19" (Dariosche et al., 2021) and appeared to include relevant literature. However, this review included studies assessing at any time period after COVID-19, was conducted in February 2021, and utilised a single database (Ovid Medline).

Therefore, in order to formulate the rationale and aims of the current research, it was deemed appropriate to conduct a specific systematic literature review exploring the question, "what is the objectively measured cognitive impairment profile of those affected by long-COVID?". Based on the scoping review, it felt important to narrow this question to just objective information. This is because cognitive testing appears to be a popular research trend, in part due to its practical utility in informing health service provision, meaning that there will likely be enough research for a robust review. At the same time, potential limits to the research in long COVID, specifically, mean that the quantity of research found should be manageable to cover within the limits of this systematic review. Additionally, subjective reports of cognitive complaints are consistently less reliable (Lezak et al., 2012). However, in line with the pragmatic philosophy of the present research (see section 1.3.1), it is acknowledged that focusing on the research in this specific area may only reflect part of the reality to be explored in the broader topic area. Answering this question should therefore provide a comprehensive, up-to-date and multi-database review that offers insight into the suspected cognitive profile of long COVID. Identified gaps in the research can then be explored to inform the present studies research questions, which will aim to incorporate a rationale based on the critical realist and constructionist stances taken.

2.3 Search Strategy

The systematic review of the literature started in December 2021 and was updated with a final search on 8th January 2022 to account for the rapidly developing pace of publications in this area. PsycNet (APA, 2022), Scopus (Elsevier, 2022), World Health Organization (WHO, 2022) and PubMed (NCBI, 2022) platforms were used for the search. PsychNet was chosen as it is a specific search platform for American Psychological Association articles, the leading professional organisation for psychology in the United States. Scopus was chosen as it 'is the largest abstract and citation database of peer-reviewed literature' (Elsevier, 2022). The WHO platform was developed specifically in response to the need for synthesising of the rapidly growing COVID-19 research and is specific to this subject only. PubMed is a commonly used search platform that comprises of biomedical literature from MEDLINE and other databases. This was chosen because of the need to include a search of the medical literature within neurology and it also offers a COVID-19 specific search. Google Scholar was also considered, however, search terms and minor variations on them brought back a large quantity of results which was deemed too large for consideration within this systematic review. Additionally, many results appeared unrelated.

Search terms in Figure 1 were combined with the Boolean Operators "AND" and "OR" to distinguish between different concepts and account for similar phrasing within each concept, respectively. The search terms were drawn from terminology commonly used within COVID-19, long-COVID and neuropsychological research (NIHR, 2022). Searches were made on abstracts, titles and keywords for Scopus, PubMed and WHO but, due to a high number of irrelevant search results, searches were only made on titles for PsychNet. As WHO provide a COVID-19 specific database search, only concepts one and two were used when searching this database. PubMed's long-COVID specific database search was conducted with concept one. Appendix B describes the search process for each of the four databases used.

Figure 1
Search terms for systematic review

Concept 1	Concept 2	Concept 3
• Cognitive • Cognitive impairment • Neuropsychological	• Long-term • Post-acute • Chronic long-COVID	• COVID-19 • SARS-CoV-2 • Coronavirus

Firstly, each study was screened and the relevance of each was considered against the following inclusion and exclusion criteria. Studies were required to be available in English, have undergone peer-review, and been published since 2020. As initial searches brought back many relevant results, criteria were adjusted to include only studies with more than 10 participants, and which reported results for more than one validated cognitive screening measure. This was to ensure that results were better able to provide detailed description of specific domains of cognition as opposed to reporting on the suspected incidence of cognitive deficit more broadly. The Population Intervention Comparators Outcomes Study design Setting (PICOSS) framework (Boland, Cherry, & Dickson, 2017) was used to describe the final focus for inclusion of studies for review:

- Population: Humans aged 18 years or over who had clinically diagnosed or polymerase chain reaction (PCR) positive COVID-19 a minimum of 12 weeks prior to testing date.
- Intervention: Any
- Comparators: Normative data sample described in testing manuals and/ or COVID-19 negative control.
- Outcomes: Cognitive assessment involving >1 cognitive screening measure.
- Study design: Cohort studies, case-control studies or cross-sectional studies with n>10.
- Setting: Any

2.4 Results

As the Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) (Page, et al., 2021) flow diagram in Figure 2 illustrates, the search brought back a total of 1801 citations (including duplicates) for which titles were screened. As they were not identified in the systematic review, 12 additional citations from the scoping review and four citations from the review by Dariosche et al. (2021) were included as titles also appeared relevant. Of these, based on their titles 188 papers underwent screening of their abstracts with a total of 59 relevant citations being identified. Full texts of these papers were checked in detail to determine if they met the PICOSS criteria. A further 39 were removed for not meeting population (n = 18), study design (n = 4) and outcomes (n = 17) criteria. Finally, 11 duplicates were removed, leaving nine papers taken forward for review.

Figure 2
PRISMA flow chart for the study selection procedure

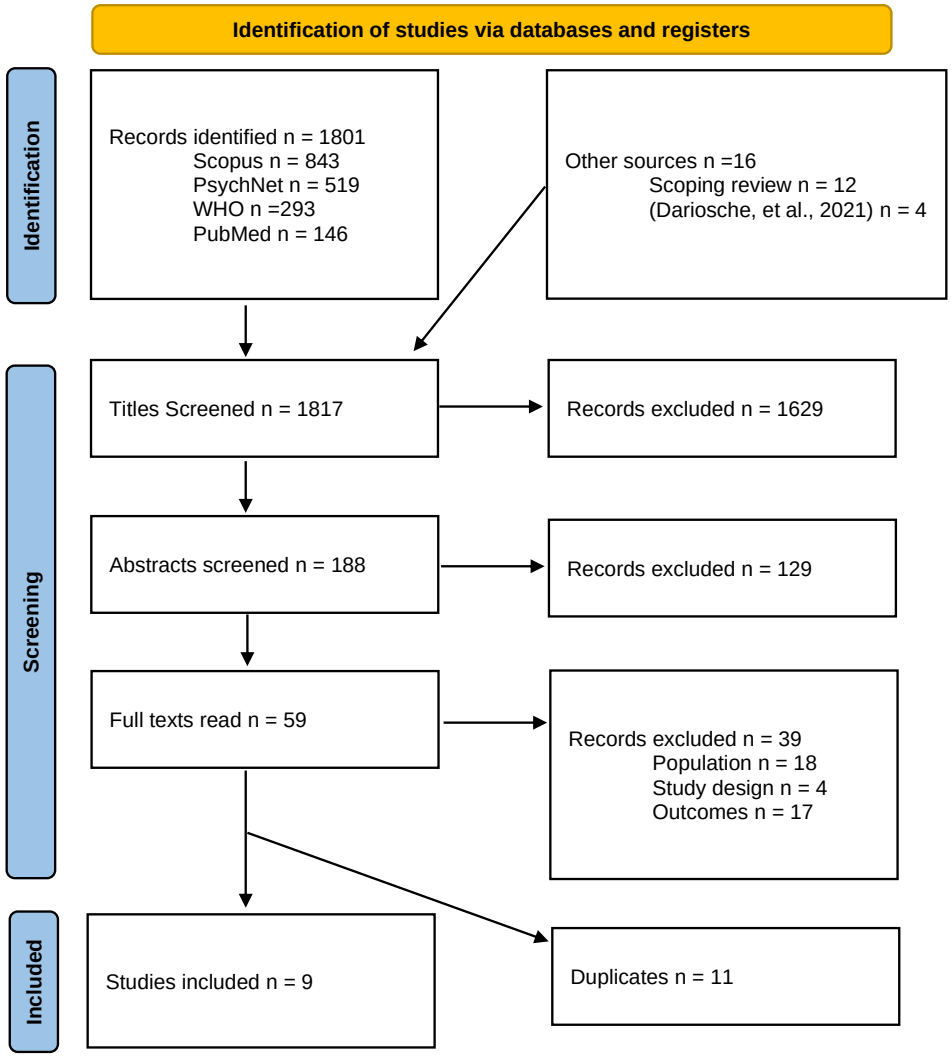


Table 2 provides a summary of details for studies included within the review, presented in chronological order.

Table 2

Summary of included studies

Reference, date and country	Aim	N (Mean age) and gender ratio M:F	Assessment time, COVID-19 "wave" and participant groups
Mazza et al. (2021) Jan, Italy	'To explore the psychopathological and cognitive status of COVID-19 survivors three months after hospital discharge.' (Mazza et al., 2021, p. 1)	130 (59) Not stated	3 months after wave 1 1 month vs 3 months and psychopathology positive vs negative
Ferruci et al. (2021) Feb, Italy	'To study the occurrence of cognitive abnormalities in the months following hospital discharge.' (Ferruci et al., 2021, p. 1)	38 (53) 71:29	5 months after wave 1 No ARDS vs ARDS
Miskowiak et al. (2021) Mar, Denmark	'To investigate the frequency, pattern and severity of cognitive impairments 3-4 months after COVID-19 hospital discharge, their relation to cognitive complaints, quality of life and illness variables.' (Miskowiak et al., 2021, p. 1)	29 (56) 59:41	4 months after wave 1 COVID-19 vs healthy controls
Mattioli, et al. (2021a) May, Italy	'To investigate if objective neurological or cognitive impairment is detectable four months after SARS-CoV-2 infection, in a group of patients who had mild-moderate COVID-19. (Mattioli, et al., 2021a, p. 1)	120 (48) 30:90	4 months after wave 1 COVID-19 vs healthy controls
Mendez, et al. (2021) Sep, Spain	'To assess neurocognitive, psychiatric and QoL outcomes in a cohort of hospitalised COVID-19 survivors one year after hospital discharge.' (Mendez, et al., p. 1)	171 (58) 58:42	12 months after wave 1 COVID-19 only
Hellgren et al. (2021) Oct, Sweden	'To report findings on brain MRI and neurocognitive function, as well as persisting fatigue at long-term follow-up after COVID-19 hospitalisation in patients identified as high risk for affection of the central nervous system.' (Hellgren et al., 2021, p. 1)	35 (59) 80:20	5 months after wave 1 Normal MRI vs Abnormal MRI
Poletti, et al. (2021) Oct, Italy	'To investigate cognitive functioning 6 months following hospital discharge for COVID-19, the impact of depression, and the consequences on quality of life.' (Poletti, et al., 2021, p. 1)	98 (55) 37:63	6 months after wave 1 3 months vs 6 months and COVID-19 vs health controls vs MDD
Vannorsdall et al. (2021) Oct, USA	'To prospectively characterise cognition, mental health symptoms and functioning approximately four months after an initial diagnosis of COVID-19 in a racially and ethnically diverse group of patients.' (Vannorsdall, et al., 2021, p. 1)	82 (54) 41:59	4 months after wave 1 Post-ICU vs Non-ICU
Mattioli et al. (2021b) Nov, Italy	'To investigate the type of neurological and cognitive impairment in COVID-19 cases of different severity.' (Mattioli, et al., 2021b, p.1)	215 (51) 37:63	4 months after wave 1 Post-ICU vs Non-ICU

Note. n = COVID-19 participants 12 weeks post infection only. Does not count controls or assessments earlier.

2.4.1 Synthesis of cognitive test findings.

The studies included within the review used various cognitive tests to ascertain cognitive function across multiple domains. As expected, this makes comparison difficult as studies will not be measuring the same set of functions across each sub-test administered. For example, some tests of memory rely on verbal functions and other tests assessing the same memory process may rely on visual functions. For the purpose of this synthesis, the study authors attributions of the main function assessed, by sub-test or index, are described. This is because it is beyond the scope of this review to identify and categorise all potential functions assessed. Similarly, authors attributions of what defines a cognitive impairment or deficit will also be used. In this way, the review takes a narrative approach (Baumeister & Leary, 1997).

Despite the barriers to comparison, where possible Table 3 summarises scores across similar cognitive sub-domains, noted in column two. In order to aid comparison and synthesis, an effort has been made to somewhat sort these based on the Core Cognitive Domains model set out in Wilson & Betteridge (2019). This model depicts the relationships between cognitive functions and how foundational functions influence those in other domains as well as depicting verbal vs visual function splits, for example. Each domain is noted in column one. Although it is unrealistic to specify an exact hierarchy, functions at the top, such as attention, working memory and processing speed, will impact on scores for tests assessing functions below, especially ‘higher order functions’, such as memory and executive functioning. Because of this, synthesis of cognitive test findings from the studies included within this review will also be described in the same order. This will describe differences between groups as well as group and total sample scores deemed to be in deficit. It should be noted that studies including comparison against healthy controls (Mattioli, et al., 2021a; Poletti, et al., 2021) did not provide a total deficit percentage. Ferruci et al. (2021) did not provide any significance statistics. Mendez et al. (2021) did not report any appropriate

statistic that would allow for comparison and was therefore excluded from this section, but will be incorporated in the summary section when discussing the authors attributions of deficit (see 2.4.1.7).

Table 3

Cognitive test scores for included studies

Domain	Sub-domain	**Reference**	**Group raw score (shown as mean (SD) or median (range))**	**Group scores in deficit (%ile)**	**Total scores in deficit (%ile)**
Attention and Working Memory	Verbal Attention	Mattioli, et al. (2021a)	COVID-19=585 (408-2748) Healthy Controls=613.5 (431-736) **p=N.S**	COVID-19=5% Healthy Controls=19%	
		Vannorsdall, et al. (2021)	Non-ICU=10.4 (2.4) Post-ICU=9.6 (2.9) **p=0.15**	Non-ICU=0% Post-ICU=2.1%	1.20%
	Visual Attention	Mattioli, et al. (2021a)	COVID-19=835 (642-1819) Healthy Controls=789 (690-1162) **p=N.S**		
	Attention Index	Hellgren, et al. (2021)	Total 87.1 (21.4)		9%
	Working Memory	Poletti, et al. (2021)	COVID-19=20.98 (6.09) Healthy Controls=21.88 (4.31) **p=N.S**		
		Mazza, et al. (2021)	No Psychiatric=20.71 (4.75) Psychiatric=19.71 (5.19) **p=0.286**	No Psychiatric=26% Psychiatric=22% **p=0.708**	24%
		Ferruci, et al. (2021)	No ARDS=43.7 (1.78) ARDS=41.13 (9.89) **p=0.503**		10.50%
		Miskowiak, et al. (2021)	COVID-19=18.2 (4.2) Healthy Controls=1.9 (2.5) **p=0.04**		
		Vannorsdall, et al. (2021)	Non-ICU=37.2 (38.6) Post-ICU=46.5 (30.7) **p=0.28**	Non-ICU=8.8% Post-ICU=16.7%	13.40%
Processing Speed	Attention and processing speed	Poletti, et al. (2021)	COVID-19=51.59 (10.83) Healthy Controls=56.78 (9.93) **p<0.001**		
		Mazza, et al. (2021)	No Psychiatric=48.08 (11.41) Psychiatric=44.24 (11.81) **p=0.098**	No Psychiatric=36% Psychiatric=27% **p=0.284**	33%
		Ferruci, et al. (2021)	No ARDS=37.15 (8.57) ARDS=38.73 (11.49) **p=0.658**		42.10%
		Vannorsdall, et al. (2021)	Non-ICU=10.3 (9) Post-ICU=10 (4.6) **p=0.85**	Non-ICU=32.4% Post-ICU=37.5%	35.40%
Visuospatial Function	Visuospatial	Mattioli, et al. (2021a)	COVID-19=34 (17.5-36) Healthy Controls=35 (28-36) **p=N.S**		
		Mattioli, et al. (2021b)	Non-ICU=34 (18-36) Post-ICU=32 (18-36) **p<0.001**	Post-ICU=5%	
	Visuospatial Index	Hellgren, et al. (2021)	Normal MRI=94.3 (11.3) Abnormal MRI = 81.8 (15.1) **p=0.031**		12%
		Poletti, et al. (2021)	COVID-19=75.83 (16.12) Healthy Controls=89.6 (12.04) **p<0.001**		

	Psychomotor Coordination	Mazza, et al. (2021)	No Psychiatric=68.37 (18.47) Psychiatric=68.28 (18.29) **p=0.977**	No Psychiatric=59% Psychiatric=56% **p=0.812**	57%
		Miskowiak, et al. (2021)	COVID-19=9.0 (3.2) Healthy Controls=10.1 (2.3) **p=0.09**		
Language	Semantic Verbal Fluency	Ferruci, et al. (2021)	No ARDS=26.99 (4.47) ARDS=23.62 (5.84) **p=0.073**		7.90%
		Mattioli, et al. (2021a)	COVID-19=48 (29-70) Healthy Controls=49 (37-71) **p=N.S**		
		Vannorsdall, et al. (2021)	Non-ICU=32.6 (9.2) Post-ICU=29.5 (9.2) **p=0.15**	Non-ICU=26.5% Post-ICU=35.4%	31.70%
		Mattioli, et al. (2021b)	Non-ICU=46 (19-61) Post-ICU=48 (29-70) **p=0.08**	Non-ICU=5%	
	Phonemic Verbal Fluency	Vannorsdall, et al. (2021)	Non-ICU=27 (8.1) Post-ICU=20.6 (8.2) **p=0.01**	Non-ICU=11.8% Post-ICU=35.4%	25.60%
		Mattioli, et al. (2021b)	Non-ICU=37 (3-58) Post-ICU=39 (15-59) **p=0.036**		
	Verbal Fluency	Poletti, et al. (2021)	COVID-19=47.82 (12.73) Healthy Controls=53.52 (13.62) **p=0.001**		
		Mazza, et al. (2021)	No Psychiatric=46.41 (12.53) Psychiatric=42.52 (9.49) **p=0.304**	No Psychiatric=32% Psychiatric=32% **p=0.929**	32%
		Miskowiak, et al. (2021)	COVID-19=14.3 (4.7) Healthy Controls=16 (4.5) **p=0.17**		
	Language Index	Hellgren, et al. (2021)	Total 90.9 (16)		14%
Memory	Immediate Verbal Memory	Poletti, et al. (2021)	COVID-23=47.86 (9.35) Healthy Controls=49.25 (9.06) **p=N.S**		
		Mazza, et al. (2021)	No Psychiatric=40.37 (10.73) Psychiatric=42.52 (9.49) **p=0.304**	No Psychiatric=9% Psychiatric=11% **p=0.871**	10%
		Miskowiak, et al. (2021)	COVID-19=19.9 (4.2) Healthy Controls=22.1 (3) **p=0.003**		
		Mattioli, et al. (2021a)	COVID-19=54 (22-71) Healthy Controls=56.5 (32-74) **p=N.S**		
		Vannorsdall, et al. (2021)	Non-ICU=46.7 (10.8) Post-ICU=39.7 (10.7) **p=0.01**	Non-ICU=14.7% Post-ICU=35.4%	26.80%
		Mattioli, et al. (2021b)	Non-ICU=70 (0-95) Post-ICU=55 (24-100) **p<0.001**	Post-ICU=5.7%	
	Delayed Verbal Memory	Ferruci, et al. (2021)	No ARDS=8.1 (2.62) ARDS=5.95 (2.56) **p=0.029**		26.30%
		Miskowiak, et al. (2021)	COVID-19=6.3 (2.8) Healthy Controls=7 (1.9) **p=0.08**		
		Mattioli, et al. (2021a)	COVID-19=13 (5-16) Healthy Controls=13 (5-16) **p=N.S**	COVID-19=5% Healthy Controls=6.6%	
		Vannorsdall, et al. (2021)	Non-ICU=8.4 (3.5) Post-ICU=6.9 (3.3) **p=0.06**	Non-ICU=14.7% Post-ICU=35.4%	26.80%

		Mattioli, et al. (2021b)	Non-ICU=86 (0-107) Post-ICU=60 (20-100) **p<0.001**	Post-ICU=7.7%	
	Verbal Storage	Ferruci, et al. (2021)	No ARDS=44.5 (13.6) ARDS=30.63 (13.33) **p=0.007**		26.30%
	Verbal Retrieval	Ferruci, et al. (2021)	No ARDS=34.42 (14.46) ARDS=25.59 (14.68) **p=0.103**		18.40%
	Immediate Visual Memory	Ferruci, et al. (2021)	No ARDS=17.49 (4.89) ARDS=17.49 (4.87) **p=0.998**		15.80%
	Delayed Visual Memory	Ferruci, et al. (2021)	No ARDS=5.73 (1.86) ARDS=5.30 (1.89) **p=0.526**		18.40%
		Mattioli, et al. (2021a)	COVID-19=18 (2-31) Healthy Controls=20 (9.5-29) **p=N.S**	COVID-19=8% Healthy Controls=3.3%	
		Mattioli, et al. (2021b)	Non-ICU=18 (2-31) Post-ICU=14.5 (5-27) **p=0.005**	Non-ICU=8% Post-ICU=9.6%	
	Immediate Memory Index	Hellgren, et al. (2021)	Total 89.8 (21.2)		25%
	Delayed Memory Index	Hellgren, et al. (2021)	Total 83.9 (18.1)		19%
Executive Functioning	Executive Functioning	Poletti, et al. (2021)	COVID-19=17.3 (2.9) Healthy Controls=15.01 (4.99) **p<0.001**		
		Mazza, et al. (2021)	No Psychiatric=14.57 (4.37) Psychiatric=13.06 (4.59) **p=0.061**	No Psychiatric=51% Psychiatric=49% **p=0.847**	50%
		Miskowiak, et al. (2021)	COVID-19=116.2 (65)		
		Mattioli, et al. (2021a)	COVID-19=16 (1-22) Healthy Controls=17 (11-22) **p=N.S**	COVID-19=15% Healthy Controls=6.6%	
		Vannorsdall, et al. (2021)	Non-ICU=7.6 (2.4) Post-ICU=6.9 (3.1) **p=0.24**	Non-ICU=11.8% Post-ICU=18.8%	15.90%
		Mattioli, et al. (2021b)	Non-ICU=16 (1-22) Post-ICU=15 (0-22) **p=0.003**	Non-ICU=15% Post-ICU=19.25%	

Note. This table describes domain sub-test or index raw scores for each of the studies included in the review as well as group and total percentages of participants' scores deemed to be in deficit. Where available, significance values are presented in bold either after raw score values or after group scores in deficit percentiles, depending on which variable was used in the statistical analysis.

2.4.1.1 Attention and working memory.

Most cognitive tests designed for assessment of attention and working memory rely on ability in both functions (Wilson & Betteridge, 2019). Therefore, synthesis of the two functions ascribed by researchers is combined in this section. Only three of the studies assessed attention. There were no significant differences found between any of the groups included in the studies. Hellgren et al. (2021) reported that the attention index was the least frequently impaired of the five indices assessed, with 9% demonstrating deficit. Verbal attention was only deemed to be a deficit for 1.2% of the sample in Vannorsdall et al. (2021). When verbal attention was compared to visual attention across similar tests administered by Mattioli et al. (2021a), raw scores appear substantially different, but no statistical test was used to measure the comparison. Based on this, it appears attention may be intact at the four to five-month period post COVID-19 assessed across the three studies.

Five studies assessed working memory. Mazza et al. (2021) reported a total 24% in deficit, Vannorsdall et al. (2021) reported 13.4% and Ferruci et al. (2021) reported 10.5%. There was a discrepancy between Poletti et al. (2021) and Miskowiak et al. (2021) as, across COVID-19 status, the latter found a significant difference ($p=0.04$, COVID-19 worse) whilst the former did not. Polleti et al. (2021) did not report the p value and the Miskowiak et al. (2021) study only just meets criterion for significance ($p<0.05$). This makes it difficult to appreciate how similar findings may have been and whether the finding is artificial as a result of research design. There were no significant differences between groups across the two studies comparing severity (Vannorsdall et al., 2021; Ferruci et al., 2021) or psychiatric diagnosis (Mazza, et al., 2021). Based on this, working memory may present an area of infrequent deficit at four-months post COVID-19, given it was assessed across many of the studies. Poletti et al (2021) study was conducted later (six months post-illness/infection) which may perhaps explain the failure to find a significant difference compared with controls.

2.4.1.2 Processing & motor speed.

Five studies assessed processing speed, although it should be noted that all of the tests used contained a substantial attention element also. As attention is deemed to be relatively intact, it is likely this does not impact on the interpretation of processing speed attributed to these tests. Ferruci et al. (2021) reported a total 42.1% deficit, Vannorsdall et al. (2021) reported 35.4% and Mazza et al. (2021) reported 33%. Poletti et al. (2021) found a significant difference across COVID-19 status ($p<0.001$, COVID-19 worse). There were no significant differences between groups across the two studies comparing severity (Vannorsdall et al., 2021; Ferruci et al., 2021) or psychiatric diagnosis (Mazza, et al. 2001). It appears that processing speed is likely to present as an area of frequent deficit across the four to six-month period post COVID-19. This may be irrespective of illness severity.

Psychomotor coordination typically encompasses assessment of psychomotor speed and visuospatial coordination. Psychomotor speed, like processing speed, is likely to impact on scores for tests described below. Only three authors assessed psychomotor coordination. Mazza et al. (2021) reported a total 57% deficit which was the largest found in their study. They did not find a significant difference in scores across psychiatric diagnosis. There was, again, a discrepancy across COVID-19 status from Poletti et al. (2021) and Miskowiak et al. (2021) who reported a significant ($p<0.001$, COVID-19 worse) and non-significant result, respectively. However, Miskowiak et al. (2021) was only slightly above significance of $p<0.05$ ($p=0.09$). It appears that this sub-domain is likely to be more frequently in deficit than visuospatial functions alone, which might suggest specific difficulty with psychomotor speed.

2.4.1.3 Visuospatial function.

Only three authors assessed visuospatial function specifically, although many of the tests included, especially in the memory domain, contain a substantial visuospatial element. Hellgren et al. (2021) reported that the visuospatial index was the second least frequently impaired of the five indices assessed, with a total 12% deficit. However, it was the only index for which there was a significant difference across MRI status ($p=0.031$, abnormal MRI worse). In the two studies by Mattioli et al. (2001a; 2001b), there were no significant difference across COVID-19 status but there was for ICU status ($p<0.001$, post-ICU worse). These findings are congruent and suggest that, although not an area of general deficit, illness severity may impact on the frequency of visuospatial deficits seen.

2.4.1.4 Language.

Language function was primarily assessed via verbal fluency tests but (similarly to visuospatial function) language skills are also tapped in other tests, particularly memory tasks. All of the studies, except for Mendez, assessed language specifically. Hellgren et al. (2021) reported that the language index had a total 14% deficit. Verbal fluency (phonemic and semantic combined) was reported by Mazza et al. (2021) to be a total 32% deficit. They did not find any significant differences between groups on psychiatric diagnosis. There was, again, a discrepancy between COVID-19 status from Poletti et al. (2021) and Miskowiak et al. (2021) as they observed a significant ($p<0.001$, COVID-19 worse) and non-significant difference, respectively. When assessed separately, Vannorsdall et al. (2021) reported a total deficit of 25.6% for phonemic and 31.7% for semantic verbal fluency. Conversely, Ferruci et al. (2021) observed total deficit for semantic fluency that was much lower at 7.9%. For semantic fluency, there were no significant differences across COVID-19 status (Mattioli, et al., 2021a) or for any of the three studies comparing severity by ICU status or Acute Respiratory Distress Syndrome (ARDS) diagnosis. For phonemic fluency, no study compared

across COVID-19 status but both studies comparing severity showed significant differences with p=0.01 (post-ICU worse; (Vannorsdall et al, 2021) and p=0.036 (post-ICU worse; Mattioli, et al., 2021b). Taken together, despite Vannorsdall et al. (2021) observing a similar total deficit across phonemic and semantic fluency, findings suggest that phonemic fluency may be a relative difficulty, especially with greater illness severity. As one of the two tests making the language index in Hellgren et al. (2021) is a semantic fluency test, it is hard to ascertain whether language functions more generally may be relatively intact.

2.4.1.5 Memory.

Memory tests were the most frequently reported in the studies reviewed as each author, except for Mendez, reported statistics on at least one sub-domain. Hellgren et al. (2021) reported that the immediate memory and delayed memory indices had a similar total deficit of 25% and 19%, respectively.

Ferruci et al. (2021) reported that immediate and delayed visual memory had a similar total deficit of 15.8% and 18.4%, respectively. For delayed visual memory, Mattioli et al. (2021a) found no significant difference across COVID-19 status, but they did observe a significant difference across ICU status (p=0.005, post- ICU worse; Mattioli et al., 2021b).

Vannorsdall et al. (2021) reported that immediate and delayed verbal memory had the same total deficit of 26.8%. Additionally, Mazza et al. (2021) reported a lower rate of 10% for immediate verbal memory and Ferruci et al. (2021) reported a similar rate of 26.3% for delayed verbal memory. For immediate verbal memory, there was a discrepancy between the three studies that reported across COVID-19 status, with Miskowiak et al. (2021) reporting a significant difference (p=0.003, COVID-19 worse) but Polleti et al. (2021) and Mattioli et al. (2021a) observing no significant difference. There was also no significant difference between groups across psychiatric diagnosis (Mazza et al., 2021). Both studies reporting across ICU

status observed a significant difference between groups with p=0.01 (post-ICU worse) (Vannorsdall et al., 2021) and p<0.001 (post-ICU worse) (Mattioli et al., 2021). For delayed verbal memory, neither of the two studies reporting on differences across COVID-19 status observed a significant difference (Miskowiak et al., 2021; Mattioli et al., 2021a). There was a discrepancy between the two studies that reported across ICU status as Mattioli et al. (2021b) reported a significant difference (p<0.001, post-ICU worse) and Vannorsdall et al. (2021) observing no difference. Finally, Ferruci et al. (20210) reported a total deficit of 26.3% for verbal storage and 18.4% for verbal retrieval.

Taken together, it appears that memory may be an area of frequent difficulty generally across the sub-domains mentioned. There are mixed findings when comparing immediate and delayed memory, but scores appear to represent a similar frequency of difficulty. Interestingly, verbal memory appears to be more likely to be intact than visual memory despite the language domain appearing stronger than the visuospatial domain. However, there is a large discrepancy between tests, and it is likely that this represents how the tests used are difficult to compare.

2.4.1.6 Executive functioning.

Six of the studies assessed executive functioning. This is a broad concept that covers many skills utilising functions from across various other domains. Because of this, it is comparisons cannot readily be made between tests of executive functioning, and variable findings are likely. This is seen with the discrepancy in total deficits observed, with Mazza et al. (2021) observing 50% and Vannorsdal et al. (2021) observing just 15.9%. Discrepancy between the two studies comparing across COVID-19 status was also observed, with Polleti et al. (2021) reporting a significant difference (p<0.001, COVID-19 worse) and Mattioli et al. (2021a) not. There was another discrepancy across ICU status as Mattioli et al. (2021b) observed a significant difference (p=0.003, post-ICU worse) and Vannorsdall et al. (2021)

observed no significant difference. Mazza et al. (2021) observed no significant difference between groups across psychiatric diagnosis. Importantly, all of these authors administered just one measure of executive functioning which did not allow for comparison of discrete functions within each study. Hypotheses cannot be drawn from this data as to the extent of executive functioning deficits observed, representing a significant methodological issue across the current literature.

2.4.1.7 Synthesis summary.

Based on this synthesis, it appears that the foundational functions of attention and (at least later on in COVID-19 recovery) working memory remain relatively intact for most of the participants included within the various studies. However, processing speed appears to be an area of specific difficulty for many which may influence performance on tests of other, "higher-order" functions (Wilson & Betteridge, 2019). Psychomotor coordination was observed to be a weaker sub-domain than other visuospatial skills, which may be, in part, influenced by psychomotor speed. Visuospatial functions generally could be a more frequent area of difficulty for those that incurred greater severity of illness during the acute stages of COVID-19 infection. Language/verbal functions, in comparison, appear to be more likely to remain intact, other than a potential specific difficulty with phonemic fluency found in one study which, as noted, may be more indicative of weaknesses in executive functioning. Additionally, when observed across immediate and delayed memory tests, verbal tests showed better performance than visual. Memory across all sub-domains appeared to be an area of difficulty. Assessment of discrete executive functions was inadequate for the purposes of synthesis or comparison between studies. This highlights an important area for future research.

It is acknowledged that this synthesis can only partially reflect the interpretations of test scores provided by the authors. Therefore, it is important to compare the synthesis to the authors own interpretations. Firstly, no authors suggested attention and/or working memory to be a concern. Processing speed was suggested as an issue by Ferruci et al. (2021), Polleti et al. (2021) and Vannorsdall et al. (2021). Psychomotor coordination was suggested by Mazza et al. et al. (2021) and Poletti et al. (2021). Mattioli et al. (2021b) suggested visuospatial skills were an issue and Hellgren et al. (2021) suggested this was worse for those with an abnormal MRI. Vannorsdall et al. (2021), being the only paper that reported on phonemic and semantic fluency, suggested phonemic fluency as a specific language domain difficulty. No other negative language domain interpretations were made. Ferruci et al. (2021), Miskowiak et al. (2021) and Mendez et al. (2021) reported verbal memory issues and none of the papers reported visual memory issues. Memory issues generally were mentioned by Hellgren et al. (2021) and Vannorsdall et al. (2021). Issues with executive functioning were reported by Mazza et al. (2021), Miskowiak et al. (2021), Mendez et al. (2021), Polleti et al. (2021) and Mattioli et al. (2021b) which suggests this is an area of specific concern but, as mentioned, methodological concerns do not allow for comparison of the discrete functions assessed. Finally, Mattioli et al. (2021a) was the only paper to suggest there were no cognitive deficit differences between those that contracted COVID-19 and healthy controls.

2.4.2 Unique contributions.

Each study will now be discussed separately, in the chronological order outlined in Table 2, so that each of the unique contributions can be highlighted.

Mazza et al. (2021) explored the emotional consequences of COVID-19 and how this related to cognition. They asked 226 COVID-19 survivors to complete multiple self-report questionnaires at one month and three months post discharge from hospital. They assessed for presence of PTSD, depression, anxiety and OCD based on the generally accepted cut offs for

these questionnaires. At three months, 35.8% of the sample rated symptoms in range for at least one of the four diagnoses. Compared to one month, there was a significant decrease in symptoms of PTSD and anxiety, but symptoms of depression maintained and OCD worsened. When compared to the cognitive testing, those scoring in range on at least one self-report measure of emotional consequences performed significantly worse on verbal fluency, processing speed and executive function tests at three months. The authors highlight that this was the only variable measured that influenced cognition; sex, previous psychiatric diagnosis, duration of hospitalisation and oxygen saturation did not. Specifically, they suggest that both depression symptoms and systemic inflammation related to the observed dysfunction in processing speed and executive function. They stated that further research was required to investigate this interaction over time.

Ferrucci et al. (2021) focused their research on interactions between cognitive impairment and oxygenation in 38 COVID-19 survivors five months post discharge from hospital. They defined ARDS based on arterial oxygen partial pressure and fractional inspired oxygen (P/F ratios), describing three groups of mild, moderate and severe hypoxia. ARDS was the only factor associated with verbal memory deficit, suggesting that this is a domain specifically sensitive to COVID-19 illness severity.

Miskowiak et al. (2021) reviewed cognitive testing for 29 COVID-19 survivors 3-4 months post discharge from hospital compared to 100 healthy controls. They also provided multiple definitions of global and selective cognitive deficit across several criteria. Global deficit frequencies were defined as moderate and severe for those participants scoring ≥0.5SD (n= 18) and ≥1SD (n =11), respectively, below a demographically adjusted total score for the whole test battery. Selective impairment was reported when ≥2 individual tests scored ≥1SD below. The authors reported a significant correlation between these and measures of subjective cognitive complaint where 83% of the sample scored in the “severe cognitive

difficulties" range. The inclusion of a control sample and clinically relevant cut-offs meant this paper appeared to be relatively robust, in terms of methodological approach, when compared to other studies in this review.

Like Miskowiak et al. (2021), Mattioli et al. (2021a) compared cognitive testing results between one sample who had contracted COVID-19 with mild to moderate acute symptoms (n=120) with a sample of healthy controls (n=30). This is the only study which reported no identified cognitive deficits across testing as a result of COVID-19, with no statistically significant differences between groups on number of tests which scored in deficit. The authors relate their findings to be in line with observations against the hypothesis that COVID-19 consistently causes direct damage to the CNS.

Mendez et al. (2021) administered cognitive testing via telephone at two (n=179) and 12 months (n=171) post discharge from hospital. Findings from the 2-month mark were reported in a separate study not reviewed here. At 12 months, the authors gathered information on persistent symptoms and noted that fatigue (48.5%) and memory complaints (32.2%) were the most frequently reported. Twenty four percent of the sample reported subjective cognitive impairment on a questionnaire measure. They mention that theirs was the first study to report on cognitive, psychiatric and QoL consequences simultaneously. However, the validity of telephone-based assessment, despite perhaps being more practical during a pandemic, remains contentious (Lezak, et al., 2012).

Hellgren et al. (2021) utilised Magnetic Resonance Imaging (MRI) to investigate brain structure in 35 COVID-19 survivors who had also undergone cognitive assessment. Participant data was split into two groups: abnormal MRI (n=25) and normal MRI (n=10). The only difference between groups was that the abnormal MRI group scored significantly lower on the Visuospatial Index. The groups did not differ on any other cognitive measure or

subjective scores on measures of fatigue, anxiety and depression. Furthermore, RBANS total scores did not correlate with any of other variable accounted for within the research, suggesting results are more likely as a result of abnormal MRI. The 25 participants with abnormal MRI "showed multiple subcortical white matter lesions, located in the cerebral hemispheres near the grey-white matter junction, particularly in the frontal and parietal lobes" (Hellgren, et al., 2021, p. 5). Additional white matter lesions were found in all six of the participants who had MRI during the acute stages of illness from COVID-19. This led the authors to hypothesis that COVID-19 impacts on the brain after this stage. They also suggest that MRI findings might not predict the degree or frequency of cognitive impairment as there were limited significant differences between groups. This emphasises the need for a multi-professional approach to assessment.

Developing on from the research by Mazza et al. (2021), Poletti et al. (2021) looked to explore the interaction between depression symptoms and cognitive impairment. They compared cognitive testing of COVID-19 survivors one month (n=92), three months (n=122) and six months (n=98) post discharge from hospital, alongside participants diagnosed with major depression (165) and healthy controls (165). They concluded that COVID-19 survivors performed better than the major depression cohort on psychomotor coordination and speed of information processing but similar on all other domains. They also found no significant difference in the COVID-19 survivors' group on scores between one, three or six months post discharge from hospital, concluding that cognitive impairment persists. Some improvement was noted between three and six months which was associated with improvement in depressive symptoms. From all of the variables accounted for within the research, the authors conclude that depressive symptoms were the factor affecting cognitive performance most in COVID-19 survivors. They suggest that the interaction of COVID-19 and depressive symptoms exacerbates and maintains cognitive deficit and quality of life.

Similarly to Mendez et al. (2021), Vannorsdall et al. (2021) conducted cognitive testing via telephone at four months but with two groups: ICU patients (n=48) and non-ICU (n=34). The sample are described as a "ethnically and racially diverse group" by the authors which is a unique contribution when compared to other research in this review. Post-ICU participants produced lower cognitive composite scores than non-ICU. The non-ICU group was further broken down in to hospitalised (n=21) vs non-hospitalised (n=13) and there were no differences in cognitive composite scores between these groups.

Finally, building on their prior research reviewed here (Mattiolia et al. 2021a), Mattioli et al., (2021b) aimed to explore the interactions between cognitive impairment and acute illness severity. The authors compared two groups: ICU (n=52) and non-hospitalised (n=163) participants. Based on raw scores, the ICU participants performed significantly lower across all tests. Tests assessing executive function (ICU=19.2%, non-hospitalised 15%), non-verbal recall (ICU=9.6%, non-hospitalised 8%), and visuospatial (ICU=11.5%, non-hospitalised 5%) were the most frequently reported as impaired across both groups. Immediate (5.7%) and delayed memory (7.7%) were also frequently reported as impaired in the ICU group. This suggests that cognitive impairment is more likely at four months for those that experienced severe acute COVID-19 illness as opposed to those that experienced mild illness. As measures of global cognitive impairment remained within normal ranges, the authors suggest that long COVID impairment is specific and not generalised.

2.5 Quality Assessment

Of the nine studies reviewed, four were cohort studies and five were cross-sectional. Where this was not explicitly mentioned it was presumed from the description of the methodology. Although only reporting on one time point, Miskowiak, et al. (2021) and Mazza, et al. (2021) define their research as a cohort study with assessment at different time points being reported in other publications. A quality assessment tool for this systematic

literature review was adapted from the Newcastle-Ottawa Assessment Scale (Wells, et al., 2022) (See Appendix C). This was chosen because variations of this scale have been validated for use when reviewing both cohort (Boland, Cherry, & Dickson, 2017) and cross-sectional studies (Moskalewicz & Oremus, 2020). The scale uses a star system to assess various domains across participant selection, comparability and outcome assessment. It has been adapted by removing the second outcome criterion as, within this review, studies were required to independently assess cognitive function as part of the inclusion criteria. This means all studies would automatically score a star based on the traditional criteria. Also, rather than reviewing based on two separate questionnaires, selection criteria four was adapted to include a different question for both cross-sectional and cohort studies. This is the only question that is typically different in previously validated tools and allows for one questionnaire to be used when comparing both types of studies. Table 4 depicts the scoring for each study in the review across these domains as well as total rating. Studies were given a "high" quality rating if they achieved five to six stars, "moderate" if they achieved three to four stars and "low" if they scored one to two stars.

Table 4

Newcastle-Ottawa Assessment Scale scores for included studies

Study	Study type	Selection				Comparability	Outcome	Total	Quality Rating
		1	2	3	4	1	1		
Mazza et al 2021	Cohort	*	*	*		*	*	5/6	High
Ferruci et al 2021	Cross-sectional		*	*		*	*	4/6	Moderate
Miskowiak et al 2021	Cohort	*	*	*		*	*	5/6	High
Mattioli et al 2021a	Cross-sectional		*	*		*	*	4/6	Moderate
Mendez et al 2021	Cohort	*	*	*		*		4/6	Moderate
Hellgren et al 2021	Cohort	*	*	*		*	*	5/6	High
Poletti et al 2021	Cohort	*	*	*		*	*	5/6	High
Vannorsdall et al 2021	Cross-sectional	*	*	*		*	*	5/6	High
Mattioli et al 2021b	Cross-sectional	*	*	*		*	*	5/6	High

2.5.1 Selection.

Most of the studies included within this review met selection criteria one, which assesses the representativeness of the sample. This is because they each describe a similar process of appropriate recruitment to invite all patients requiring neuropsychological assessment, usually as a result of hospitalisation, to take part in the research. They describe the population recruited at least in terms of age and gender, which appear to be at a minimum somewhat representative of local populations of interest. However, samples are likely to be biased toward those more likely to access services. Miskowiak et al. (2021) and Hellgren et al. (2021) also provide information on the recruitment strategy, describing how many participants were excluded at different points and why. Hellgren et al. (2021) justify their sampling by specifying criteria that included only participants requiring additional neuropsychological assessment as a result of their illness. Two studies did not meet selection criteria one; Ferrucci et al. (2021) did not sufficiently describe their sampling strategy and Mattioli et al. (2021a) selected the sample from healthcare workers only.

Selection criteria two was met by all of the studies, as sample sizes were justified and satisfactory for each of the studies aims and statistical analysis methods used. Selection criteria three was also met by each of the studies as they each ascertained exposure to COVID-19 via PCR test, which is a globally validated measurement tool (WHO, 2021). They did not state which variant of COVID-19; although as they each recruited from wave one of the pandemic, there is a high likelihood they assessed the same variant. Selection criteria four was not met by any of the studies as the cross-sectional studies did not compare respondents with non-respondents and none of the studies assessed cognition prior to infection with COVID-19.

2.5.2 Comparability.

As part of the criteria for inclusion within the review, each study was required to assess cognitive ability using psychometric tests with a normative sample to compare to. They all did so by using at least the criterion of age, and some included education. Further to this, all of the studies met the comparability criteria as they describe a process of controlling for an important confounding variable of illness severity, and/or at least one additional factor. To define illness severity, the study used various variables, including blood oxygenation, inflammatory markers and ICU status, most commonly. Hellgren et al (2021) used the WHO Clinical Progression Scale which categorises severity across a ten-point scale ranging from uninfected, ambulatory mild disease, hospitalised moderate disease, hospitalised severe disease and dead. Severe disease categories are broken down further by level of ventilation or blood oxygen levels. A similar scale from NIH used by Mattioli et al. (2021b) defines five categories ranging from asymptomatic, mild, moderate, severe and critical illness. This scale also defines primarily on blood oxygen levels but also other evidence of lower respiratory disease. The additional factors controlled for have been outlined above as unique contributions from each of the studies. Generally, each of these has provided an original contribution to the literature for comparison against cognitive test findings. Variables such as experience of fatigue, mental health and quality of life are often only explored via questionnaires. This allows for comparability to other research within the field, as well as more broadly, but lacks a richness of information that is typically gained through qualitative research within these areas.

2.5.3 Outcome.

Most of the studies included appropriate statistical tests to analyse their data. Due to the differences in sample size, test selection, domains assessed and method for ascertaining cognitive deficit, methods for analysis were varied. A full description of analysis methods

used is beyond the scope of this review. However, there appears to be sufficient information available from parametric and non-parametric analysis for future meta-analysis as confidence intervals and probability levels are appropriately described. Only one study (Mendez et al., 2021) did not meet the outcome criteria. This was because the statistical test metric was not appropriate and only presented as a population equivalent percentile.

2.5.4 Summary.

Taken together, six of the studies included within this review were rated as high-quality, scoring five out of six stars, and the remaining three were moderate, scoring four stars. Most importantly, all of the studies presented information on a cognitive profile that was relatively comparable and valid to draw assumptions from in the final synthesis. Within neuropsychological research it is often the case that control groups are not used, pre-morbid cognitive ability is not assessed, and selective samples are used. This is because of the nature of cognitive testing, which is a time-intensive resource requiring qualified professionals to administer and interpret (Goldstein & McNeil, 2013). It is also typical for research to make assumptions from testing alone, in stark contrast to how assessment is conducted in clinical practice. Mixed method research that includes qualitative analysis of interviews enquiring about the appreciation of findings may have supported a better understanding of how well objective test findings correlate with subjective experience of cognitive deficit.

Another quality issue and methodological limitation was considered beyond what was described in the Newcastle-Ottawa Assessment Scale. This was that the studies were single-centre and mainly European-based (five from Italy, one from Denmark, one from Spain and one from Sweden). These studies did not provide any information on race or ethnicity. This limits generalisability of findings. The one study that was conducted outside of Europe, in the USA, acknowledged this methodological limitation in the broader long-COVID research and reported findings for a sample that were 65% from racial-ethnic minority groups.

2.6 Other Systematic Reviews

It is worth noting that shortly after completing the final systematic literature search a similar search was published by Ceban et al. (2021) in March. The aim for this search was to describe the incidence of cognitive impairment, rather than the specific profile, but criteria for inclusion were partially similar in that they identified studies reporting objectively measured cognition. Importantly, despite identifying 81 studies for final review, the search did not include any studies that would have been relevant for review here. There were six studies that were not initially identified in the systematic review that appeared relevant but upon reading abstracts only contained a short screen of cognition. Two further studies would have been relevant but were pre-prints and therefore would have also been excluded. Mazza et al. (2021), Ferruci et al. (2021), Miskowiak et al. (2021) and Mattioli et al. (2021) were all identified in the other review, but the rest of the studies included within the present one were not. This supports confirmation that the present review was likely to have captured most of the relevant literature. The key findings from the review by Ceban et al. (2021) were that, based on meta-analysis, the incidence of cognitive impairment was 22% and fatigue was 32%. However, they did not provide a breakdown of how this incidence relates with time after contracting COVID-19 or strain of virus.

More recently, Crivelli et al., (2022) completed another systematic literature review, described in more detail in the previous chapter (see 1.4.5). A full review of studies included in order to compare to the present review was not possible within the time frame of submission. However, it appears that, of the studies that would relate to long COVID, five of the studies reviewed in their systematic review were also covered here. There were four other studies for which titles appeared relevant, but abstracts have not been read in order to sufficiently comment.

2.7 Rationale for Research

Despite the rapidly developing literature on cognitive impairment relating to long-COVID, this review highlights a mixed and unclear picture of the expected profile which is complicated further by varying illness severity. This is perhaps also, in part, due to the limited extent of relatively short test batteries used and the large variability found between these measures. Although this review highlights that it is likely a longer battery will be influenced by the high incidence of fatigue experienced within this cohort, there is a need for a more extensive battery of tests. This would support a more nuanced picture of an expected cognitive profile where any similarities found would build on interpretations made from previous research with, likely, larger sample sizes. It would also build on previous research as the research contained within the review includes assessment from shortly after acute illness up to 12 months post COVID-19, in the case of one of the papers (Mendez, et al., 2021). As of yet, there has been no research published exploring the progress of cognitive impairment past this point despite people initially contracting COVID-19 nearly two years ago (Worldometer, 2022). Assessment at this stage might help highlight the rate at which cognitive impairments can recover and/ or the need for additional, longer term, support from services.

Although using shorter test batteries, the previous research appears to rely heavily on cognitive testing scores to interpret functional capacity. Whilst common in neuropsychology research, this can often be inaccurate or misleading if specific variables, such as prior cognitive ability, disease severity and other confounders aren't controlled for. Although valid methods for estimating prior cognitive ability are reported, none of the studies included were able to explore changes in cognitive test scores pre and post COVID-19. This is to be expected as it is unlikely that otherwise healthy participants would have required a cognitive assessment prior to contracting COVID-19. It mirrors what is often the case in clinical

practice and is part of the reason why it can be helpful to consider a client's subjective experience of cognitive difficulty during clinical interview, also. By triangulating cognitive test scores, subjective experience and neurological information a more accurate cognitive profile can be understood (Wilson & Betteridge, 2019). Although much of the literature has collected some information on subjective cognitive impairment from questionnaires, this has mainly been superficial regarding incidence. Like in clinical practice, there is need for research comparing objectively measured cognitive test scores with rich, subjective experience of impairment and impact on daily life. In this way, research would better align to the epistemological and ontological position describe in the first chapter (see 1.3.1). This would move toward a decolonising approach by not assuming knowledge based purely on western cognitive tests, but by embracing an understanding of the participants' appreciation for these findings and their personal experience (Thambinathan & Kinsella, 2021).

Finally, although not covered within this systematic review specifically, many of the papers have observed a high incidence of reported emotional consequences of illness from COVID-19. Neuropsychological support for those experiencing long COVID is likely to involve intervention for cognitive rehabilitation as well as psychological therapy. It is important that research aims to appreciate these areas separately as well as the interaction between the two, in order to inform clinical practice (Goldstein & McNeil, 2013).

2.8 Research Aims

Based in part on this systematic review, the present study will aim to explore to following questions:

1. What are the objectively measured cognitive and emotional consequences of COVID-19/ long COVID at 20-24 months?
2. How does this relate to the subjective experience of illness from COVID-19?

Methodology

3.1 Overview of Methodology

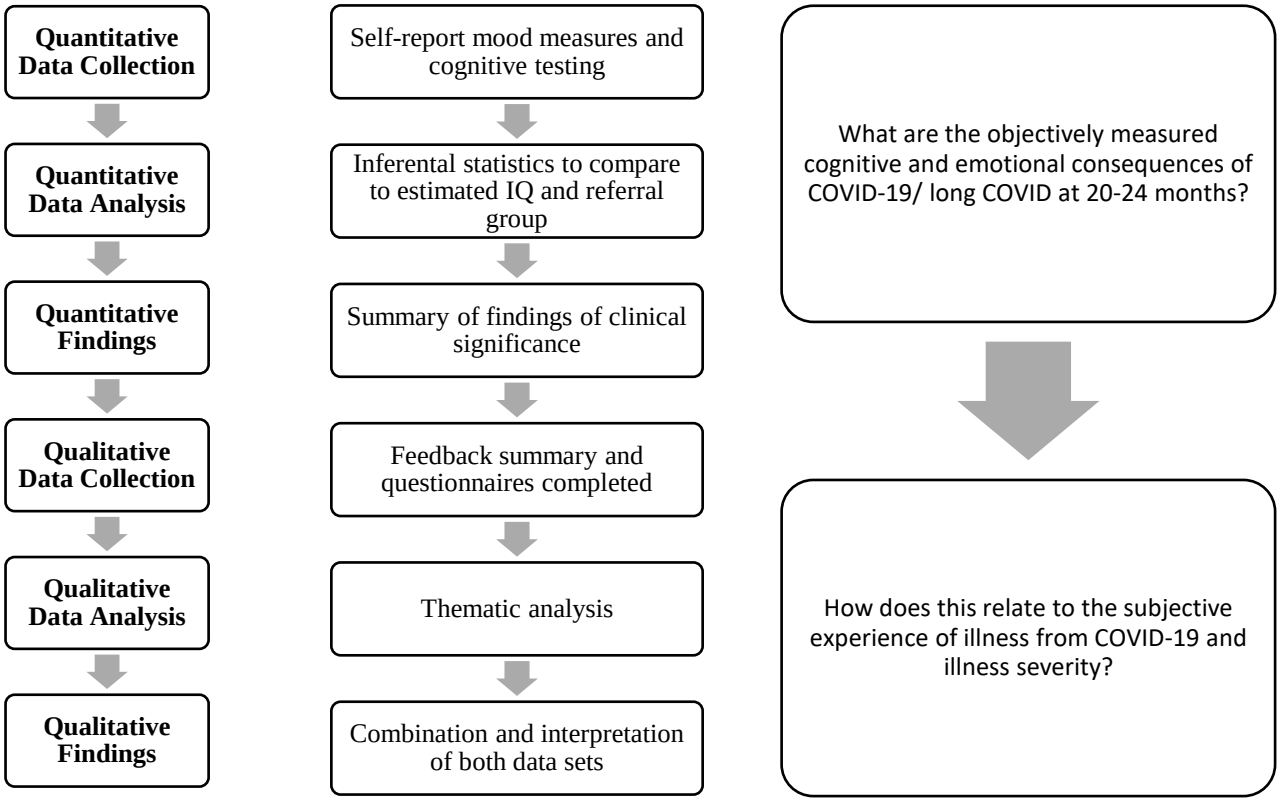
This chapter outlines the study design, including a discussion of the rationale for the chosen approach, the recruitment process, and a description of the study samples' characteristics. Ethical issues are reviewed followed by steps taken to consult with, and the value added by, an Expert by Experience (EBE). Finally, the procedure for participants is described alongside a summary of measures used and intended data analysis.

3.2 Design

This study involved a two-part sequential explanatory mixed methods design that primarily collected quantitative data; qualitative data was incorporated after to enhance an explanation of findings (Creswell, et al., 2003). Figure 3 illustrates the design process. The first part of the study gathered data from a cross-sectional observation of neuropsychological assessment, comprised of cognitive test scores and self-report mood measures. This utilised a quantitative, quasi-experimental design. The independent variables were estimated (pre-COVID-19) IQ and referral group. Estimated IQ was a continuous variable and referral group had two levels, virtual hospital (VH) and long COVID (LC). The dependent variables were scores for each of the measures used. Descriptive and inferential statistics were used to explore the data within the sample as well as between groups. Following cognitive assessment, a summary of findings alongside individual feedback was provided to participants. As this was a clinical intervention, interpretations were made with supervision from the external supervisor who is a Consultant Clinical Neuropsychologist. Participants were asked to complete a feedback questionnaire for the second part of the study. Their responses were analysed using Thematic Analysis (Braun & Clarke, 2006). This aimed to enrich understanding of how participants experienced cognitive and emotional consequences of COVID-19 and long COVID, as well as how they appreciated the cognitive test findings.

Figure 3

Study design process



3.2.1 Rationale for methodological design.

The aim for this study was to explore the research questions:

1. What are the objectively measured cognitive and emotional consequences of COVID-19/ long COVID at 20-24 months?
2. How does this relate to the subjective experience of illness from COVID-19 and illness severity?

The design for the study was chosen primarily on the basis that, at the time of initial scoping review in February 2021, only a few studies had reported on the cognitive deficit profile associated with COVID-19 and even fewer on long COVID (Wilson, 2021). The practical utility of such findings within the broader field of neuropsychology (see Lezak, et al., 2012) justified the priority for quantitative analysis of cognitive testing. Although

research has since developed rapidly within COVID-19 literature, the updated systematic literature review conducted still highlighted a number of gaps in current research findings. Firstly, most of the cognitive testing completed consisted of either screens for general impairment and/ or a small number of tests for specific functions. This is why a comprehensive battery of tests, suggested by a neuropsychology COVID-19 special interest group, was deemed to be appropriate. Doing so supports a clearer formulation of deficit allowing for greater precision. Self-report mood measures were included to capture the prevalence of symptoms of depression, anxiety and PTSD and to allow for consideration of these when interpreting cognitive test findings. The extended battery and inclusion of self-report mood measures therefore better replicates typical best practice in neuropsychological assessment (Goldstein & McNeil, 2013). Due to the time needed to set up the study and gain ethical approval, participants were approaching two years post-COVID-19 at the time of assessment. This meant that, to my knowledge, this study was the first to assess participants at this time point, and indeed at any point past one year.

The study developed further to comprise mixed methods, including qualitative analysis. This was appropriate firstly because there had been limited exploration of subjective experience of cognitive difficulties, in order to compare with cognitive testing, in the prior research reviewed. In clinical practice, extended assessment gathering information on subjective experience would be triangulated with pathology and objective cognitive deficits (Wilson & Betteridge, 2019) to reach a formulation. Some research had utilised self-report questionnaires to elicit information about subjective experience. However, research conducted with conditions presenting with similar symptoms, such as Multiple Sclerosis, has shown that these can be incongruent with objective findings (Akbar, et al., 2010). Secondly, existing research had commented on the emotional consequences of COVID-19 (Cenat et al., 2021) as well as the relationship between these and cognitive consequences (Mazza et al.,

2021). However, most relied upon self-report mood questionnaires which, although useful in cataloguing the severity and prevalence of these difficulties, lack a more nuanced and rich description. Finally, ethnic minority health inequalities seen in COVID-19 (ICNARC, 2020) and long COVID (Wilson, 2021) (see 1.4.1.1) highlight a need for greater cross-cultural competence within neuropsychological research, an area that remains a substantial challenge for the field. A full review of such issues is beyond the scope of this research but can be found in Irani (2022). Briefly, in relation to this research, there is a lack of culturally diverse assessment methods which can lead to an overreliance on cognitive testing that is typically underpinned by western norms. If not representative of the sample, this causes issue largely due to linguistic barriers but also with cultural and educational comparisons, as there is a lack of research appreciating differences in concepts of 'intelligence' and cognitive functioning.

With these three issues in mind, qualitative analysis of information regarding participants' cognitive and emotional experiences serves to shift the focus of explanatory, quantitative methods typically utilised in the research field. The exploratory qualitative element seeks to describe in rich detail the meaning that participants make of their experiences (Braun & Clarke, 2022), which are often felt to be misunderstood or minimised (Volpe & Diamond, 2021). Conducting research in this way aligns with the epistemological position I adopt as a researcher (see 1.3.1) and, to some extent, decolonising of neuropsychological research through acknowledgement of cross-cultural considerations (Irani, 2022). This recognises that the research field has prioritised the use of westernised neuropsychological assessment which may not be representative for all potential participants, given the apparent health inequalities. Offering participants the opportunity to describe their experiences perhaps allows for a greater appreciation of other 'knowledges' (Thambinathan & Kinsella 2021), somewhat offsetting potential overreliance on cognitive testing and self-report mood measures alone.

3.2.1.1 Use of Thematic Analysis.

Thematic Analysis offers 'an accessible and robust method for those new to qualitative analysis' (Braun & Clarke, 2022, p. 4). Having had limited prior experience with qualitative methods, it was important to select a methodology that both met the aims of the study and aligned with my knowledge and experience level, such that this would be properly conducted and do justice to the contribution of the participants. Having learnt about the approach and trialling it once before in a previous study, it felt sufficiently broad enough to capture information about both cognitive and emotional experiences. Thematic analysis aligns with the epistemological position adopted, as conceptualisations are deemed to be constructions, rather than whole truths. It is also the type of analysis commonly used within mixed methods research (Creswell, et al., 2003). Initially, interviews were planned to gather data for the Thematic Analysis. However, due to time constraints, and following consultation with the research team, it was agreed to gather data via questionnaires provided that questions remained sufficiently open-ended to elicit appropriately detailed information.

3.3 Participants

3.3.1 Recruitment.

Provisional estimates for an ideal sample size sufficient for inferential statistics were made using 'ClinCalc' (2022) power calculations, based on psychometrics of IQ. This suggested that, to observe a statistically significant ($p<0.05$) and clinically relevant ($\geq$1SD) (Lezak, et al., 2012) deficit in cognitive test scores between groups, using a confidence interval of 15, a minimum of 32 participants split between groups should be recruited. Practically, uncertainty around restrictions to the study because of COVID-19 meant that multiple procedures for analysis were reviewed throughout project proposals. As a result of this the study aimed to recruit up to 60 participants, with a minimum threshold based on requirements

for qualitative analysis. Guest, Bunce and Johnson (2006) suggest that this should be between 6-12 participants to reach data saturation within thematic analysis, in most fields of research.

The study included two streams of recruitment via simple random sampling of service referrals. This is therefore a convenience sample of the wider population of those affected by COVID-19 and long COVID in the region. The VH group of participants were recruited from the virtual hospital pathway (see 1.5.1) and identified from a database of patients that had been referred to the service during the acute stages of illness. The LC group were recruited from the long COVID pathway (see 1.5.2) from a database of patients that had been referred to the service a minimum of 12 weeks after initial infection. Potential participants received an email (Appendix D) included the Participant Information Sheet (Appendix E) which asked them to email the lead researcher to express interest and/ or to find out more information. Participants were then invited to have a phone call to clarify inclusion/exclusion criteria and to ask questions about the study before agreeing to take part.

3.3.1.1 Inclusion criteria.

Participants were eligible for inclusion if they were aged 18 or over, had been referred to the virtual hospital or long COVID service and had contracted COVID-19 during wave 1 of the pandemic. Limitations in testing during the early phases of the pandemic meant that not everyone who became unwell was formally tested. Excluding these participants would mean excluding a cohort of participants with unique experiences of symptoms and healthcare. Therefore, participants were included if the diagnosis of COVID-19 had been confirmed by contemporaneous medical professional assessment of symptomatology, as well as those who had documented a positive lateral flow test or PCR. Due to limitations of researchers in speaking only English, validity of cognitive measures developed in languages other than English, and the validity in comparison of testing between languages (Lezak et al., 2012), all participants were required to speak sufficiently fluent English.

3.3.1.2 Exclusion criteria.

People reporting a significant history of major psychiatric disorder and/ or neurological disorder unrelated to COVID-19 were excluded from the study to ensure that the study explores differences independent of a pre-existing mental health comorbidity. This included diagnosis such as current psychosis or dementia, for example, and was was assessed via participants' self-report to the lead researcher during the phone call after expression of interest. Criteria included diagnoses made by a GP or mental health professional that required treatment prior to COVID-19 infection. Potential participants were also excluded if they had been referred to both the virtual hospital and long COVID service, to avoid confounds between groups.

3.3.2 Recruitment process.

Table 5 summarises the recruitment process. At the time of recruitment in November 2021, there were 1527 virtual hospital and 818 long COVID service referrals, totalling 2345 potential participants. Of these, 68 had been referred to both services and were therefore excluded, leaving a total of 2209 participants (94%). Of these, 1473 (67%) participants had email addresses recorded and, subsequently, a total of 1000 (68%) email invitations were sent out to these participants. Six hundred were sent to the virtual hospital and 400 to the long COVID referrals. Of these, 45 virtual hospital and 40 long COVID service potential participants expressed interest, totalling 85 (9%). When invited to speak on the phone, 21 did not respond and 29 did not meet the inclusion/exclusion criteria. Thirty five (41%) were therefore eligible and interested in taking part but, unfortunately, due to time constraints on the study and both researchers needing to isolate due to COVID-19 illness during the period of data collection, only 20 (57%) of these participants were accepted to take part in the study. The remaining 15 potential participants were thanked for their expression of interest in the study and informed they were unable to take part.

Table 5

Summary of recruitment process

Recruitment stage	Virtual Hospital	Long COVID	Both	Total	Percentage
All referrals	1527	818	68	2345	-
Both services excluded	1459	750	0	2209	94%
With email addresses	832	641	0	1473	67%
Emails sent	600	400	0	1000	68%
Expressed interest	45	40	0	85	9%
Eligible	20	15	0	35	41%
Final sample	10	10	0	20	57%

Note: This table describes the recruitment process where each row represents the number of potential participants at each stage, which is a proportion of those in the row above. The percentage of the sample that filtered from the sample above is displayed in the right-most column.

3.3.3 Final sample.

Twenty participants took part in the study. Data was later excluded for one participant who disclosed previous major psychiatric disorder, meeting the exclusion criteria during data collection which had not been identified in pre-screening. Table 6 describes demographics of all referrals to the two services, those that expressed interest, and study participants, compared to the local area (ONS, 2022). Each group was older than the local area average. Only two participants were male (10%) which is not representative of the local area (49%), referrals (42%) or those that expressed interest (41%). An effort was made to compare ethnicity to referrals and expression of interest; however, a large amount of data (45%) was unavailable for the referrals which likely invalidates useful comparison. The final sample was representative of the local area in terms of ethnicity. Those that expressed interest as well as the study participants had slightly higher Indices of Multiple Deprivation (IMD) score, but referrals and local area were also higher than national average. IMD measures and ranks relative deprivation in small areas of England from 1-10, 10 being least deprived. It is the official measure used in the UK. The most recent data referred to here was recorded in 2019 (ONS, 2022). Comparisons between study participants and the wider UK cohort of patients with COVID-19 and long COVID will be reviewed in the discussion section (see 5.3.2).

Table 6

Recruitment demographics

Sample		Age (Mean years)	Gender (% male)	Ethnicity (% white)	IMD
Local area		40	49%	88%	7.3
All referrals	Virtual hospital service	55	47%	65%	6.8
	Long COVID service	50	34%	69%	7.3
	Total	53	42%	67%	7.0
Expressed interest	Virtual hospital service	59	46%	86%	8.0
	Long COVID service	52	35%	88%	7.9
	Total	56	41%	87%	8.0
Study participants	Virtual hospital service	56	10%	90%	7.1
	Long COVID service	51	10%	90%	8.5
	Total	54	10%	90%	7.8

3.4 Procedure for Data Collection

3.4.1 Neuropsychological assessment.

All assessments took place at an NHS hospital. Participants were asked on arrival if they had any further questions before they signed the consent form (Appendix F) and completed the self-report mood measures, if not completed electronically previously. They were then taken through to a quiet room to complete cognitive testing. Seventeen of the testing sessions were completed by me and a further three by the external supervisor. So that cognitive testing was as comparable as possible, a procedure was discussed between the two testers, outlining processes for collecting consent, completing forms, order of test administration and arranging of feedback sessions. A brief description of tests was offered, explaining that they were all pen and paper-based tasks, that some may be harder than others and that the tester was only allowed to offer specific instruction. This is standard procedure for neuropsychological assessment (Goldstein & McNeil, 2013). Participants were asked to break for 10 minutes halfway through testing and all testing was completed in around two hours 30 minutes, which was longer than initially expected. After the assessment, a telephone appointment was arranged with participants to go through feedback from the cognitive testing.

3.4.1.1 Measures.

The full battery of cognitive tests and self-report mood measures was provided on advice from a neuropsychology COVID-19 special interest group, with the aim to standardise research in the UK for the assessment of the cognitive and emotional consequences of COVID-19. Table 7 presents these tests alongside the reference for the published manuals that include data from normative samples for the cognitive tests and cut-offs/ domains for self-report measures. These were used for analysis.

Table 7
Measures used

Cognitive test: Sub-test	Reference
Test Of Memory Malingering (TOMM)	(Tombaugh, 1997)
Test Of Premorbid Function (TOPF)	(Wechsler, 2011)
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Line orientation, Coding	(Randolph, 2013)
Wechsler Adult Intelligence Scale (WAIS-IV): - Similarities, Matrix Reasoning, Digit Span	(Wechsler, 2008)
Behavioural Assessment of the Dysexecutive Syndrome (BADS): Zoo map	(Wilson, et al., 1996)
Delis-Kaplan Executive Function System (D-KEFS): Trail Making Task, Color-Word Interference	(Delis et al., 2001)
Kaplan Baycrest Neurocognitive Assessment (KBNA): Sequences, Spatial Location, Word lists, Complex Figure, Clock Drawing, Verbal Fluency, Practical Problem Solving, Conceptual Shifting, Picture Naming, Picture Recognition	(Leech, 2000)
Self-report mood measures	**Reference**
Patient Health Questionnaire 9 (PHQ-9)	(Kroenke et al., 2001)
Generalised Anxiety Disorder 7 (GAD-7)	(Spitzer et al., 2006)
Post-Traumatic Stress Disorder Checklist for DSM-5 (PCL-5)	(Weathers et al., 2013)
The European Brain Injury Questionnaire (EBIQ – Self-Report)	(Sopena et al., 2007)

Prior to the assessment session, participants were asked to complete the self-report mood measures. The PHQ-9 and GAD-7 measures symptoms of depression and anxiety, respectively. They are often cited as the most reliable and valid measures for this (Richardson & Yeebo, 2018) and are in widespread use across physical and mental health services in the UK, allowing for good comparability. Similarly, the PCL-5 is also commonly used in the UK as a measure for symptoms of PTSD and scores can be interpreted based on Diagnostic and Statistics Manual-5 diagnosis symptom clusters. Finally, the EBIQ is typically used within neuropsychological services to assess perceived experience of somatic, cognitive, motivational, impulsivity, depression, isolation, physical and community related difficulties.

During the assessment session, participants were asked to complete the cognitive tests. A description of the tests psychometrics, scoring and normative data can be found in Appendix G. Table 8 provides a summary of the sub-tests, their order of administration and the cognitive functions assessed within each sub-test. Although it is acknowledged that there are no 'pure' tests of any individual cognitive function, with each subtest likely tapping multiple domains of cognition, the primary domain(s) assessed (as defined by the relevant test manuals) are presented. In total, 22 sub-tests were administered covering a broad range of functions based on the Core Cognitive Domains model set out in Wilson & Betteridge (2019). This includes attention & working memory, processing speed, visuospatial, language, memory, and executive functions. The TOPF was completed first as this is relatively easy test to understand and exemplifies many other tests, easing participants into the process of testing. Generally, the tests from the KBNA were administered next, except for inclusion of the two D-KEFS tasks after the Clocks task to allow sufficient time to elapse prior to administration of the delayed memory tasks (Word Lists 2 and Complex Figure 2). The 10-minute break was offered after Verbal Fluency at around the halfway mark to again allow for sufficient time between Picture Naming and associated memory task, Picture Recognition.

Table 8

Summary of cognitive tests used

Order	Test	Summary	Function
1	TOPF	Word reading list	Premorbid IQ estimation
2	KBNA Sequences	Mental-control tasks such as reciting months in reverse order	Sustained attention
3	KBNA Word Lists 1	Immediate recall of a list of verbally presented words	Immediate verbal memory
4	KBNA Complex Figure 1	Copying and immediate replication of a complex figure	Immediate visual memory
5	KBNA Clocks	Drawing of clocks and reading of clock times	Visuospatial function
6	D-KEFS Trail Making Test	Drawing of a line connecting points on a page	Motor speed and switching
7	D-KEFS Colour Word Interference	Reading of names of colours, filled with different coloured ink	Inhibition and switching
8	KBNA Word Lists 2	Delayed recall of a list of verbally presented words	Delayed verbal memory
9	KBNA Complex Figure 2	Delayed replication of a complex figure	Delayed visual memory
10	KBNA Picture Naming	Identification of pictures of common objects	Word-finding
11	KBNA Spatial Location	Identification of the location of dots in a grid	Visuospatial function
12	KBNA Verbal Fluency	Recall of as many first names, animals and words beginning with a certain letter, as possible, in a minute	Semantic and phonemic language
13	KBNA Picture Recognition	Delayed recall of pictures of common objects	Delayed memory
14	KBNA Practical Problem Solving	Description of a solution to common emergency situations	Problem solving
15	KBNA Conceptual Shifting	Identification of patterns in a series of shapes	Cognitive flexibility and conceptualisation
16	TOMM	Recall of a series of pictures, choosing between two possible options	Effort and malingering
17	RBANS Line orientation	Identification of the orientation of lines in space	Visuospatial function
18	RBANS Coding	Utilising a list of number-symbol codes to complete a series of coding within a time limit	Processing speed
19	WAIS-IV Similarities	Identification of a word that can be used to categorise two other presented words	Verbal reasoning
20	WAIS-IV Digit Span	Immediate recall of a list of numbers in order, backwards and in sequence	Attention and working memory
21	WAIS-IV Matrix Reasoning	Identification of the appropriate shape that fits logically at the end of a series of shapes, based on a specific pattern	Visual reasoning
22	BADS Zoo map	Planning and organising a visit around a map of a zoo based on specific instructions on what to see and in what order.	Planning

3.4.2 Feedback sessions.

After the assessment session, cognitive tests were scored according to procedures and norms found in core testing manuals (see Table 7). Interpretation of cognitive profiles for the total sample and comparisons between groups were discussed with the research team. Individual cognitive profiles were discussed with the external supervisor who provided brief written formulations of these for review by me. After review, findings were collated and summarised into individual feedback summary documents (see Appendix H for example). These were verbally discussed with participants during feedback telephone calls and subsequently shared with them via email. During this telephone appointment, participants were also invited to take part in the second stage of the study and offered the opportunity to ask questions regarding this or their feedback before consenting. Due to the lower-than-expected sample size for the quantitative phase of the study, all participants (except for the one excluded post-assessment) were invited to take part in the qualitative phase of the study.

3.4.3 Feedback questionnaires.

Eighteen of the 19 participants expressed interest in the second part of the study and copies of the feedback questionnaire (Appendix I) were sent out via email along with their feedback summaries. The study design is considered a two-part 'sequential' design due to the fact that quantitative data from cognitive testing was shared in order to generate qualitative data (Creswell, et al, 2003). Of those that expressed interest, 13 participants (72%) returned the completed feedback questionnaires, seven from the LC and six from the VH group. The feedback questionnaire was devised to include questions relating to the cognitive and emotional consequences of COVID-19 and long COVID as well as appreciation for the cognitive testing feedback. Once collected, Microsoft Excel (Microsoft Corporation, 2018) was used to delineate responses into shorter quotes across different rows of a spreadsheet. Data was anonymised and saved securely on an NHS encrypted laptop, ready for analysis.

3.5 Ethical Issues

The study was first considered during a DClinPsy research conference where the study was presented to the course team and other cohort members. Ethical issues were reviewed after presenting and a formal proposal was then submitted to the university for initial approval. Upon agreement that the study appeared feasible, the University of Hertfordshire Health and Human Sciences ethics committee were informed of the study and the University agreed to act as sponsor.

As the study required recruitment of patients from NHS settings, ethical approval was requested from the Health Research Authority (HRA) via submission of an Integrated Research Application System (IRAS) form (Appendix J) which subsequently required a Research Ethics Committee (REC) review. There was a request for eight amendments following HRA (Appendix K) and a request for further information following REC review, which was provided (see Appendix L for email reply). After the amendments were made to the IRAS form, approval was received on 21st September 2021 (Appendix M). The IRAS project ID was allocated as 300361 and the REC reference was 21/NS/0114. Once the NHS services had reviewed the approved IRAS form they agreed to acting as a Participant Identification Centre (virtual hospital service) and Research Site (long COVID service). The long COVID service then signed off on the capacity and capability (Appendix N).

Finally, UH were informed of the various approvals and the protocol number LMS/PGT/NHS/02967 was issued/ sponsorship approved for the study on 10th December 2021 (Appendix O).

3.5.1 Confidentiality and consent.

Participants were provided with a copy of the participant information sheet and consent form via email before being given the chance to ask questions about the study and consenting to take part. As the study involved neuropsychological assessment, consent included agreeing to contact GPs to inform them of participation. Copies of the letter sent to GPs (Appendix P) and signed consent forms were saved to patient files, as per the NHS Trust requirements. All other identifiable information was kept confidentially by the two researchers and anonymised findings were shared with the wider research team. Hard copies of all participant data, such as psychometric test scores and self-report mood measures, were secured in a locked cabinet in an NHS building until information was transferred to an NHS encrypted laptop. All data was anonymised at each stage of interpretation and analysis.

3.5.2 Potential distress.

The research team reviewed the potential for distress caused to participants of the study at several stages throughout planning and development. Neuropsychological assessment was not deemed likely to be distressing but consideration was given to how participants might react if they perceived themselves to have performed less than expected. The feedback questionnaire was deemed to have more potential to cause distress as it asked participants to reflect on what may have been a particularly difficult experience of illness from COVID-19. A distress protocol (Appendix Q) was developed with clear instructions on how either of the two testers should and could react to participants experiencing distress. This included information on support available if required. Two participants were referred back to the long COVID service due to concerns raised and were subsequently assessed by a senior clinician.

3.5.3 Travel expenses.

Participants were required to travel to the NHS site to take part and would have likely incurred travel related expenses. To compensate for this, participants were offered a £10 "Love2Shop" voucher upon completion of the neuropsychological assessment. Love2Shop is a company which provide voucher codes, redeemable online, for over 90 high street brands (Love2Shop, 2022). Twelve participants opted to receive vouchers, which were sent to them via email along with instructions for how to redeem. The vouchers were acquired through the University of Hertfordshire research funding.

3.5.4 COVID-19.

During the initial development of the study, the research team considered conducting cognitive assessment via online materials. However, due to the limitations in online assessment, it was felt important to attempt face to face assessment. At the time, studies were being accepted by UH and HRA for higher risk face to face research, as long as they had completed specific COVID-19 risk assessments outlining the rationale and risk management. For this study, it outlined the use of larger rooms and PPE, as well as other mitigations, summarised in the final IRAS form. Although both examiner and participant wore masks, care was taken to ensure this did not impede understanding of task instructions and this was generally not considered to have impacted on test performance.

A two-month period was allocated to complete cognitive assessments. Unfortunately, during this time both of the researchers separately contracted COVID-19 themselves and were required to isolate for 10 days. This substantially impacted on the number of assessments that could be completed and led to recruitment being capped at 20 participants, with the 15 remaining eligible participants who had expressed interest but had not yet completed assessment being informed they were unfortunately unable to take part.

3.6 Consultation with Expert by Experience.

The study was supported by an EbE who had utilised the virtual hospital and was also a healthcare professional working at the trust at the time. They were contacted via the Research Lead for the recruiting NHS Trust and invited to the research team meetings. We had considered completing a pilot cognitive assessment together, but due to timeframes and the COVID-19 advice in place at the time were unable to do so. Instead, the EbE supported all subsequent phases of the project. This included reviewing the format of the feedback and feedback questionnaire for the second part of the study by advising on whether the terminology used made intuitive sense. They also attended each research team meeting, commenting on how they would perceive the feedback as well as advising on how the questionnaire could appropriately capture relevant information, for example. Finally, they supported thematic analysis in a process of member checking (Creswell, 1994) by reviewing the initial themes I had identified and suggesting whether the themes felt relatable to their experience. They were offered £30 in vouchers for their time on the project but refused with their thanks. A table further describing specific suggestions made by the EbE along with changes made can be found in Appendix R.

3.7 Data Analysis

3.7.1 Cognitive testing and self-report mood measures.

Quantitative data analysis of cognitive testing and self-report mood measures aimed to explore the first research question, i.e., ‘what are the objectively measured cognitive and emotional consequences of COVID-19/long COVID at 20-24 months?’. To do so, IQ percentile was estimated using three means in order to acquire reliable options: TOPF test scores, estimated IQ calculations from Crawford & Allan (1997) and IMD. These were used in analysis to compare to cognitive sub-test age equivalent percentiles, taken from the

appropriate testing manuals (see Table 7). The data was analysed using Statistical Package for Social Science (SPSS) (IBM Corp, 2020) with inferential statistical techniques to compare groups. This allowed for exploration of tests that were either the same, above or below an expected performance. These statistical techniques were then used to explore differences between the LC and VC groups, accounting for the variance from estimated IQ. They were also used to compare the groups on scores for the four mood measures. Additional analyses were conducted using inferential statistical techniques to explore the relationship between sub-test score and test order to explore the potential impact of fatigue during the assessment session. Further to statistical analysis, clinical significance was explored for the cognitive sub-tests by calculating the proportion of scores that fell in the ranges 1, 1.5 and 2 Standard Deviations (SD) below or above expected, based on the estimated IQ, as is common in neuropsychological practice (Lezak, 2012). This is similar to how Vannorsdall, et al. (2021) conducted their analysis, also. Clinical significance of scores on mood measures was assessed by calculating the proportion of scores that fell above cut-offs for symptoms of depression on the PHQ-9 (Kroenke et al., 2001), anxiety on the GAD-7 (Richardson & Yeebo, 2018) and PTSD on the PCL-5 (Weathers, et al., 2013). The EBIQ subscale scores (Sopena, etl al., 2007) are also presented.

3.7.2 Feedback questionnaires.

Qualitative data analysis of feedback questionnaire responses aimed to explore the second research question, i.e., ‘how does this (objectively measured cognitive and emotional consequences of COVID-19/long COVID) relate to the subjective experience of illness from COVID-19 and illness severity?’. To do so, feedback questionnaire responses were analysed using the six phases of Reflexive Thematic Analysis guidelines provided by Braun & Clarke (2006).

Firstly, for phase 1 (familiarising yourself with the dataset) I began by reading and re-reading each of the questionnaires as a whole before entering each sentence of the responses into a separate row on Excel, in a similar method to Bree and Gallagher (2016). This helped with phase 2 (coding) which involved systematically going through the dataset and labelling interesting and meaningful sections with initial codes. To begin with, I had done so with an inductive approach at the semantic level, moving toward the latent level for many concepts (Braun & Clarke, 2022). Each row of data had a column related to the participant ID, their group, the question number and the initial code. An example of the Excel spreadsheet used can be seen in Appendix S. For phase 3 (generating initial themes) I began grouping codes into sub-themes and overarching themes by reviewing possible relationships between them. However, it became clear during this phase that themes were not unexpected or novel because they made sense based on my preconceived understanding of the research literature as well as the questions asked in the questionnaire. Therefore, during phase 4 (developing and reviewing themes) I decided that analysis should take more of a deductive approach which subsequently sought to categorise themes based on my preconceived understanding. Having completed analysis again with this in mind, final themes were brought to phase 5 (refining, defining and naming themes) where they were reviewed whilst considering the transcripts as a whole, so that they reflected how each participant had responded during the interview. They were then sent for review by the external supervisor and EBE for further quality assurance. The process was therefore recursive (Braun & Clarke, 2006) and was supported with use of the Excel sort and filter functions to visualise how themes related to one another. One participant returned their questionnaire after analysis had been conducted but it was evident that they had spent considerable time responding. Instead of excluding the data, this transcript was utilised to see if the themes that had already been generated were valid upon reviewing new data. Having confirmed this, I moved on to the final phase 6 (writing up).

Results

4.1 Overview of results

This chapter describes demographics of the final sample before presenting the results from quantitative and qualitative analysis. In coherence with the sequential explanatory mixed methods design, data from cognitive testing and self-report measures were analysed first and are therefore presented first. This leads to a summary of the findings from thematic analysis of feedback questionnaires. Incorporation of these findings is made throughout the discussion section after.

4.2 Demographics of the final sample

Table 9 describes the demographics of the final sample, ordered by study ID to preserve anonymity. Study ID is defined firstly by group and then in order of most to least cognitive test scores in deficit (see 4.3.1.3). Estimated IQ was ascertained using Crawford & Allan's (1997) regression equation method and based on age, education and occupation (see 4.3 for rationale). Occupation code was ascertained according to Office for National Statistics (2022), where lower numbers represent higher occupation level. Acute illness severity was categorised using the NIH severity scale (2021), with levels 1 = Asymptomatic, 2 = Mild, 3 = Moderate, 4 =Severe and 5 = Critical illness. Participants were well matched across groups on most demographic variables except for an expected substantial difference in acute illness severity where the VH group had a higher severity score than the LC group. Across the total sample, participants were mainly White British and female with a mean age of 54 years. IMD for participants was high, averaging in the top 22nd percentile nationally. Years of education and occupation were also high, meaning that the subsequent estimated IQ was observed to be in the High Average range (Lezak, et al., 2012). Acute illness severity ranged from mild to severe but not asymptomatic or critical. Most participants were infected with COVID-19 in February and March 2020, subsequently all being assessed 20-24 months post infection.

Table 9

Demographic information for participants

Study ID	Age (Years)	Gender	Ethnicity	IMD	Years of education, Occupation score	Estimated IQ	NIH (2021) Illness Severity	Date of COVID-19 infection, months to assessment
VH1	42	Male	British Indian	8	13.5, 1	114	3	03/20, 22
VH2	59	Female	White British	7	19, 1	126	2	03/20, 22
VH3	59	Female	White British	6	13, 3	105	4	03/20, 21
VH4	51	Female	White British	10	18, 2	118	3	02/20, 23
VH5	68	Female	White British	7	13, 2	112	4	03/20, 21
VH6	54	Female	Not disclosed	3	17, 1	122	4	03/20, 21
VH7	57	Female	White British	6	14, 2	112	3	03/20, 21
VH8	48	Female	White British	7	17, 4	105	3	03/20, 22
VH9	71	Female	White British	10	12.5, 3	107	4	03/20, 22
LC1	34	Female	British Indian	5	17, 2	113	2	04/20, 20
LC2	56	Female	White British	10	17, 2	118	2	02/20, 22
LC3	38	Female	White British	10	15, 2	110	2	01/20, 24
LC4	60	Female	White British	7	19.5, 2	122	2	04/20, 22
LC5	60	Male	White British	9	14, 2	112	2	03/20, 22
LC6	42	Female	White British	10	16, 2	113	2	03/20, 21
LC7	56	Female	White British	9	15, 2	114	2	03/20, 21
LC8	55	Female	White British	7	13, 1	115	2	02/20, 22
LC9	52	Female	White British	9	13, 1	114	3	02/20, 23
LC10	61	Female	White British	9	18, 2	120	2	03/20, 22
VH Group	56.55 (42-71)	89% Female	77.7% White British	7.11 (3-10)	15.22 (12.5-19), 2.11 (1-4)	113.41 (105-126)	3.33 (2-4)	2.88 (1-4), 21.66 (21-23)
LC Group	51.4 (34-61)	90% Female	90% White British	8.5 (5-10)	15.75 (13-19.5), 1.8 (1-2)	115.10 (110-122)	2.1 (2-3)	2.6 (2-3), 21.9 (20-24)
Difference	5.16	-0.50%	-12.3%	1.39	-0.53, 0.31	-1.69	1.23	0.29, -0.23
Total Sample	53.84 (34-71)	89.5% Female	84.2% White British	7.84 (3-10)	15.5 (12.5-19.5), 19.4 (1-4)	114.30 (105-126)	2.68 (2-4)	2.73 (1-4), 21.78 (20-24)

Note. Bottom rows summarise means for the LC and VH group, differences and total sample, with ranges.

4.3 Quantitative Analysis of Cognitive Testing and Self-Report Mood Measures

The 22 tests administered as part of the assessment generated 22 analysis variables for each of the 19 participants. This is because some tests produce multiple variables and others were not explicitly used in analysis. This includes Picture Naming and Recognition which are not normally distributed tasks. This means that most participants are expected to make very few errors, which was the case for both tests with all participants. The TOMM was used to ascertain concerns with effort or malingering, which did not show evidence for any of the participants. The TOPF was initially used to provide a source of estimated IQ comparison data, as it is often cited as a 'gold standard' assessment of this (Lezak et al., 2012). However, initial scoring demonstrated that participants were consistently performing better than expected when compared to the TOPF, suggesting that the measure was underestimating participants' abilities. This is a commonly reported issue with tests measuring estimated IQ in samples with higher ability (Joseph, et al., 2019). Instead, the estimated IQ regression equation (Crawford & Allan, 1997) based on age, education and occupation was used, as it is likely that this more accurately depicted ability levels for a sample with high scores on the IMD. This allowed for better detection of the more nuanced and subtle deficits highlighted in the systematic literature review

Table 10 displays the descriptive statistics for each variable used in analysis. Cognitive tests are listed in order of delivery during assessment. One participant, LC1, did not complete Zoo Map 1, 2, or Coding due to fatigue at the end of testing. Scores were instead replaced with their average score for analysis. Estimated IQ was converted into equivalent percentile for accessibility and to compare with cognitive tests. Raw cognitive sub-test scores were converted into equivalent scaled scores according to the normative samples supplied in published test manuals (see Table 7) and then into the equivalent percentile ranks. Due to the low sample size, conflation of multiple individual high scores

and the degree of variability in individual scores contributing to composite scores, KBNA domain subscales and total IQ were not utilised in analysis. A new variable was transformed from the mean of the Estimated IQ score and participant averages across sub-tests, in order to provide a variable that could explore additional analysis into assessment fatigue. Total scores from the PHQ-9, GAD-7, PCL-5 and EBIQ are displayed in the final rows.

Table 10

Descriptive statistics for analysis variables

Variable	Mean (SD)	Median (IQR)	Range	Skewness and Kurtosis	Kolmogorov-Smirnov statistic	Histogram and Normal Q-Q Plot	Parametric viable?
Estimated IQ percentile	81.36 (9.35)	82 (79, 88)	62.93 - 96	-0.57, 0.05	0.19 (p=0.07)	Yes	Yes
Sequences percentile	79.99 (12.04)	84.13 (74.86, 90.82)	50 - 90.82	-0.97, 0.46	**0.24 (p=0.01)**	Yes	Yes
Word Lists 1 percentile	81.21 (22.18)	90.82 (62.93, 97.72)	25.14 - 99.62	**-1.34, 0.75**	**0.29 (p<0.00)**	**No**	**No**
Complex Figure 1 percentile	68.62 (29.82)	84.13 (50, 90.82)	4.75 - 99.01	**-1.21, 0.34**	**0.22 (p=0.01)**	**No**	**No**
Clocks and Complex Figure 1 percentile	67.50 (28.33)	74.86 (37.07, 95.25)	15.87 - 97.72	**-0.51, -1.16**	0.16 (p=0.2)	**No**	**No**
Trail Making Test 4 percentile	63.10 (25.74)	74.86 (50, 84.13)	2.28 - 90.82	-0.87, 0.07	**0.2 (p=0.04)**	Yes	Yes
Trail Making Test 5 percentile	56.39 (23.99)	62.93 (37.07, 74.86)	0.13 - 84.13	-0.94, 0.13	**0.2 (p=0.04)**	Yes	Yes
Color-Word Interference percentile	67.58 (28.33)	84.13 (37.07, 90.82)	0.13 - 90.82	**-1.16, 0.14**	**0.3 (p<0.00)**	**No**	**No**
Word Lists 2 percentile	83.85 (19.73)	95.25 (74.86, 97.72)	37.07 - 99.62	**-1.33, 0.5**	**0.32 (p<0.00)**	**No**	**No**
Word Lists Recognition percentile	86.98 (7.44)	90.82 (84.13, 90.82)	62.93 - 95.25	**-2.21, 5.64**	**0.33 (p<0.00)**	**No**	**No**
Complex Figure 2 percentile	63.95 (31.65)	74.86 (50, 90.82)	2.28 - 99.01	-0.74, -0.69	0.16 (p=0.2)	**No**	Yes
Complex Figure Recognition percentile	66.83 (28.49)	84.13 (50, 84.13)	2.28 - 90.82	**-1.29, 0.43**	**0.31 (p<0.00)**	**No**	**No**
Spatial Location percentile	59.35 (26.70)	62.93 (50, 84.13)	2.28 - 90.82	-0.76, -0.28	0.15 (p=0.2)	Yes	Yes
Verbal Fluency Phonemic percentile	70.54 (25.53)	74.86 (50, 95.25)	9.18 - 95.25	-0.98, 0.13	0.2 (p=0.05)	**No**	**No**
Verbal Fluency Semantic percentile	76.47 (28.69)	90.82 (62.93, 90.72)	2.28 - 97.72	**-1.55, 1.75**	**0.22 (p=0.01)**	**No**	**No**
Practical Problem Solving and Conceptual Shifting percentile	73.05 (17.67)	74.86 (62.93, 90.82)	25.14 - 90.82	**-1.46, 2.38**	**0.28 (p<0.00)**	Yes	**No**
Line Orientation percentile	56.68 (19.59)	64 (38, 75)	21 - 75	**-0.65, -1.12**	**0.28 (p<0.00)**	**No**	**No**
Coding percentile	61.55 (31.33)	50 (35, 90.82)	9.18 - 99.01	**-0.29, -1.31**	0.19 (p=0.08)	**No**	**No**
Similarities percentile	49.33 (25.90)	50 (25.14, 74.86)	4.75 - 95.25	0.3, -0.9	0.16 (p=0.2)	Yes	Yes
Digit Span percentile	63.23 (26.68)	62.93 (37.07, 90.82)	15.87 - 99.62	**-0.31, -1.24**	0.15 (p=0.2)	Yes	Yes
Matrix Reasoning percentile	64.57 (28.64)	74.86 (37.07, 90.82)	15.87 - 97.72	**-0.6, -1.14**	**0.22 (p=0.02)**	**No**	**No**
Zoo Map 1 percentile	67.37 (21.41)	50 (50, 92)	35 - 99	**0.22, -1.69**	**0.32 (p<0.00)**	**No**	**No**
Zoo Map 2 percentile	67.63 (24.24)	80 (50, 92)	17 - 99	-0.36, -0.99	**0.24 (p=0.01)**	**No**	**No**
Difference of estimated IQ and average sub-test score percentile	13.37 (9.36)	13.82 (7.46, 18.28)	-5.62 - 32.03	-0.31, -0.05	0.15 (p=0.18)	Yes	Yes
PHQ-9 score	9.421 (5.61)	10 (3, 13)	2 - 23	0.66, 0.38	0.14 (p=0.2)	Yes	Yes
GAD-7 score	6.894 (4.78)	6 (3, 10)	0 -18	0.67, -0.11	0.16 (p=0.2)	Yes	Yes
PCL-5 score	21.89 (15.64)	18 (8, 38)	0 - 50	**0.33, -1.26**	0.18 (p=0.12)	Yes	Yes
EBIQ-S score	110.2 (16.78)	111 (99, 124)	76 - 134	-0.52, -0.36	0.12 (p=0.2)	Yes	Yes

Note. Information depicting that parametric testing is not viable highlighted in bold.

Each of the variables was explored to assess for normal distribution and subsequent appropriateness of parametric vs non-parametric analysis. Measurements for skewness, kurtosis, Kolmogorov-Smirnov test of normality and visual observations of histograms & normal Q-Q plots were undertaken to do so. Findings that invalidate normality are highlighted in bold and a final suggestion, based on these criteria, as to whether parametric testing appears viable is made in the last column for each variable.

Most cognitive sub-test variables were not normally distributed and therefore analysis of differences between Estimated IQ and cognitive sub-test as well as differences between groups used non-parametric tests. Many were negatively skewed, perhaps illustrating the substantial increase in difficulty for achieving higher percentile scores. The transformed variable for differences in estimated IQ and average sub-test score as well as all the mood measures appear to be normally distributed and so parametric testing was deemed viable.

4.3.1 Cognitive testing.

4.3.1.1 Statistical analysis of differences between estimated IQ and cognitive sub-tests.

A series of Wilcoxon Signed Rank Tests were conducted to analysis differences in estimated IQ and the cognitive sub-tests. Table 11 displays the *z* statistic and probability (*p*) values for each. A Bonferroni adjustment was made to account for multiple comparisons, meaning the *p* value required for statistical significance was set to $p<0.002$. Analysis revealed a statistically significant difference in scores for four of the sub-tests, each with large effect sizes: Trail Making 5, Trail Making 4, Line Orientation and Similarities. The median score for each of the sub-tests was lower than estimated IQ (see Table 10).

Table 11

Wilcoxon Signed Rank Tests for differences between estimated IQ and sub-test score

Test	*Z*	*p*	*r*
Sequences	-0.98	0.327	
Word Lists 1	-0.89	0.372	
Complex Figure 1	-1.57	0.117	
Clocks and Complex Figure 1	-1.85	0.064	
Trail Making Test 4	**-3.10**	**0.002**	**-0.71**
Trail Making Test 5	**-3.18**	**0.001**	**-0.73**
Color-Word Interference	-1.53	0.126	
Word Lists 2	-1.09	0.277	
Word Lists Recognition	-2.29	0.022	
Complex Figure 2	-1.89	0.059	
Complex Figure Recognition	-1.77	0.077	
Spatial Location	-2.86	0.004	
Verbal Fluency – Phonemic	-1.29	0.199	
Verbal Fluency – Semantic	-0.04	0.968	
Practical Problem Solving and Conceptual Shifting	-1.77	0.077	
Line Orientation	**-3.62**	**0.000**	**-0.83**
Coding	-2.21	0.027	
Similarities	**-3.58**	**0.000**	**-0.82**
Digit Span	-2.33	0.020	
Matrix Reasoning	-2.03	0.043	
Zoo Map 1	-2.17	0.030	
Zoo Map 2	-1.76	0.078	

Note. Significant statistics highlighted in bold.

4.3.1.2 Statistical analysis of differences between VH and LC on cognitive sub-test deficit.

A series of Mann-Whitney U Tests were conducted to analyse comparisons between the LC and VH groups on the difference between estimated IQ and cognitive sub-tests. Table 12 displays the Mann Whitney U Test (*u)* statistic and probability (*p*) values for each. A Bonferroni adjustment was made to account for multiple comparisons, meaning the *p* value required for statistical significance was set to $p<0.002$. Analysis revealed no statistically significant difference in any of the sub-tests between groups.

Table 12

Mann-Whitney U Tests for differences between VH and LC groups

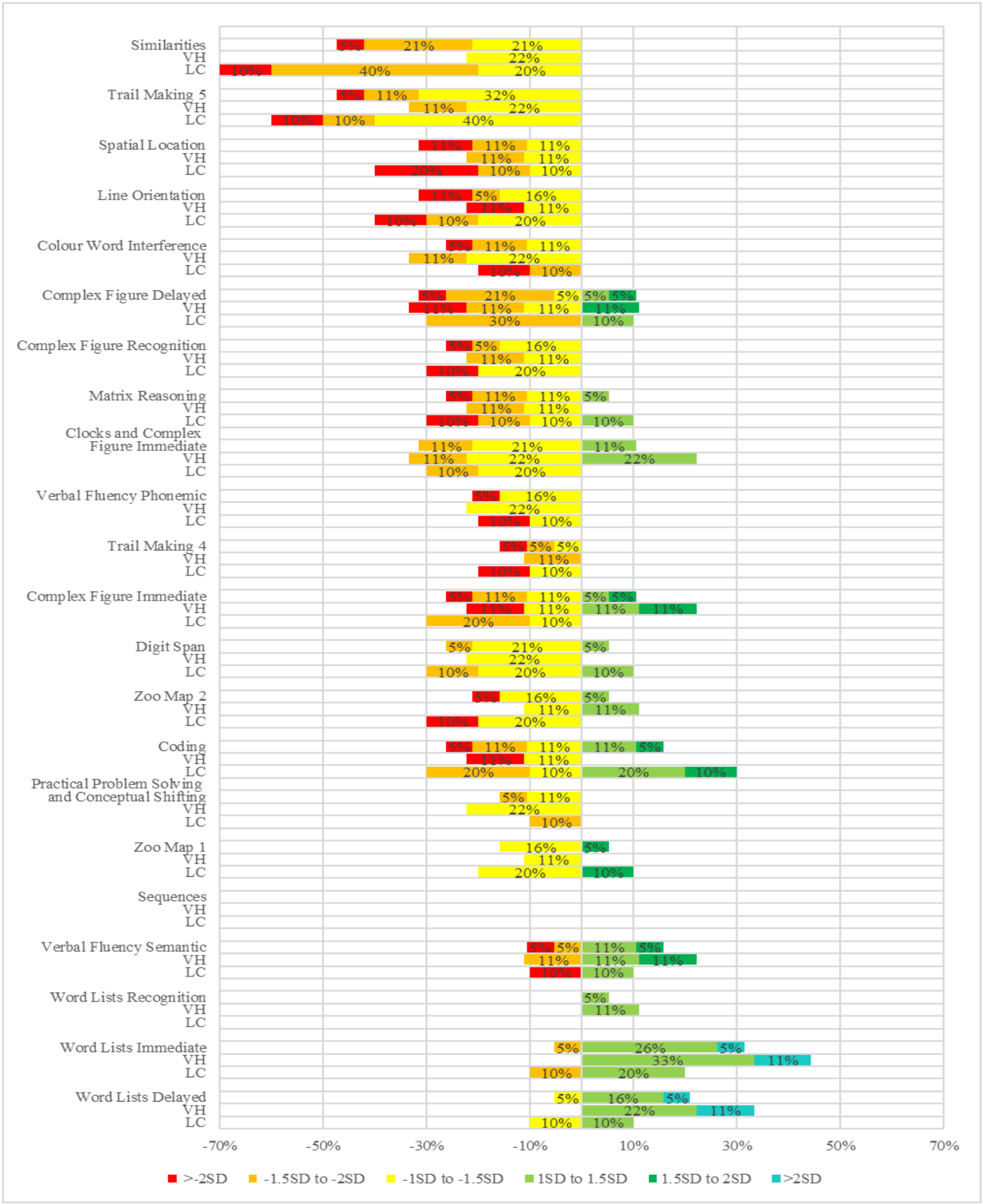
Test	*u*	*p*
Sequences	50.5	0.661
Word Lists 1	50	0.720
Complex Figure 1	42.5	0.842
Clocks and Complex Figure 1	49	0.780
Trail Making Test 4	43	0.905
Trail Making Test 5	62.5	0.156
Color Word Interference	40.5	0.720
Word Lists 2	51.5	0.604
Word Lists Recognition	46.5	0.905
Complex Figure 2	54	0.497
Complex Figure Recognition	66	0.095
Spatial Location	51	0.661
Verbal Fluency – Phonemic	35	0.447
Verbal Fluency – Semantic	52.5	0.549
Practical Problem Solving and Conceptual Shifting	56.5	0.356
Line Orientation	60.5	0.211
Coding	48.5	0.780
Similarities	65	0.113
Digit Span	39.5	0.661
Matrix Reasoning	40.5	0.720
Zoo Map 1	58	0.315
Zoo Map 2	64.5	0.113

4.3.1.3 Clinical significance.

Figure 4 presents a stacked cluster bar chart that displays the percentages of participants scoring at each interval of 1, 1.5 and 2 SD above and below estimated IQ, for each of the cognitive sub-test scores. Scores are presented in order of the most frequently in deficit to the least.

Figure 4

Percentage of participants scoring at 2, 1.5 and 1SD above or below normative sample



Based on Figure 4, many of the cognitive sub-tests appear to show evidence of deficit for some participants. Two of the four scores reaching a statistically significant difference in cognitive sub-test score and estimated IQ were also the highest in frequency of clinically significant deficit. Similarities and Trail Making Test 5 each, individually, observed nearly half (n=9) of participants scoring at least 1SD below estimated IQ. Another score to reach statistical significance, Line Orientation, was also high on this list with very similar frequencies to the Spatial Location. Both of these individually observed nearly a third (n=6) of scores falling at least 1SD below estimated IQ. Color-Word Interference was the next highest, with 5 participants scoring at least 1SD below. All of the scores mentioned so far showed a similar ratio between the amount scoring 1, 1.5 and 2SD below, with no scores observing at least 1SD above. Complex Figure Delayed had 6 participants scoring below 1SD but also observed 2 participants score above 1SD, subsequently ranking higher than Color Word Interference. Complex Figure Recognition and Matrix Reasoning score observed the same amount below 1SD as Color Word Interference score (n=5) but Complex Figure Recognition had slightly fewer participants with 1.5SD or below and Matrix Reasoning had 1 participant scoring 1SD above. Clocks and Complex Figure Immediate observed 6 participants below 1SD but, unlike those mentioned so far, did not have any participants score 2SD below and also had 2 participants perform 1SD above. Four participants scored below 1SD on Verbal Fluency Phonemic. Despite observing a statistically significant difference, only three 3 participants scored below 1SD on the Trail Making Test 4.

The next few subtests listed had only a few participants scoring below 1SD and/or have a higher proportion of participants scoring above 1SD, than those listed prior. Complex Figure Immediate observed 5 participants below 1SD with 2 participants above 1SD. Similarly, Digit Span observed 5 participants below 1SD, none below 2SD and 1 above 1SD. Zoo Map 2 had 4 participants below 1SD and 1 above 1SD. Coding scores were diverse, with

5 participants scoring 1SD below but also 3 1SD above. Practical Problem Solving and Conceptual Shifting observed 3 participants below 1SD. Zoo Map 1 also observed 3 participants below 1SD but 1 above 1SD. All participants performed as expected on Sequences, with no scores above or below 1SD.

Finally, four of the scores were observed to be above estimated IQ for some participants. Verbal Fluency Semantic was diverse, with 2 participants observed to be below 1SD but also 3 above 1SD. No participants performed 1SD below on Word Lists Recognition and 1 scored 1SD above. One participant scored 1SD below on Word Lists Immediate and 6 performed 1SD above. One participant also scored 1SD below on Word Lists Delayed, although, unlike Word Lists Immediate, scored 1.5SD below. Four participants scored 1SD above.

Between the two groups, LC generally scored more frequently in deficit across cognitive sub-tests when compared to estimated IQ. Notably, the most difference can be observed in the first four listed scores, Similarities, Trail Making Test 5, Spatial Location and Line Orientation. Also Zoom Map 2, Word Lists Immediate and Word Lists Delayed, in part due to the frequency of scores above 1SD in the VH group. Coding was the only score to be perceivably lower in the VH group than LC.

Table 13 displays how each individual participant scored on the cognitive sub-tests, represented again as 1, 1.5 and 2 SD above or below estimated IQ. This information was presented to the research team for discussion of individual cognitive profiles, which was then used to inform each participant's feedback phone call and summary document. From this table, individuals scoring on sub-tests assessing similar domains can be identified, strengthening conviction in interpretations for feedback summaries.

Table 13

Individual cognitive subtest scores

ID	Si	T5	SL	LO	CWI	CD	CR	MR	CCI	VP	T4	CI	DS	Z2	C	PPC	Z1	Se	VS	WR	WI	WD
VH1	0	0	0	0	-1.5	0	0	-1.5	-1.5	-1	-1.5	0	0	0	-2	0	0	0	-1.5	0	0	0
VH2	0	-1.5	-1	-2	0	-1.5	-1	0	-1	-1	0	0	0	0	0	-1	0	0	0	0	0	0
VH3	0	0	0	0	0	-2	-1.5	-1	0	0	0	-2	-1	0	0	0	0	0	0	0	1	1
VH4	0	0	-1.5	0	0	0	0	0	0	0	0	-1	0	-1	0	0	-1	0	0	0	1	0
VH5	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	-1	-1	0	0	0	0	0	0
VH6	-1	-1	0	-1	0	-1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
VH7	-1	-1	0	0	-1	0	0	0	-1	0	0	1.5	-1	0	0	0	0	0	1	0	0	1
VH8	0	0	0	0	0	1.5	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0
VH9	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1.5	1	2	2
LC1	-2	-2	-2	-1	-2	0	-1	-1.5	-1.5	-2	-2	0	-1.5	x	x	0	x	0	-2	0	0	0
LC2	-1.5	-1	-2	-1.5	0	-1.5	0	-2	0	0	-1	-1	-1	-2	-1.5	-1.5	-1	0	0	0	-1.5	-1
LC3	0	-1	0	0	0	-1.5	-2	0	0	0	0	-1.5	0	0	-1.5	0	0	0	0	0	0	0
LC4	-1	0	-1	-2	0	0	0	0	-1	0	0	0	-1	-1	1	0	-1	0	0	0	0	0
LC5	-1	0	-1.5	0	0	-1.5	-1	0	0	0	0	-1.5	0	0	1.5	0	0	0	0	0	0	0
LC6	-1.5	0	0	-1	0	0	0	-1	0	-1	0	0	0	0	0	0	0	0	0	0	0	0
LC7	-1.5	-1.5	0	0	0	0	0	0	-1	0	0	0	0	0	1	0	0	0	1	0	0	0
LC8	-1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
LC9	0	-1	0	0	-1.5	0	0	1	0	0	0	0	0	0	0	0	1.5	0	0	0	1	0
LC10	0	-1	0	0	0	1	0	0	0	0	0	0	1	-1	-1	0	0	0	0	0	1	1

Note. Si = Similarities score, T5 = Trail Making Test 5 score, SL = Spatial Location score, LO = Line Orientation score, CWI = Colour Word Interference score, CD = Complex Figure Delayed score, CR = Complex Fig Recognition score, MR = Matrix Reasoning score, CCI = Clocks and Complex Figure Immediate score, VP = Verbal Fluency Phonemic score, T4 = Trail Making Test 4 score, CI = Complex Figure Immediate score, DS = Digit Span score, Z2 = Zoo Map 2 score, C = Coding score , PPC = Practical Problem and Conceptual score, Z1 = Zoo Map 1 score , Se = Sequences score, VS = Verbal Fluency Semantic score, WR = Word Lists Recognition score, WI = Word Lists Immediate score and WD = Word Lists Delated score. Scores displayed as 1,1.5 and 2 SD above or below estimated IQ, with 0 meaning within -1 and 1SD. x represents where a score was obtained.

4.3.1.4 Correlational analysis of score and assessment duration.

The relationship between test administration order and cognitive sub-test score was investigated using Pearson product-moment correlation coefficients. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. There was a medium, positive correlation between the two variables (r=0.38) (Cohen, 1988, p. 79-81), with cognitive sub-test score lowering as test administration order increased. However, this was not found to be significant (p=0.074).

4.3.2 Self-report mood measures.

4.3.2.1 Statistical analysis of differences between VH and LC on mood measure scores.

A one-way between-groups multivariate analysis of variance was performed to investigate differences in mood measures scores. Four dependent variables were used: PHQ-9, GAD-7, PCL-5 and EBIQ total score. The independent variable was group with level LC and VH. Preliminary assumption testing was conducted to check for linearity, univariate and multivariate outliers, homogeneity of variance- covariance matrices, and multicollinearity, with no serious violations noted. There was a statistically significant difference between VH and LC on the combined dependent variables, F (4, 12) = 3.32, p=0.041; Wilks' Lambda =0.51; partial eta squared =0.02. When the results for the dependent variables were considered separately, using a Bonferroni adjusted alpha level of 0.012, none of the tests reached statistical significance. An inspection of the mean scores indicated that VH reported slightly higher scores across the combined mood measures than LC.

4.3.2.2 Clinical significance.

Table 14 presents percentages for the frequency of participants scoring above cut-offs for symptoms of depression (PHQ-9), anxiety (GAD-7) and PTSD (PCL-5) across both the LC and VH groups as well as total. Over half of the participants (n=10) scored above cut-off for symptoms of depression, nearly half (n=9) for anxiety and nearly a third (n=6) for PTSD. Between the two groups, the LC group observed a substantially higher frequency of scores above cut-off for symptoms of anxiety and were also higher for PTSD. The VH group had a higher frequency reporting symptoms of depression above cut-off.

Table 14
Frequency of participants scoring below cut-off on self-report mood measures

Measure	VH	LC	Difference	Total
PHQ-9	44%	60%	-16%	53%
GAD-7	77%	20%	57%	47%
PCL-5	44%	20%	24%	32%

Table 15 presents means for responses on the EBIQ across subscales suggested by Sopena et al. (2007). Higher scores indicate greater reported symptoms/difficulties. Somatic concerns were the most commonly reported. Others were reported in a similar range, with a mean response ranging from 1.53 to 1.89. The two groups were mostly similar, the main differences being higher mean scores for General and Cognitive subscales for the LC group.

Table 15
Mean participant scores across EBIQ domains

Measure	VH	LC	Difference	Total
EBIQ - Somatic	2.07	2.10	-0.03	2.09
EBIQ - General	1.56	2.20	-0.64	1.89
EBIQ - Cognitive	1.61	1.92	-0.30	1.77
EBIQ - Community	1.64	1.85	-0.21	1.75
EBIQ - Motivation	1.73	1.76	-0.03	1.75
EBIQ - Depression	1.70	1.72	-0.02	1.71
EBIQ - Isolation	1.69	1.68	0.02	1.68
EBIQ - Impulsivity	1.65	1.66	-0.01	1.66
EBIQ - Physical	1.46	1.58	-0.12	1.53

Table 16 displays how each individual participant scored on the self-report mood measures. Seventy seven percent of the VH participants and 60% of the LC group scored above cut-off for either symptoms of depression, anxiety or PTSD. This accounted for 68% of the total sample.

Table 16

Individual self-report mood measure scores

				EBIQ								
ID	PHQ-9	GAD-7	PCL-5	Somatic	Cognitive	Motivation	Impulsivity	Depression	Isolation	Physical	Community	General
VH1	7	**12**	**38**	2.63	1.92	1.4	2.15	1.44	2	1.5	1.5	2
VH2	2	2	8	1.63	1.23	1.2	1.23	1.11	1	1	1	1
VH3	3	6	8	1.63	1.23	1.2	1.31	1.11	1.25	1.17	1	1
VH4	**12**	**11**	**33**	1.88	1.54	2	1.46	1.89	1.75	1.5	2	1
VH5	8	**8**	7	2.25	2	2.4	1.38	2.22	1.75	2	2	2
VH6	**14**	**8**	**31**	2.25	1.85	2.2	1.69	2	1.75	1.83	2.75	2
VH7	**14**	**18**	**39**	2.13	1.69	1.8	1.92	2	1.75	1.5	1.25	2
VH8	**11**	**9**	**43**	2.25	1.38	1.8	2.08	1.78	2	1.33	1.25	2
VH9	6	**10**	13	2	1.69	1.6	1.62	1.78	2	1.33	2	1
LC1	**13**	2	15	2.25	2.31	1.8	1.77	1.56	1.75	2	2.25	3
LC2	3	3	18	1.75	1.85	1.8	1.31	1.67	1.75	1.67	1.75	2
LC3	**11**	5	16	2.38	1.46	1.6	1.15	1.78	1.75	1.33	1.75	2
LC4	**10**	3	28	2.5	2	1.6	2.62	1.78	1.75	1.83	1.5	3
LC5	**10**	**10**	**43**	2.25	2	1.6	2.38	2	2.25	1.67	2.25	2
LC6	3	3	0	1.88	1.62	1.6	1.38	1.56	1.25	1.5	1.75	2
LC7	**23**	**14**	**50**	2.5	2.54	2	1.46	2.56	2	1.5	2.25	3
LC8	3	3	6	1.75	1.85	1.8	1.31	1.22	1	1.33	1.75	1
LC9	**18**	4	18	1.75	1.92	2	1.92	1.89	2	1.67	2	2
LC10	8	0	2	2	1.62	1.8	1.31	1.22	1.25	1.33	1.25	2

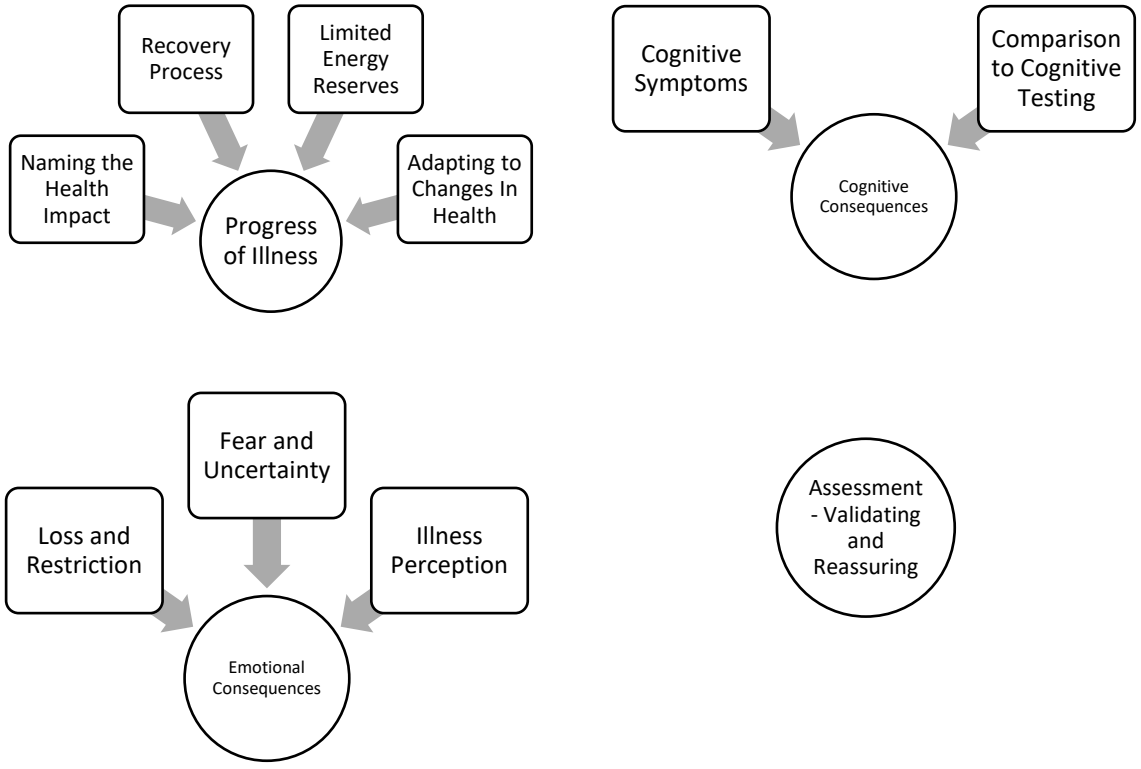
Note. Scores above cut-off for the PHQ-9, GAD-7 and PCL-5 highlighted in bold.

4.4 Qualitative Analysis of Feedback Questionnaires

Thematic analysis of questionnaires responses for the 13 participants constructed four main themes: ‘Progress of Illness’ with four subthemes; ‘Cognitive Consequences’ with two subthemes; ‘Emotional Consequences’ with three subthemes; and ‘Assessment – Validating and Reassuring’ without subthemes. Figure 5 displays the Thematic Map of these themes and subthemes. Where quotes are referred to, participant names have been replaced with the participant number to preserve anonymity. Appendix T displays information on the number of quotes provided per participants per question on the questionnaire.

Figure 5

Thematic Map of themes and subthemes



4.4.1 Progress of Illness.

The first theme describes how participants evaluated the progress of illness from initial infection with COVID-19 through to their current experience of recovery and/or long COVID. This theme occurred the most during analysis. The impact that symptoms had on participants' health was named by all participants therefore the first sub-theme represents and illustrates the diverse, multi-organ, range of issues. The second sub-theme describes participants' comments on how the illness influenced their energy reserves and how exertion often exacerbated symptoms. The next sub-theme describes participants' process of recovery from symptoms, with the final sub-theme describing adaptations that were made to account for longer standing changes in health.

4.4.1.1 Naming the health impact.

Symptoms ranged across several areas of health including gastric, renal, respiratory, musculoskeletal, and cardiac. Participants most frequently commented on respiratory symptoms, such as shortness of breath:

'I had SOB even at rest & could not move or speak without breathing becoming too difficult' (LC3).

The number of and diversity in symptoms reported varied between participants. Some reported a widespread health impact:

'High temperature. Breathlessness. Cough. Loss of taste and smell, Sore throat. Kidney pain (Kidneys were and still are dry). Very dry mouth and burning tongue. Very tired. No appetite. Blood grains in sick. Blood in stools. Geographic tongue. Blood test indicated I was going into heart failure.' (VH5).

Others reported less so:

‘Very severe headaches and fatigue’ (LC4).

Generally, participants described a more severe health impact during the acute stages of illness. However, except for one participant, the long COVID group tended to describe more detailed information about symptoms that persisted. Many participants commented on feeling that various health concerns had occurred since COVID-19 and it appeared that they infer this may be as an indirect result of initial illness:

‘Since having COVID 19, I have suffered other physical problems (slipped disc, heart attack, replacement knee) so I feel my general health has suffered and it is not all due to ageing.’ (VH9).

Interestingly, descriptions of neurological symptoms, such as headache and loss of taste/smell, were made noticeably more frequently by the long COVID group.

4.4.1.2 Limited energy reserves.

Fatigue was one of the main symptoms reported across both groups. In the acute stages this was more related to expressions of physical tiredness which usually had a substantial impact on participants’ abilities to carry out activities of daily living:

‘Extreme fatigue, I was unable to walk far or use stairs’ (LC9) and ‘(I was) effectively bed bound for two weeks’ (VH4).

Questions asking about fatigue and long-term impacts of COVID-19 elicited responses that depicted how fatigue was more easily brought on through physical or cognitive exertion:

‘The fatigue is a concern as I don’t have the energy like I had before COVID and cannot do as much in a day prior to COVID and get tired much quicker’ (VH3).

One participant, a retired GP, identified that their experience was similar to that of 'post-exertional malaise' (LC9). The impact of this was substantial for most, for example:

'I was previously very fit and active but can now only do very limited physical activity. I can no longer lead a full, active, fulfilling life. I have to go to bed by 8pm every night.' (LC9).

Participants also commented on how limited energy reserves impacted on their experience of testing. Some felt tired during the second half of the assessment and two participants commented on feeling tired the following week, with an exacerbation of symptoms:

'I had brain fog for a few days afterward' (LC6).

4.4.1.3 Recovery process.

As a result perhaps of the wide range of symptoms described, participants also catalogued a wide range of different services they had been involved with for support in their recovery process. This included the NHS website, GP, NHS 111, various tests such as ECG and EEG, chest x rays, various medications and supplements, specialist medical consultancy, counselling, oxygen at home and support from family. They also frequently mentioned aspects of the time taken for various symptoms to recover and it appears that the virtual hospital group reported more acute severe symptoms whilst the long COVID group were more likely to report persistence of symptoms.

'My gastric symptoms have cleared up but I continue to suffer with debilitating brain fog and painful inflammation in my hands and head.' (LC8).

Importantly, there is rich detail on how most participants made significant improvements in most areas of health over the past two years:

'My illness is less pronounced 2 years on but I continue to have relapses which mean I have to take to my bed for about a week in order to be able to function.' (LC8).

4.4.1.4 Adapting to changes in health.

Participants talked about their difficulties in adapting to changes in health and subsequent impact on physical and cognitive abilities. Mostly this was related to practical strategies to manage fatigue and cognitive symptoms which impacted on their ability to carry out activities of daily living to the standard they had been used to prior to illness with COVID-19. Fatigue management strategies involved pacing, taking regular breaks and taking on less responsibilities at home, socially or at work. For many this meant substantial reductions to working hours:

'I've reduced the length of my working day to cope with fatigue' (LC10).

Support from others appears to have been particularly important:

'Fortunately, I have a very supportive husband who helps me greatly with these issues.' (LC9).

Although, some commented on feeling they had needed to withdraw socially in order to cope:

'Now I have to ration what I do, and it's almost always my social life that pays the price.' (VH6).

Cognitive strategies were also mentioned, including spending more time planning, making notes in meetings and/ or using other sources of information such as video or audiobooks, for example:

'I listen to audiobooks rather than reading. I turn off all external sources of noise – e.g. the TV, music, podcasts, audiobooks etc unless I am specifically listening to them.' (LC9).

4.4.2 Cognitive consequences.

This theme depicts how participants described difficulties with cognitive abilities as well as how related these issues were to the group and individual feedback from cognitive testing in the first stage of this study. The theme was often directly related to the sub-themes of 'Limited Energy Reserves' and 'Adapting to Changes in Health'.

4.4.2.1 Cognitive symptoms.

Symptoms were described as poor concentration, brain fog, memory impairment, word-finding difficulties, multi-tasking, coping in busy environments, taking longer to do tasks, comprehending instruction and/or following conversations, films & books. Alongside fatigue, these issues were cited by most as having a substantial long-term impact on their quality of life, in comparison to other physical health symptoms which seemed more concerning during the acute stages. Interestingly, cognitive symptoms were more frequently reported in the long COVID group and there was a similar emphasis on the theme across questions enquiring about acute and long-term consequences. Only few mentioned improvements in symptoms. 'Brain fog' and concentration, especially, appear to remain an issue for most, which often intersects with participants' experience of fatigue.

'Brain fog has made what used to be simple everyday tasks a real difficulty and the regular relapses and constant underlying fatigue still limits my ability to live a full life.' (LC8)

4.4.2.2 Comparison to cognitive testing.

In general, most participants commented feeling that the feedback provided on cognitive testing made sense and related well to their subjective experience of cognitive symptoms:

'The deficits picked up tally with my own experience of my cognitive functioning on the whole.' (VH4).

Some participants related more to group feedback and others related more to the individual feedback:

‘The individual feedback was more relevant to me, but there were lots of the group feedback remarks that I related to myself.’ (VH5).

A few participants commented feeling that feedback wasn’t representative of their experience in some way, feeling that it overestimated their abilities. Some mentioned that this may have been because of the environment:

‘My results would have been very different if the tests weren’t done in such a quiet environment – ie any noise or external distractions would have made the tests MUCH more difficult!’ (LC9).

And others commented feeling that, due to improvements in cognition throughout their recovery from COVID-19, they would have performed poorly if tested earlier:

‘Things would have looked very different for me a year ago.’ (VH6).

4.4.3 Emotional consequences.

The third theme attempts to capture some of the descriptions made by participants of the emotional impact of COVID-19. Although this was often a varied experience for individuals, relating to their COVID-19 illness as well as national lockdown restrictions, a number of sub-themes were apparent across most of the participants. Generally, during the acute stages participants were more likely to report fear but also a sense of having to cope, as illustrated with the quote ‘Too weak physically to be concerned about mental health’ (VH9). As the course of the illness progressed participants reflected more on feelings of loss but also, for some, a sense of hopefulness in noticing significant improvements in certain areas.

4.4.3.1 Loss and restriction.

Participants described the relationship between restrictions on their cognitive abilities and energy levels, with a loss of time, health, income, opportunity and sense of self:

'It restricts my freedom (going into town, activities with my children, seeing friends) and it impacts on my husband who has to do more than he would if I was well.' (LC6).

4.4.3.2 Fear and uncertainty.

This sub-theme highlighted fears for many participants of dying, primarily in the acute stages, and of how much their health may recover after:

'Bad as thought I was dying and it went on for over 12 weeks with small recovery from week to week' (VH7).

This was often related to a sense of uncertainty about these factors which was correlated by some to the wider social uncertainty around COVID-19 as a whole:

'A lot of fear because it was all new and uncertain. It was early in the pandemic, so people were really scared of catching it and stayed away, understandably.' (VH6).

Some participants also commented on the impact of news and media regarding prognosis:

'It has left me a bit anxious about longer term effects that might not yet be apparent, e.g. recent reports of brain shrinkage and possible links to premature brain ageing, and I am more attuned to issues with my cognitive functioning than I perhaps otherwise would be' (VH4).

4.4.3.3 Illness perception.

Illness perception concerns were two-fold. Firstly, many participants commented on feeling frustrated or let down by services supporting them, as they often feel long COVID (in particular) has been dismissed as 'being classified as "tiredness" or "laziness" or "only happening to the vulnerable"' (VH6). This linked to the characteristic invisible symptoms:

‘People were a lot more understanding during the acute infection, as it was so obvious I was ill. This is not always the case with Long COVID as the majority of the symptoms are hidden.’ (LC9).

Secondly, some participants spoke of how they perceive themselves differently as a result of their illness with COVID-19, perhaps inferring critical thoughts about themselves and what they are able to do:

‘I have gone through guilt/shame over struggle to work & felt loss in identity of my former life’ (LC3).

4.4.4 Assessment – Validating and Reassuring.

When asked to comment on their appreciation for cognitive test findings, the relationship to their subjective experiences, and their experience of testing procedures, most participants made positive comments about the assessment. Some found that, conversely to comments made in the ‘Illness Perception’ sub-theme, the assessment felt validating to their current difficulties of managing COVID-19 and long COVID illness:

‘The findings have validated what I have experienced but that others fail to appreciate.’ (LC9).

Others described feeling validated and reassured to know that they weren’t alone in going through this experience:

‘(Assessment was) helpful as I thought I was the only one and was going mad as I forget things.’ (VH7).

Others commented on finding that it was reassuring because it highlighted that cognitive function was relatively intact: ‘Reassuring that I have none / little significant impairment.’ (LC10).

Discussion

5.1 Overview of Discussion

The final chapter will describe how each of the two research questions have been answered, in turn, by drawing on interpretations made from cognitive testing, self-report mood measures and questionnaire feedback. The chapter will then discuss the relative strengths and limitations of the study as well as reflections on the process of research before outlining some of the clinical implications and recommendations.

5.2 Interpretation of Results

In order to answer the first research question: 'what are the objectively measured cognitive and emotional consequences of COVID-19/ long COVID at 20-24 months?', interpretations were made based on data from cognitive testing and self-report mood measures. This included both statistical analysis and review of scores deemed to be clinically significant.

5.2.1 Interpretation of data from cognitive testing.

The Core Cognitive Domains model set out by Wilson & Betteridge (2019) is used both in the systematic review and again here for the cognitive tests used in the study to allow for ease of comparison. In line with the critical realist ontological and constructionist epistemological positions, there is a recognition that this is one of many possible models for conceptualizing cognitive function and intelligence. This is complicated further as there is still much debate within the field of neuroscience on to generalisation versus localisation of function within the brain (Lezak et al., 2012). Therefore, associations between the test and area of function measured are made based on abilities defined in the according testing manuals (see Table 7), with support from the external supervisor and consultant. For a full review of test to function associations see Lezak et al. (2012).

5.2.1.1 Attention and working memory.

As with the systematic literature review, attention and working memory are described together here due to how cognitive tests designed to assess these areas often rely on ability in both functions (Wilson & Betteridge, 2019). One of the cognitive measures, Sequences, primarily assessed attention whilst also requiring some working memory ability. The score was not significantly different from estimated IQ, and it was the only one where all participants scored within 1SD. Digit Span, which was also non-significant and showed few participants scoring 1SD below, primarily assesses short-term memory, attention and working memory. This suggests that attention and working memory function remain intact for the study participants. There were no differences between the VH and LC groups on these tests. These findings appear to be concordant with the existing literature on attentional functioning following COVID-19. Some of the research studies showed evidence for working memory deficits at four-months, which were not observed at six-month follow-up (Poletti et al., 2021). This would be consistent with the present findings, which assessed after a significantly longer interval post-infection and hence opportunity for recovery. In accordance with the formulation model presented by Wilson & Betteridge (2019), attention and working memory are central to all other cognitive functions and therefore we can better rely on subsequent testing given these appear to remain intact.

5.2.1.2 Processing & motor speed.

Coding was the only test used in the study that primarily assessed processing speed. Coding did not significantly differ from estimated IQ, but substantial individual differences were observed with some participants performing well and others worse. There were also differences in scores between the VH and LC group. Firstly, three participants in the LC group were observed to have scores greater than 1SD above expectations, and three with scores at 1SD below. The VH group differed to LC in that two participants scored 1SD below

expectations whilst none scored above, and one participant showed substantial deficit, scoring 2SD below expectations. Because of this, it is difficult to make exploratory interpretations of processing speed based on Coding. However, it is worth highlighting that this was the only sub-test that the VH group were more likely than the LC group to perform in deficit, on. The systematic literature review suggested that processing speed was a frequent area of deficit at four to six months. It may be that, for some people, processing speed may be affected initially but show recovery through the two-year period post-infection.

Interpretation of processing speed findings is complicated by a related finding that psychomotor speed was also poorer than expected. The Trail Making Test 5 measures psychomotor speed and was statistically significantly different to estimated IQ, showing the second highest number of participants scoring 1SD or more below expectations. The LC group had notably higher frequency of scores below than the VH group. This may highlight a difficulty with psychomotor speed, particularly for the LC group. These results correspond with the deficits in psychomotor speed observed in previous research (Mazza et al., 2021).

5.2.1.3 Visuospatial function.

Scores on Line Orientation were lower than estimated IQ, which was statistically significant. This is a measure primarily of visuospatial function suggesting that, coming up to the two-year period, this may remain a deficit. Other measures of visuospatial function, Spatial Location and Clocks, although not statistically significant, were also frequently observed to be below 1SD from estimated IQ for many participants. For 4 participants, Spatial Location was below 1.5SD, consistent with a substantial deficit. Another test conducted, Matrix Reasoning, primarily assesses abstract reasoning skills (an executive function) but also relies on visuospatial skills, with many participants scoring 1SD or more below expectations. When comparing between groups, there were some notable differences between LC and VH on Spatial Location and Line Orientation, suggesting the LC group may

be more susceptible to deficit. When compared to the systematic literature review, results are somewhat concordant as a visuospatial deficit was identified. However, this tended to be suggested for those with greater illness severity, which is converse to the present findings.

5.2.1.4 Language.

The Verbal Fluency Semantic and Phonemic measures were included to assess language functioning. The Verbal Fluency Semantic task require participants to recall words of a particular category, such as first names, whereas the Verbal Fluency Phonemic task requires the person to recall words beginning with a certain letter. The former resembles functions used more often every day and the latter is a novel challenge drawing heavily on mental flexibility and use of strategy to perform optimally. Neither were statistically significant when compared to estimated IQ. Clinically significant deficits in phonemic fluency were observed in some participants but fewer showed deficits in semantic fluency whilst more scored 1SD above estimated level. This discrepancy highlights a difficulty for some in retrieving words that do not have a conceptual organising principal to connect to and therefore requires a greater reliance on novel strategies utilising executive functions (Shao, Janse, Visser, & Meyer, 2014). This conclusion is supported by the fact that none of the participants were observed to have scores of concern on Picture Naming, which assesses language related deficit in word-finding. When comparing groups, they performed similarly on Verbal Fluency Phonemic but the VH group had more scores 1SD above estimated IQ on Semantic. The identification of specific phonemic fluency deficit in some participants appears to correspond with the systematic literature review, which highlighted a similar pattern of phonemic fluency deficit in the context of otherwise preserved language function.

5.2.1.5 Memory.

Complex Figure Immediate, Delayed and Recognition all assess visual memory function, and these measures observed a high frequency of participants scoring below 1SD

across groups. Conversely, Word Lists Immediate, Delayed and Recognition all assess verbal memory function but were the three measures that participants performed best on, with some participants scoring 1SD or more above estimated IQ. None of these tests observed a statistically significant difference. Given that the Word Lists scores were observed to be the lowest ranked in terms of clinically significant deficit, this might suggest that auditory-verbal short-term, long-term and recognition memory remain relatively intact for participants. Interpretation of findings on visual memory tasks are complicated by weaknesses on visuospatial function and may also be secondary to a broader pattern of weakness on tasks tapping executive functions (see 5.2.1.6). There was no clear pattern of discrepancy between immediate and delayed memory performance across modalities. A conclusion that memory appears relatively intact is supported by the fact that none of the participants scored below expected on Picture Recognition, which assesses delayed memory. Scores were similar between groups on the Complex Figure measures, but LC performed worse than VH on the Word List measures. As observed in the systematic review, verbal memory appeared more intact than visual, despite a large discrepancy observed between papers reporting on these.

5.2.1.6 Executive functioning.

Executive function is likely to encompass many related but discrete independent cognitive functions that draw on the other domains described above (Wilson & Betteridge, 2019). A number of tests were included in the battery to assess these executive function domains. Firstly, visual and verbal abstract reasoning were assessed with Matrix Reasoning and Similarities, respectively. They both observed many participants scoring 1SD or more below expectations, particularly on Similarities. For the Similarities score, the difference compared to estimated IQ was also statistically significant. This suggests that abstract reasoning may be a specific area of deficit for participants. However, it’s worth noting that on the Similarities test, participants frequently reported feeling that they knew the concept

required for response but couldn't find the word. The lower score on this test, then, may be influenced by the executive word finding difficulties identified in the discrepancy between phonemic and semantic fluency.

Another area that many participants performed worse on was with tasks assessing inhibition and switching. Trail Making Test 4 and Color Word Interference observed 3 and 5 participants, respectively, scoring below 1SD. Trail Making Test 4 was statistically significantly different to estimated IQ despite fewer individual participants scoring below expectations. This may largely be due to the observed potential deficit in psychomotor speed, as measured by the Trail Making Test 5 score.

The higher frequency of scores below 1SD on executive function tasks with a significant verbal component (Similarities and Color Word Interference) as opposed to those weighting on visual functions (Matrix Reasoning and Trail Making Test 4) may align with the finding of greater difficulty on phonemic vs semantic fluency tasks. Like Phonemic Verbal Fluency, the Similarities and Color Word Interference tests both require participants to retrieve words from a stored language lexicon whilst also utilising executive functions related to inhibition, problem solving and abstract reasoning of the novel task. It may be, therefore, that participants' experience a specific verbal executive function deficit related to processes of word-finding.

Some executive functions assessed appear relatively intact. Two of these were assessed with the Practical Problem Solving and Conceptual Shifting score. This is a combined score for two tests measuring problem solving and conceptualization, respectively. Only a few participants performed below 1SD on this score. Similarly, Zoo Map 1 and Zoo Map 2 are measures of planning and organization and were both observed to have few participants scoring 1SD or more below estimated IQ.

When comparing the LC and VH groups across executive functioning, Zoo Map 1,

Practical Problem Solving and Conceptual Shifting, Matrix Reasoning, Trail Making Test 4 and Color Word Interference appeared relatively similar. Zoo Map 2 observed slightly more LC participants scoring 1SD or more below estimated IQ, whilst Similarities observed a substantial difference, which was the greatest difference across all sub-test scores. The LC group performed more poorly than the VH group, indicating that functions related to verbal reasoning may be of specific concern only to the LC group.

Methodological issues with the research papers included in the systematic literature review meant that executive function was not assessed at a level of detail that would allow for comparison with the findings presented here.

5.2.1.7 Summary of cognitive testing.

Based on comparisons of tests at 1, 1.5 and 2SD above or below estimated IQ, it appears that the foundational functions of attention and working memory remain relatively intact for most of the participants included in the study. However, processing speed may be an area of specific difficulty for some, which may influence performance on tests of other, 'higher-order' functions (Wilson & Betteridge, 2019). Psychomotor speed/ coordination, visuospatial function and executive functions related to abstract reasoning, inhibition and switching were observed to show deficit in several participants. There was also a suggestion of specific deficit for processes involved in verbal executive functions utilised when completing novel tasks.

Of these functions that observed clinically significant deficit, measures of switching (Trail Making Test 4), psychomotor speed/ coordination (Trail Making Test 5), visuospatial function (Line Orientation) and verbal abstract reasoning (Similarities) also observed a statistically significant difference. We can be surer that these findings were not observed by chance alone, especially given the stringent Bonferroni adjustments made. Other functions such as language function, memory and executive functions related to planning, organizing

and problem-solving appear relatively intact. Importantly, despite identifying some exploratory evidence for a pattern of deficit seen in the sample, there was a high amount of variance in scores suggesting that individual differences were prevalent.

Between the VH and LC group, the VH group only performed worse on tests assessing processing speed. The LC group performed worse, generally, but especially across tests assessing psychomotor speed/ coordination, visuospatial function, verbal memory and executive functions related to verbal reasoning. These findings were only observed when comparing frequencies of scores above or below clinically significant SD cut-offs and there were no statistically significant differences found.

When comparing these findings to those identified through systematic review of the existing literature, there appears concordance in deficits in psychomotor coordination and visuospatial function as well as perceivably intact functions across attention, working memory, language and phonemic fluency. The only discernable difference appears to be in memory, which was found to be an area of difficulty in previous research at the earlier time-points of assessment. It was not possible to compare executive functioning findings due to limitations in the reporting of existing evidence.

It is important to consider that it will be expected for participants to score worse on some sub-tests and better on others, due to normal variance in testing performance (Lezak et al, 2012). Additional analysis could have been conducted to account for this with a larger sample or if it were plausible to utilize KBNA index scores if there was less variance between cognitive sub-tests. Instead, comparisons can be made to a binomial probability distribution reported by Ingraham & Aiken (1996). For a cognitive battery yielding 22 sub-tests it is expected that 2%, 20% and 70% of participants obtain 3 or more scores 1, 1.5 and 2SD below estimated IQ, respectively. The present study observed 11%, 37% and 79%, respectively. This suggests that scores were observed to be in deficit slightly more than expected.

5.2.2 Interpretation of data from self-report mood measures

The self-report mood measures provide insight into the prevalence of depression, anxiety and PTSD symptoms experienced by the participants in the study, as well as the impact of illness from COVID-19. Two thirds of the VH group and just over half of the LC group scored above cut-off for at least one of the total scores for the PHQ-9, GAD-7 and PCL-5. Symptoms of depression and anxiety had a similar prevalence (at about half of the total participants) whereas PTSD symptoms were observed in a third. The largest impact of illness, as observed by the EBIQ, appeared to be related to somatic symptoms, however all other subscales were also reported frequently. When comparing groups, MANOVA observed a statistically significant difference on total scores when all of the four mood measures were considered together, with a higher prevalence of self-reported emotional consequences to COVID-19 for the VH group. No single test reached a statistically significant difference between groups in post-hoc testing. Despite this, when observing the frequency of scores above clinically significant cut-offs, there was a substantial difference between groups on the GAD-7; seven participants from the VH group scored above cut-off and 2 from LC. This suggested more frequent symptoms of anxiety reported by the VH group. For the EBIQ, main group differences were observed on the cognitive and general subscales, with the LC group rating higher. This suggests that experience of cognitive issues may be slightly more prevalent for this group. When compared to the systematic literature review, these findings appear to suggest that participants reported a slightly higher prevalence of anxiety, depression and/ or PTSD symptoms than Mazza et al.'s (2021) study conducted at three months post infection. Comparison of the relationship between self-report mood measures and cognitive testing, especially symptoms of depression (Poletti, et al., 2021), was beyond the scope of this study primarily as it would require a substantially larger sample of participants.

5.2.3 Exploration of findings from thematic analysis

In order to answer the second research question ‘How does this (objectively measured cognitive and emotional consequences of COVID-19/long COVID) relate to the subjective experience of illness from COVID-19 and illness severity?’ findings from thematic analysis of questionnaire responses were reviewed. Each theme is explored here in relation to data collected from cognitive testing and self-report mood measures in order to enhance understanding from the interpretations made.

5.2.3.1 Progress of illness.

This theme captured how participants described their experience of illness from COVID-19. Participants reported a range of symptoms and symptom severity during the acute stages of infection with mixed recovery leading up to the current assessment at the 2-year mark. Many of the symptoms were expected given the CDC (2021) commonly reported symptoms (see Table 1) and correspond with the highest rank response on the EBIQ: somatic symptoms. The distinction in illness severity between groups, based on the NIH illness severity scale, was affirmed in the responses participants gave. Participants from the VH group more often described rich detail about the symptoms experienced during the acute stages of infection whereas the LC group commented more on persisting symptoms. Of the symptoms that persisted, an interaction between cognitive concerns and fatigue appeared to be most prevalent and concerning to participants. Physical and cognitive exertion was noted to make participants feel tired and, in turn, tiredness impacted substantially on cognitive and physical abilities. These reports cohere with the previous literature (Davis, et al., 2021) that has examined the relationship between COVID-19 and post-exertional-malaise. Adaptations to changes in health were mainly targeted towards coping with these concerns and participants reported a variety of strategies or approaches. These appear similar to those typically recommended by various psychological therapies (Carr & McNulty, 2016).

5.2.3.2 Cognitive consequences.

Participants reported a variety of subjective experiences linked to cognitive difficulties, either linked explicitly by the participant or in interpretation during the process of thematic analysis. The LC group reported more cognitive symptoms in the feedback questionnaire, which appeared to correspond with the difference observed between the groups on the cognitive subscale of the EBIQ. Although quite varied, general reports of poorer cognition such as 'brain fog' and difficulty concentrating were commonly mentioned across both groups, persisting up to the point of assessment. Many participants didn't describe a more nuanced experience of cognitive symptoms which be due to difficulty articulating the specific issues and/or the brief nature of much of the responses to the questionnaire.

When prompted, participants reflected on how cognitive testing findings compared to their subjective experience of cognitive symptoms. For the most part, participants felt feedback made sense and related well. Of those that did specify specific concerns about their own cognition, these appeared to validate the cognitive testing findings. For example, some participants commented on word-finding difficulties which may be as a result of the specific deficit highlighted with verbal executive function during novel tasks. Others also commented on visuospatial concerns, such as when driving, and some reported feeling they 'slow down' when fatigued, which may be experienced as a result of deficit in psychomotor speed/ coordination. The general findings of 'brain fog' and difficulty concentrating could also be attributed to the specific executive function deficit in abstract reasoning, inhibition and switching. Switching, specifically, may have also contributed to concerns raised by some participants that the cognitive testing didn't capture the full extent of their subjective difficulties, as the testing environment was quiet with limited distraction. Finally, some participants reflected how findings would have perhaps been quite different if undertaken a year or more before they were, evidencing some suggestion that symptoms have improved.

5.2.3.3 Emotional consequences.

This theme elaborates on the prevalence of anxiety, depression and PTSD symptoms reported by participants on self-report mood measures. Most participants commented on a fear of uncertainty surrounding the pandemic, illness disability and/or mortality. The VH group described more about fear and uncertainty, generally, but also regarding mortality and illness disability. This helps explain why the VH group were observed to have a higher frequency of scores above cut-off for symptoms of anxiety on self-report mood measures. The VH group, as expected based on their NIH severity rating, highlighted difficult experiences during acute stages of infection related to fear of suffocation and/ or being treated in hospital. It may be that this period of illness was traumatising for some with more severe acute symptoms (Dutheil, et al., 2020), providing further reason as to why this group reported more symptoms of anxiety and PTSD. Loss and restriction was mentioned by most participants in relation to cognitive ability and fatigue but it was acknowledged that this was also conflated by lockdown restrictions. For many this was substantial, with restrictions to abilities resulting in loss of their job, health and time for activities or to be with family. Given this, it is perhaps understandable that many participants scored above cut-off for symptoms of depression, as it is often associated with processes related to grieving of a loss (Carr, 2016).

A common aspect that connected most participants' emotional experiences of COVID-19 was how their disability from fatigue or cognitive consequences was perceived and misunderstood by others. This was particularly pertinent during the initial stages of illness whereas more recently it was felt that others had started to appreciate these difficulties. Despite this, some participants experienced guilt and shame about how they have been able to manage. The Y-Shaped Model (Gracey, Malley, & Evans, 2009) is useful here in appreciating how, as is common with neurological conditions, there is a new discrepancy that has developed between the 'ideal-self' and the capabilities of the 'post-COVID-19-self'.

5.2.3.4 Assessment – validating and reassuring.

The final theme captures how participants reviewed their experience of cognitive testing. Most participants spoke highly of this, suggesting that the findings validated their experience of illness from COVID-19 and long COVID. This makes sense when contrasted with previous research alluding to the experience of invisible symptoms from COVID-19 (Volpe & Diamond, 2021) and how participants in the present study described feeling misunderstood within the emotional consequences theme. Often, subtle cognitive deficit can have a substantial impact on quality of life, especially if the individual frequently requires a high level of ability for a working or social role, for example. This was perhaps the case with the study participants as they were mostly observed to have a high occupation status as determined by criteria from IMD. As a result, participants may have commented on finding the assessment process reassuring to know that many cognitive functions remained intact.

5.2.4 Summary of interpretation of results

Cognitive testing at the 20–24-month mark highlighted that the study participants mostly performed at an expected High Average level of ability on most sub-tests, when compared to estimated IQ. This was notably better than observed in the systematic review of research conducted at the three-to-12-month mark. However, there was still some evidence of cognitive deficit for most participants, often varying in the domains affected. Despite this variance, some patterns of deficit between participants across the two groups was observed. This was seen with visuospatial function, psychomotor speed/ coordination, executive functions related to abstract reasoning, inhibition, switching and verbal executive functions involved in novel tasks. The LC group had a higher frequency of scores than the VH group at clinically significant deficit of 1, 1.5 and 2SD, despite less severe acute symptoms as measured by the NIH severity scale. However, there was no statistically significant differences between test scores for the two groups.

Self-report mood measures completed by the participants demonstrated a high prevalence of symptoms of depression, anxiety and PTSD when compared to previous research in the systematic literature review. Across all of the mood measures, the LC group had lower scores than the VH group, which was statistically significant. This may be in part due to the VH group having a substantially higher frequency of scores above clinical cut-off on the measure of anxiety, however, neither this nor any of the other measures observed statistically significant differences alone.

Questionnaire responses from participants largely enhanced interpretations made from cognitive testing and self-report mood measures. Subjective experiences of cognitive deficit were described generally as poor concentration and brain fog as well as specific difficulty remembering, word-finding, multi-tasking, coping in busy environments, taking longer to do tasks, comprehending instruction and/or following conversations, films & books. Each of these areas may relate to one or more of the observations made from cognitive testing. Participants often recognised that they had improved in function since acute stages of illness. Fatigue had a perceivably substantial interaction with cognitive performance which mirrors suggestions from previous research (Davis et al., 2021). Although correlational analysis was conducted to see if test performance got worse as testing continued, this was non-significant despite finding a medium effect size (Cohen, 1988). The prevalence of depression, anxiety and PTSD was better understood with sub-themes of fear and uncertainty as well as loss and restriction. Again, this corresponds with previous research (Cenat et al., 2021; Hussan, 2022) as well as clinical approaches in neuropsychology practice, such as the Y Shaped model (Gracey, et al., 2007). Other findings of interest from thematic analysis were that assessment was mostly deemed to be a positive experience by participants as it was both validating of current concerns and reassuring.

5.3 Comparison with Neurological Literature

The findings from this research can be triangulated (Wilson & Betteridge, 2019) with pathological findings from the neurological literature to consider associations, as was previously explored in the systematic review (see 1.4.5.1). Firstly, the identified visuospatial function deficit may relate to high levels of ACE2 in the pons, visual cortex (Cui et al., 2021), or occipital lobe (Wilson, 2021). Most other functions in deficit related to executive functions, which are typically thought to be maintained in the frontal lobes (Goldstein & McNeil). This suggests that frontal lobe lesions (Butowt & Bilinska, 2020), specifically fronto-parietal lesions (Ellul, et al., 2020) along with evidence of hippocampal (Lu, et al., 2020), right medial temporal lobe (Guedj, et al., 2021) and parahippocampal gyrus lesions (Douaud, et al., 2022) may associate with the observed deficit. Further to this, the specific difficulty suggested with verbal executive functions involved in novel tasks, primary indicated by phonemic fluency tasks, may correlate with the posterior-dorsal left inferior frontal gyrus (Costafred, et al, 2022). Interestingly, this is further away from viral entry points than intact semantic functions assessed in similar cognitive tests (Ellul, et al., 2020). Finally, psychomotor speed is associated with the motor cortex in the frontal lobe (Goldstein & McNeil, 2013). Importantly, scores on tests may be somewhat affected by mood and fatigue issues reported by participants (Goldstein & McNeil, 2013). The finding that the LC group, with less severe acute symptoms, performed worse on cognitive testing also perhaps contradicts some of the associations made here.

5.4 Critical review

5.4.1 Strengths

To my knowledge, the present study is the only completed to date that utilises mixed methods to explore the cognitive and emotional consequences of COVID-19. This is a relative strength of the study firstly because most research, as covered in the systematic literature review, relies heavily on the scoring of cognitive testing to draw assumptions. By enquiring about subjective experience of cognitive symptoms, experience of cognitive testing and perceived relatedness of findings from cognitive testing, this study was able to more reliably draw conclusions about deficit. This was especially important given the smaller sample size recruited as part of the research. Additionally, constructing research in this way better replicates the process of assessment in neuropsychological clinical practice (Wilson & Betteridge, 2019) whereby interpretations are made through a process of triangulation between cognitive testing, knowledge of diagnosis/pathology/investigation findings, and subjective experience (self and collateral reports). The mixed methods approach was also useful in enhancing findings from self-report outcome measures. Whilst self-report measures are useful in describing the prevalence of clinically significant symptoms within a population, they lack the ability to capture the nuance of how these symptoms manifest and why. Conversely, qualitative research, such as reviewed by Macpherson, et al. (2022), is helpful in cataloguing these detailed descriptions, however, lacks generalisability.

Another strength is the comprehensive cognitive battery administered. To my knowledge no other published study has utilised such a broad range of tests that are capable of providing insight into discrete cognitive functions, especially within executive functioning. Most research, including many studies screened but excluded from systematic literature review, administer cognitive screens that draw broad, non-specific inferences about deficits in global cognition. Although assessment sessions were quite long and required a lot of effort

from participants, this enabled exploration of a range of executive functions, consideration of potential explanations for poorer performance on some memory tests, and comparisons of visual vs verbal abilities. For example, inclusion of a semantic vs phonemic fluency task illustrated a specific deficit in function that may have also influenced the lower scores seen in other executive function tasks, such as the similarities sub-test.

Due to the timepoint at which data was collected, and that recruitment focused on those that contracted COVID-19 during the first wave of the pandemic, the study is the first (to my knowledge) to assess cognitive and emotional consequences coming up to two years post infection. This is substantially different to other research covered in the systematic review, where assessment intervals ranged from three to 12 months. This meant that comparisons could be made and suggestions about the recovery prognosis could be posed. This was also useful in contrasting the recovery prognosis for those with more acute symptoms in the VH group with those that had self-reported persistent symptoms via referral to a long COVID service, observed in the LC group.

5.4.2 Limitations

Potential strengths of the proposed research methodology, such as the utility in analysis of the intersection between cognitive and emotional consequences, were unfortunately not met, in part due to the low sample size. The research had aimed to recruit around 60 participants, assessing over a much longer data collection interval, which would have allowed for more detailed statistical analysis of cognitive testing and self-report mood measures. For example, analysis of covariance could have been utilized to account for the impact of different mood states on cognitive testing (Lezak, et al., 2012). Similarly, the low sample size meant that differences between the VH and LC groups was primarily explored through qualitative or descriptive statistics. The small sample size also reduces the reliability and validity of interpretations made. This is because the statistical techniques used to explore

differences from estimated IQ and between groups generally require larger sample sizes to observe statistically significant findings. Although observation of clinically significant cut-offs was perhaps helpful in generating individual feedback and interpreting suspected cognitive profiles, further research will be required to confirm these exploratory suggestions.

Related to this, the sample demographics were limited to white British, female, and those with high IMD score. Although the high IMD score was relatively representative of referrals to the service and the local area supported by these services, due in part to the sample size, other demographic variables were perhaps not sufficiently diverse. For example, although ethnicity was representative of the local area, it is not representative of those referring to services for which this study recruited from. This discrepancy makes sense given the research on health inequalities reviewed in section 1.4 (Bambra et al., 2020; Wilson, 2021) and is an especially important consideration because of this. Additionally, 90% of respondents were female and there is some conflicting evidence to suggest that, for example, males may be more adversely affected in the acute stages (Dessie & Zewotir, 2021) and females in the long-term (Bai, et al., 2022). As the research was focused on a single center this perhaps limits the generalizability of findings to wider populations, for example, to more deprived areas of the UK as a defined by differences in IMD.

The qualitative element of the study was restricted due to time constraints. It was initially planned to collect data from interviews or focus groups, but this was changed to an open-ended question questionnaire. This limited the nuance and detail of responses for many participants, although it was notable that many participants still provided substantial information. Discussing the questions in person would have allowed me to probe further on areas that appeared relevant and would have encouraged generation of rich information about subjective experience. For these reasons, we also could not consider the potential role that support from services had played in experience of symptoms as had been hoped. Time could

have potentially been saved at the analysis stage if a deductive approach was planned from the start instead of attempting to draw themes inductively from the responses. Another option could have been to conduct a content analysis on questionnaire findings in order to assess the frequency with which participants reported different themes. This would have perhaps allowed for quantitative comparison with cognitive testing but would have also meant that meaningful information may have been missed if not reported at a high frequency.

It is important to recognise my expertise as a researcher in the field of neuropsychology. As a trainee clinical psychologist, I am not a registered Clinical Neuropsychologist myself and therefore have less experience of both cognitive testing administration and interpretation. Therefore, conclusions made from the research, which is typically conducted by Clinical Neuropsychologists with specialised training in the area, could be invalidated by administration, scoring or interpretation error. In order to account for this, each of the sub-tests were practiced thoroughly and the process of cognitive testing sessions were designed with close supervision from the external supervisor, who is a registered Consultant Clinical Neuropsychologist. Scoring and interpretation of cognitive profiles was completed with close supervision from both the external supervisor and the research consultant, who is a Professor of Clinical Neuropsychology working closely with the Division of Neuropsychology toward understanding the impact of COVID-19.

To summarise the study limitations, Table 17 describes a quality assessment based on the Newcastle-Ottawa Assessment Scale (Wells, et al, 2022; appendix C), displayed in the same format as for the systematic review. For the selection criterion, firstly the study was somewhat representative of the target population in terms of age, but as described, was limited in many demographic areas. The sample size was not satisfactory based on the initial research justifications. Ascertainment of COVID-19 was stated as via clinical assessment, which is what could be expected at the time of participants exposure. As a cross-sectional

study, criteria 4 was not met as there was a low response rate, reducing comparability. For the comparability criteria, estimated IQ was controlled for, as it was used in the primary analysis. Finally for the outcome criteria, despite a low sample size the statistical tests used were deemed appropriate and enhanced by qualitative analysis. Based on this quality assessment, the study is deemed to be of moderate quality.

Table 17

Newcastle-Ottawa Assessment Scale scores for present study

Study	Study type	Selection				Comparability	Outcome	Total	Quality Rating
		1	2	3	4	1	1		
Present study	Cross-sectional	*		*		*	*	4/6	Moderate

5.4.3 Reflections

Overall, I feel that this research has been useful in improving my skills as a novice researcher, hoping to publish their first paper, whilst providing recommendations for future research and clinical practice. Before discussing the clinical implications, I will review the findings in the context of how the research developed, over the course of the project. Importantly, I recognise how decision-making and consideration of how to navigate setbacks has been influenced by personal experience of long COVID within my immediate family. I hope that the way I have approached the research process reflects my compassion for those that continue to suffer. Three examples of extracts from my research diary used to catalogue reflections as research continued can be found in Appendix U.

During the early stages of the project, I had meetings with many professionals to discuss the project in order to ascertain how my final year thesis may be clinically useful. I spoke with my external supervisor and research consultant as well as the respiratory consultant that ran the virtual hospital, the clinical lead of the long COVID pathway and the research leads at both NHS Trusts that had been involved with prior COVID-19 research. I had also listened to advice from the Division of Neuropsychology specialist interest group. At the time, it felt that my ideas were being influenced by many different schools of thought. For

example, some emphasised the need to explore their anecdotal experience that virtual hospital patients, with more severe acute symptoms, did not go on to develop long COVID symptoms at the same rate as the general population. Alternatively, some suggested that there was limited information about what a subjective experience of 'brain fog' objectively meant and others suggested the research focused on the psychological impact. There was also substantial debate as to whether the research should attempt data collection virtually, given the context of COVID-19 restrictions, or endeavor to justify face to face.

Given the above, I knew this would be a large study requiring a lot of time, part of which was agreed inclusive of placement competencies. Because of this, I also made sure to start the IRAS application as soon as possible. Unfortunately, despite my best efforts, this was a lengthy process that involved a great detail of consideration in order to agree upon an ethically viable study that would be suitable in meeting the research aims despite various barriers, such as national lockdown restrictions. This meant that the project started much later than planned, despite efforts to free-up time to complete the required assessments through December to January. Adding to this, myself and the external supervisor both came down with COVID-19 ourselves. As we had to isolate for 10 days, this took a substantial chunk of assessment time from the study. This was perhaps the main reason why the study was only able to recruit less than half the desired number of participants. COVID-19 potentially also impacted on how available different research leads were at each of the trusts involved, which caused further delays. Accordingly, some of the questions we had originally hoped to consider during data analysis, such as the relationship between receiving support from virtual hospitals and symptom experiences, were not possible to address. Instead, we re-focused on the primary and more straightforward aims of characterising the cognitive and emotional profiles of this group and considering how these aligned or did not align with subjective experiences reported through questionnaires.

5.5 Research and Clinical Implications

Limitations to analysis, primarily in terms of sample size and its effect on the power of the study, mean that this study should be considered as taking an initial exploratory approach. Despite this, it has provided meaningful data that has supported generation of hypotheses about cognitive and emotional consequences of COVID-19 and long COVID. The various provisional recommendations for research and clinical practice resulting from this are described here.

Firstly, to my knowledge, this study is the first to explore these cognitive and emotional consequences at the 2-year mark post-infection, with a comprehensive cognitive testing battery that utilized mixed methods to correlate findings with subjective experience. This validates the need for future research to consider comprehensive cognitive testing, beyond simple 'bedside' screening tools, when exploring the nuance of cognitive deficit. For example, ensuring that scores for phonemic and semantic verbal fluency are distinguished in order to confirm or refute the hypothesis that there may be specific verbal executive function difficulty. However, it is also true that these larger batteries of tests would be more susceptible to participant fatigue, an important consideration given the population. Future research could attempt to ameliorate this by administering tests in a random order for each participant and/ or by spreading the administration of tests over two or more testing sessions. Where possible large sample sizes would be beneficial as this would aid statistical analysis of the multiple variables that would be produced by testing. It would also allow the opportunity for greater diversity in sample demographics. This is an important consideration given the health inequalities evident with COVID-19 (Bambra et al, 2020), which may predict adverse consequences of long COVID more so than acute illness severity (Bai et al., 2022).

Future research should also ensure steps are taken to validate cognitive test findings, either by utilising mixed methods to explore subjective experience and/ or comparing to

controls/ pre-COVID cognitive testing. Given the high prevalence of anxiety, depression and PTSD symptoms observed in this sample, and the relationship these can have with subjective and objective cognitive difficulties, future research should take care to account for these confounding variables in the data collection and analysis stages. An exploration of self-efficacy in mitigating some of the cognitive and emotional consequences of long COVID (Paredes et al., 2021) could also be meaningful.

Taken together, it may be difficult for future research to meet all of these recommendations due to limitations in resources within the NHS where a large amount of UK health research is conducted. Another consideration may be the use of case series methodology in which medical records are searched to identify neuropsychological assessment information. This information, perhaps also in combination with interviews of professionals that had conducted the assessments, could be examined to draw out the individual interpretations made on cognitive functioning. This negates the need to rely on complex statistical analysis and/ or retrospective reports of subjective experience as the professional involved, alongside the client, will have already justified these interpretations. This could perhaps be completed as part of regular audit processes within a service.

As a result of its pandemic status, COVID-19 and long COVID have a high prevalence in the general population with many people self-reporting persistent symptoms. Long COVID services across the country often utilise an MDT approach to support patients. A specific public health recommendation stemming from this research would be to emphasise the importance of detailed assessment for those suffering with long COVID. This can be supported by the role of a neuropsychologist both directly at the point of assessment with the client, for example by including comprehensive cognitive assessment, but also indirectly through provision of consultation to the wider MDT. This would be important as the participants in the present study have suggested that the process of cognitive assessment can

be helpful in validating their experience and reassuring them of the extent of cognitive difficulties and recovery. Like other neurological conditions, cognitive rehabilitation strategies can also be offered to support patients in managing symptoms (Goldstein & McNeil, 2013). It is especially important that these be individually tailored according to thorough neuropsychological assessment, as there was some variability in test findings. A neuropsychologist may also support service delivery with informing psychological support, such as individual or group therapy. Some of the participants commented in the questionnaire that the assessment process was reassuring as they had felt isolated and alone in experiencing their illness, without knowing of others going through similar difficulties. Again, this is perhaps similar to other neurological conditions where group therapy is often recommended and viable (Yeates & Ashworth, 2020). Although this research suggests that many may likely recover from long COVID with time, up to the assessed 2-year mark, some may still experience substantial difficulty and so regular follow up intervals for review may also be helpful.

The benefit to the above recommendations is potentially widespread, as, like other neurological conditions, supporting patients with strategies to manage fatigue, cognitive deficit and improve quality of life can support an increase in independence. There is hope that this could lead to increase of (or return to) work as well as other vocational activities. This may broadly reduce the future strain on NHS services and is supporting patients to return to work is a specific requirement outlined by NICE (2021) guidelines for COVID-19 support services. Additionally, it is worth considering the unfortunate reality that, given the increase in globalisation (Yacoub & El-Zomer, 2020), COVID-19 may not be the last pandemic. There may also be more aggressive variations of COVID-19. It is possible that findings from this research, in combination with the vast prior multidisciplinary research conducted, will be useful in understanding future cognitive consequences for viruses with similar pathology.

5.6 Conclusion

Long COVID has a substantial impact on quality of life for many, with international prevalence because of the worldwide pandemic (WHO, 2020). Like previous coronavirus diseases and respiratory conditions, severe acute symptoms may increase the likelihood of persistent symptoms (Marks et al, 2011). However, there is some anecdotal evidence that those with less severe symptoms could also be adversely affected, especially in cognition. This may be due to specific neurotropic mechanisms of the virus (Aghagoli et al., 2021).

In light of this, a systematic review of the current literature asking the question: ‘what is the objectively measured cognitive impairment profile of those affected by long-COVID?’ was conducted. This found mixed results based on research conducted between three-12 months post-infection using cognitive screening tools. Research appeared to heavily rely on cognitive testing alone to draw conclusions.

With this in mind, this research focused on two questions: ‘what are the objectively measured cognitive and emotional consequences of COVID-19/long COVID at 20-24 months?’ and ‘how does this relate to the subjective experience of illness from COVID-19 and illness severity?’. Using a two-part sequential explanatory mixed methods design, thematic analysis of questionnaire responses was used to enhance findings from comprehensive cognitive testing of 19 participants.

Exploratory findings highlighted possible deficits in visuospatial function, psychomotor speed/coordination, executive functions related to abstract reasoning, inhibition, switching and verbal executive functions involved in novel tasks. Thematic analysis found subjective experiences which related to these and provided insights into reasons for the emotional consequences experienced, including loss and restriction, fear and uncertainty and illness perception. Cognitive test findings, subjective experience and brain pathology triangulated relatively coherently, strengthening the validity of interpretations made.

Despite various limitations, the study nevertheless provides an original contribution to the current research and generates specific recommendations for further research and clinical practice.

These include:

- Acute illness severity may not predict long-term outcome
- Neuropsychologists may support MDT thinking in long COVID services
- Detailed cognitive assessment appears clinically important due to the variability in deficits seen between individuals (in this research and past research); persisting difficulties may be subtle and relative to individual baseline ability, and therefore 'bedside' screening tools are unlikely to be sensitive enough to detect effects
- Visuospatial function, psychomotor speed and certain executive functions may be especially vulnerable in those affected by COVID-19/ long COVID
- Distress experienced associated with long COVID may be understood in part as a discrepancy between ideal-self and post-COVID-19-self. Self-efficacy may mitigate this.
- Cognitive rehabilitation and therapy, as required and based on person-centered assessment, will be important for supporting those affected return to activities of daily living (e.g., returning to work).

Finally, mixed methods research appears to have been a worthwhile endeavor in this particular field of research within neuropsychology. A broader recommendation for researchers to utilise such methodology to explore subjective experience in relation to objective findings may be important. In this way, neuropsychological research might seek to take a critical realist and constructionist approach that may support decolonising of neuropsychological research practices.

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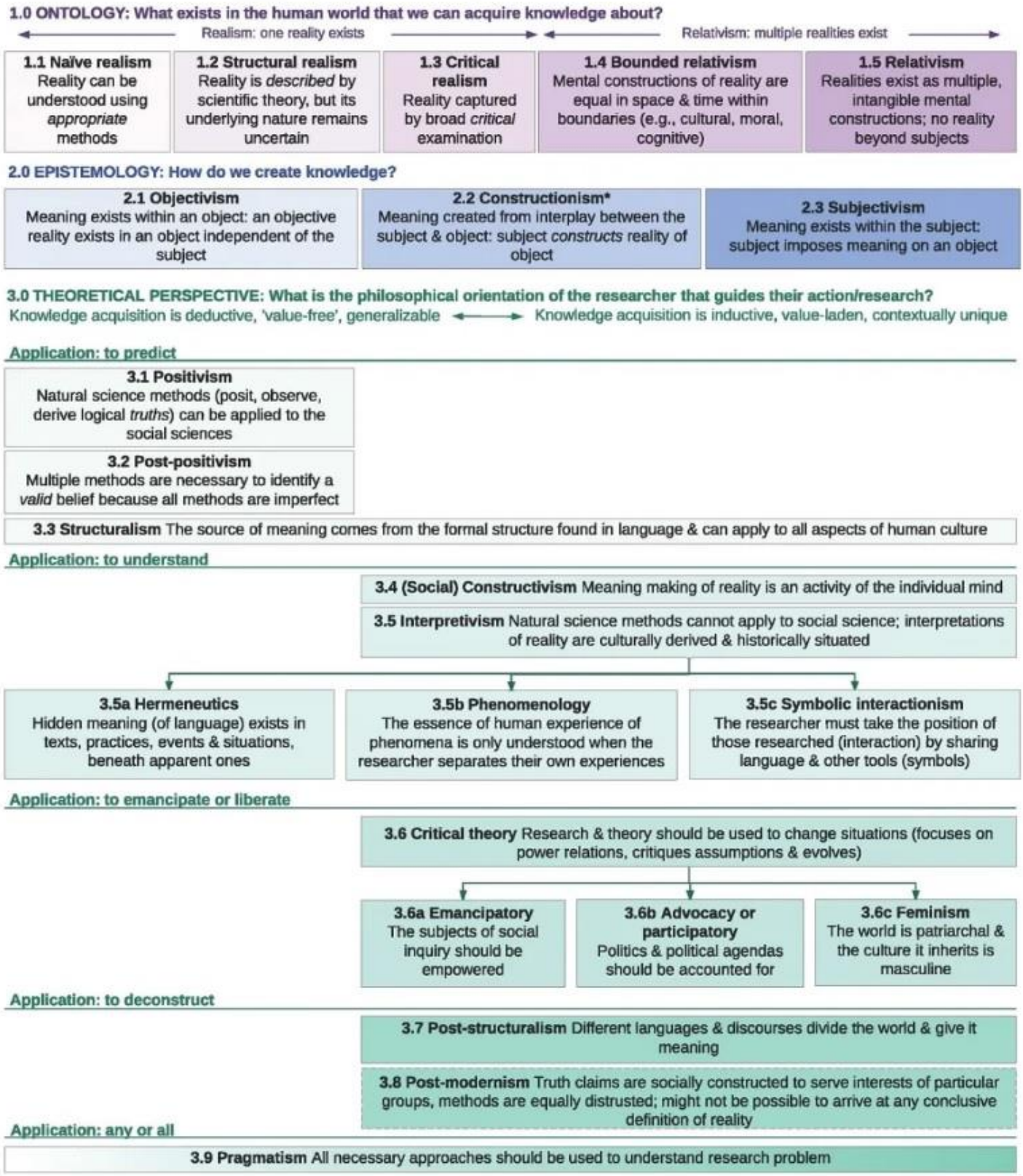
Appendix

Appendix A: Moon and Blackman (2014) framework for ontology, epistemology and philosophy



Appendix B: Systematic review electronical search strategy

Database	Search input	Search criteria
Scopus	Cognitive OR Cognitive impairment OR Neuropsychological AND Long-term OR Post-acute OR Chronic long-COVID AND COVID-19 OR SARS-CoV-2 OR Coronavirus	Abstracts, titles and keywords
PubMed		
WHO	Cognitive OR Cognitive impairment OR Neuropsychological AND Long-term OR Post-acute OR Chronic long-COVID	
PsychNet	Cognitive OR Cognitive impairment OR Neuropsychological	Titles

Appendix C: Adapted Newcastle-Ottawa Scale

Adapted Newcastle-Ottawa Scale for Cross-Sectional and Cohort Studies
(Adapted from Moskalewicz & Oremus (2020) and Wells, et al. (2022))

Selection: (Maximum of 4 stars)

1. Representativeness of the sample:
a) Truly representative of the average in the target population. (Random sampling) *
b) Somewhat representative of the average in the target population. (Non-random sampling) *
c) Selected group of users.
d) No description of the sampling strategy.

2. Sample size:
a) Justified and satisfactory.*
b) Not justified.

3. Ascertainment of exposure (COVID-19):
a) Validated measurement tool (Positive PCR test).*
b) Non-validated measurement tool, but the tool is available or described (clinical assessment method).*
c) No description of the measurement tool.

4. **(Cross-sectional studies)** Non-respondents:
a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory.*
b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
c) No description of the response rate or the characteristics of the responders and the non-responders.

4. **(Cohort studies)** Demonstration that the outcome of interest was not present at start of study
a) Yes.*
b) No.

Comparability: (Maximum of 2 stars)

1. Confounding factors are controlled:
a) The study controls for the most important factor (Estimated IQ).*
b) The study controls for at least one additional factor.*
c) No additional factors controlled for.

Outcome: (Maximum of 1 star)

1. Statistical test:
a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals or probability level (p-value).*
b) The statistical test is not appropriate, not described, or incomplete.

Appendix D: Recruitment email sent to potential participants

Subject: Invitation to participate in new ‘Long COVID’ research study

Dear potential participant

We are emailing you to invite you to take part in a new ‘Long COVID’ research study titled: “Neuropsychological Consequences of COVID-19: Long COVID and the role of ‘Virtual Hospitals’”.

You have been contacted as our records suggest that you have received support from the [redacted]. Please find attached to this email the participant information sheet provided by the lead researcher. If you would like to express interest in taking part in this study or would simply like to find out more information, please get in touch with Luke Phelps by emailing him at luke.phelps@nhs.net.

Kind regards

Appendix E: Participant Information Sheet

Participant Information Sheet: Neuropsychological Consequences of COVID-19: Long COVID and the role of "Virtual Hospitals"

We would like to invite you to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. If you express interest, one of the research team will be available to go through the information sheet with you and answer any questions you have on the phone. You will be given at least 24 hours and more time if you need it to consider whether or not you wish to take part

Why is this study being done?

'Long COVID' can be experienced by some as a complex consequence of COVID-19 and there is growing evidence to suggest a neurological component to this. This may impact on the how the brain functions day to day. We aim to assess the neuropsychological consequences for those affected by Long COVID and explore the utility of "virtual hospitals" in mediating the impact to the individual. We are hoping that this understanding will help services to provide better support for those affected.

How many people will participate in the study?

It is expected that between 30-60 participants will take part in this study.

Do I have to take part?

No. It is up to you to decide whether to take part and this choice will not affect your current or future care. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form of which you will be given a copy.

You can withdraw from the study at any time point, including during the assessment and up to 14 days after the interview. You can withdraw for any reason, and you do not have to tell Luke the reason you would like to withdraw. Withdrawal from the study would have no impact on the care you receive.

What does participation involve?

Participation consists of 2 parts. Part 1 would involve completing a series of psychometric tests during a 1- 1.5-hour assessment session, face to face in [redacted]. The appointment would be arranged at a time convenient for you. The tests would look to assess various areas of cognition and you will also be asked to complete several short questionnaires relating to current mood.

Part 2 would involve an interview or questionnaire regarding your experiences of COVID-19 illness, the support you received and how you felt you coped, as well as feedback on identified differences between groups on assessment during part 1. It is expected that this session should take between 15-30 minutes and can be completed either virtually via video call, over the phone or, again, face to face at [redacted] You may choose to decline to answer any questions that you do not feel like answering. At this appointment, you will also be provided with a brief individual psychometric report and offered the chance to ask questions regarding.

Additionally, patient data such as on COVID-19 symptomatology during the acute stages of infection as well as Long COVID symptom information may be collected from [redacted] to support data analysis.

Will I be paid any expenses incurred?

A £10 voucher contribution toward any and all travel expenses will be provided upon receiving evidence of petrol, train travel or other travel expenses accrued by participants.

Are there any potential benefits in taking part?

Upon completing of neuropsychological assessment, during part 2 of the study, we will share a brief assessment feedback report to you for review. We hope to provide a space where you can share your story and experiences of Long COVID. Also, you will be contributing to a growing area of research, which may have service delivery implications for those affected by Long COVID.

Are there any potential risks in taking part?

There are no risks associated with any of the pen and paper tests conducted during neuropsychological assessment. However, there is a chance that the questionnaire or interview may be emotionally distressing for some. Luke has experience in providing emotional support to people who are experiencing distress and will be sensitive to this. A distress protocol is in place for the study with specific guidance on how the research team can support individuals in distress as well as guidance for further support if required.

Will my GP be informed?

Yes, your GP will be sent a letter with a copy of this participant information sheet, informing them of the study.

Who is organising and funding the study?

The research team includes:

Name	Role
Luke Phelps	Lead researcher for the project and Trainee Clinical Psychologist University of Hertfordshire
Dr. Keith Sullivan	Senior Research Fellow University of Hertfordshire
Dr. Gaby Parker	Consultant Clinical Neuropsychologist [redacted]

The study is sponsored by the University of Hertfordshire and organised in collaboration with [redacted]

What will you do with the information I give you?

All information collected is strictly confidential. Psychometric test documents will be stored in a locked filing cabinet that is only accessible to the research team. Electronic documents such as consent forms and interview transcripts or questionnaire responses will be stored on an encrypted NHS laptop accessible only to Luke. Information that could identify you, such as your name and other details, will be removed or changed. We will ask you to choose your own pseudonym so that your real name will not be used.

If interviews take place and are completed face to face, it will need to be audio recorded. If it happens via video call, then the interview will need to be video recorded. This is because it is then transcribed for analysis later in the research. These recordings will be accessed by Luke.

How will you use this information?

The results of the research will be written up in a report for Luke's Doctorate in Clinical Psychology. This may contain anonymised quotes from the questionnaire or interview. The research will be written up for submission to peer-reviewed academic journals and conferences, so that other health professionals can learn from the research.

Are there any situations when information I tell you will be shared?

Disclosure of any personal information from the interview would only occur in exceptional circumstances, such as if you revealed information that may indicate a risk to yourselves or others.

How will you use information about me?

We will need to use information from you and your medical records for this research project.

This information will include your NHS number. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are my choices about how my information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can I find out more about how my information is used?

- at www.hra.nhs.uk/information-about-patients/
- or contacting the University of Hertfordshire's Data Protection Team on dataprotection@herts.ac.uk.
- by sending an email to the Luke on luke.phelps@nhs.net

Who has reviewed the study?

The North of Scotland Research Ethics Committee 2

Who to contact for further information and to express interest in taking part:

Luke Phelps
Trainee Clinical Psychologist
luke.phelps@nhs.net

Thank you for considering taking part in this study.

Appendix F: Consent form

IRAS ID: 300361

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Neuropsychological Consequences of COVID-19: Long COVID and the role of "Virtual Hospitals"

Name of Researcher: Luke Phelps

	Please initial box
1. I confirm that I have read the information sheet dated 9/8/21 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that quotes from questionnaires or transcribed interviews will be mentioned in any research publications of the study, including for the researchers Doctorate in Clinical Psychology thesis at the University of Hertfordshire.	☐
4. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.	☐
5. I understand that interviews, if conducted, will be audio recorded and my responses transcribed for data analysis.	☐
6. I agree to my General Practitioner being involved in the study, including any necessary exchange of information about me between my GP and the research team. This may include, for example, sharing of information regarding Neuropsychological assessment.	☐
7. I agree to take part in the above study.	☐

Name of Participant	Date	Signature

Name of Person seeking consent	Date	Signature

Appendix G: Information on cognitive test scoring, reliability, validity and normative sample

Test	Scoring and interpretation	Reliability and validity	Normative population
KBNA	The KBNA consists of 25 sub tests, 12 of which are used to generate the 7 index scores. These 12 were used within the study to provide the bulk of the battery. They subsequently generate 12 scores for which normative data is provided for comparison. The Clocks and Complex Figure 1 test scores combine into one score, as does Practical Problem Solving and Conceptual Shifting. Conversely, Verbal Fluency splits into two scores of Phonemic Fluency and Semantic Fluency. Raw scores are converted in to scaled scores based on age. These scaled scores can then be summed to provide an index score. This was not deemed appropriate for this research due to the variance in scores.	Manual references expected information on content validity and construct validity. It discusses the intercorrelations between tests as well as appropriate information on comparison with other tests such as WAIS-III, WMS-III and Dementia Rating Scale, among others. Reliability coefficient / Test-Retest stability Sequences 0.67 / 0.77 Word Lists 1 0.87 / 0.82 Complex Figure 1 0.81 / 0.52 Clocks and Complex Figure 1 0.71 / 0.33 Word Lists 2 0.90 / 0.79 Word Lists Recognition 0.80 / 0.54 Complex Figure 2 0.80 / 0.75 Complex Figure Recognition 0.78 / 0.32 Spatial Location 0.76 / 0.77 Verbal Fluency - Phonemic 0.64 / 0.64 Verbal Fluency - Semantic 0.66 / 0.81 Practical Problem Solving 0.77 / 0.34	700 divided into groups of 100 based on age (20-29, 30-39, 40-49, 50-59, 60-69, 70-79 and 80-89). Approximately census proportions for sex and race/ ethnicity, based on a US sample. Stratified sample of five educational levels dependent on years of education (<8, 9-11, 12, 13-15 and >16). Proportionate recruitment from US geographic regions NE, NC, S and W.

WAIS-IV	The WAIS-IV is another battery of tests which is largely considered the "gold standard" of cognitive testing. Three tests that make up three scores were taken from the WAIS-IV to add to the research battery. Raw scores are converted in to scaled scores based on age.	Manual references expected information on content validity and construct validity. It discusses the intercorrelations between tests as well as appropriate information on comparison with previous versions and specific diagnostic groups. Reliability coefficient / Test-Retest Stability Similarities 0.87 / 0.87 Digit Span 0.93 / 0.83 Matrix Reasoning 0.90 / 0.74	2200 divided into 13 groups based on age (16-17, 18-18, 20-24, 25-29, 30-34, 35-44, 45-54, 65-69, 70-74, 75-79, 80-84 and 85-90). Approximately census proportions for sex and race/ ethnicity, based on a US sample. Stratified sample of five educational groups (<8, 9-11, 12, 13-15 and >16). Proportionate recruitment from US geographic regions NE, NC, S and W.
D-KEFS	The D-KEFS is a battery of executive function tests. Two sub tests were taken from the D-KEFS which usually provide a range of scores from sub tests of various functions. For the purposes of this research only the three scores related to executive function were used. Raw scores are converted in to scaled scores based on age.	Manual references expected information on content validity and construct validity. It discusses the intercorrelations between tests, broken down for each age group, as well as appropriate information on comparison with other tests such as the California Verbal Learning Test. Test-Retest Stability Trail Making Test 4 0.38 Trail Making Test 5 0.77 Colour Word Interference 0.80	1750 divided into groups of 75-175 based on age (8, 9,10, 11, 12, 13, 14, 15, 16-19, 20-29, 30-39, 40-49, 40-59, 60-69, 70-79, 80-89). Approximately census proportions for sex and race/ ethnicity, based on a US sample. Stratified sample of five educational levels dependent on years of education (<8, 9-11, 12, 13-15 and >16). Proportionate recruitment from US geographic regions NE, NC, S and W.
RBANS-A	The RBANS-A is a shorter screening battery of tests. Two tests that make up two scores were taken from the RBANS-A to add to the research battery. Raw scores are converted in to scaled scores based on age.	Manual references expected information on content validity and construct validity. It discusses the intercorrelations between tests, broken down for each age group, as well as appropriate information on comparison with other tests such as the WAIS-III and WMS-III. Reliability statistics only provided for Index level scores. Reliability coefficient / Test-Retest Stability Line Orientation 0.78 / 0.69 Coding 0.85 / 0.75	540 divided into 6 groups based on age (20-39, 40-49, 50-59, 60-69, 70-79 and 80-89). Approximately census proportions for sex and race/ ethnicity, based on a US sample. Stratified sample of three educational levels dependent qualification level (less than high school, equal to high school and greater than high school). Proportionate recruitment from US geographic regions NE, NC, S and W.

BADS	The BADS is a battery of executive function tests. One test providing two scores was taken from the BADS. Raw scores were converted by age using supplementary material not supplied within the test manual, with permission from the author.	Some validity information on comparison with other tests, such as the WAIS-III and Wisconsin Card Sorting Test. No presented information on reliability statistics within manual.	216 divided into 4 groups based on age (16-31, 32-47, 48-63 and 64+). Describe an appropriate process of sampling in interpretative manual for this smaller sample. Stratified sample of three education groups based on National Adult Reading Test IQ equivalent scores (<89, 90-109 and >110).
TOPF	The TOPF is a test specifically designed to estimate preinjury ability that is co-normed with the WAIS-IV. Raw scores are converted in to scaled scores based on age.	Manual references expected information on content validity and construct validity. It discusses the intercorrelations between tests, broken down for each age group, as well as appropriate information on comparison with other tests such as the WAIS-IV VCI and WIAT-II Word Reading. Reliability coefficient Test-Retest Stability 0.98 0.89	2200 divided into 13 groups based on age (16-17, 18-18, 20-24, 25-29, 30-34, 35-44, 45-54, 65-69, 70-74, 75-79, 80-84 and 85-90). Approximately census proportions for sex and race/ ethnicity, based on a US sample. Stratified sample of five educational groups (<8, 9-11, 12, 13-15 and >16). Proportionate recruitment from US geographic regions NE, NC, S and W.
TOMM	The TOMM is a test specifically of malingering and provides a face valid test of memory where it is expected that performance will be above the 50% chance of getting each item correct. Only trial 1 was necessary for all participants as there were no identified issues.	Manual references expected information on content validity and construct validity as well as reliability. No presented information on reliability statistics within manual.	405 aged between 16-84. 54, 65-69, 70-74, 75-79, 80-84 and 85-90). Approximately census proportions for sex and race/ ethnicity, based on a US sample.

Appendix H: Example feedback summary

Brief Cognitive Assessment Report Summary for Research Project "Neuropsychological Consequences of COVID-19: Long COVID and the role of 'Virtual Hospitals'"

Not to be interpreted as neuropsychological assessment for professional use, for information only. Assumptions made on individual test scores alone without clinical interview.

Dear **

Thank you for supporting the research project by attending for cognitive assessment. For your information, here is a summary of the domains assessed as well as a brief outline of some of the areas you achieved a high or low score for. Scores were compared to people of a similar age to you and deemed high or low based on an estimate of your overall IQ.

Domains assessed:

Attention - is the ability to actively process specific information in the environment while tuning out other details.
Working memory - is the capacity to maintain and manipulate visual and verbal information in one's mind.
Processing speed – is the time required to respond to and/or process information in one's environment.
Language – is an individual's ability to understand, use and think with spoken language.
Visuospatial – is the ability to organize visual information into meaningful patterns, understanding how these patterns change, rotate, and move through space.
Memory – is an individual's ability to store and retrieve information immediately and after a delay.
Executive functioning – executive functions are broad and multi-process, they are involved in in planning, organising, problem solving, abstract reasoning, multi-tasking, inhibition, initiation and mental flexibility

Group Feedback

On average, the participants within this study were estimated to have a general ability in the "High Average" range and this ability was mostly observed across testing. However, there was a similar pattern of weaker than expected test scores for some participants, which was often consistent with previous research exploring cognitive ability at 4-12 months post COVID-19. Assessments in the current study took place mostly between 20-24 months post COVID-19 and, promisingly, the frequency at which a weaker score was observed appeared to be less than prior research. Participants that had less severe acute symptoms of COVID-19, but that had been referred to specific long COVID services, reported a slightly higher frequency of poorer test scores than participants who had more severe acute symptoms. This suggests that acute illness severity may not predict the cognitive impact of long COVID.

One area of the specific pattern of poorer scores observed was with visuospatial tasks that drew on participants abilities to perceive object locations in space and/ or manually manipulate spatial information to make a design. Another area was with language tasks that drew on participants abilities to retrieve words or phrases. This was harder for participants on a task that required them to find a word or phrase that linked two other similar words. On another task, participants found it harder to spontaneously mention words beginning with a certain letter as opposed to first names or animals. This is likely because there is no organising principle or conceptual link between words of the same letter, making it more difficult to retrieve and articulate novel words/ phrases. For many participants, a test that assessed psychomotor speed was also weaker. For some participants, task that assessed switching/ multi-tasking were weaker. In particular, a task that required participants to switch between reading a word and reading the colour of the ink the word was printed in. Lastly, processing speed was weaker for some participants.

Scores for other areas assessed were generally observed to be in the "High Average" range, as expected. This included tests of verbal memory, which suggests that immediate and delayed memory might be better now as opposed to what has been reported previously at the 4–12-month post COVID-19 mark. On tests of visual memory, poorer performance is likely influenced by the suggested specific visuospatial difficulty. Across the tasks used within this research, executive functions, other than switching, appear to be mostly intact. When there were poorer performances observed, this could be in part due to tests appearing toward the end of the testing session and being influenced by fatigue levels.

Individual Feedback

Overall performed very well and your scores were in the range we would expect for the vast majority of tests. Your scores were a little lower than we might have expected on an immediate memory task, and a verbal reasoning task. It is normal for people to show some scatter in their scores and therefore it is possible that these were tasks you might have been relatively weaker at anyway regardless of Covid. It is also usually the case that people may notice more difficulties in daily life than are apparent on testing, because in daily life demands are higher and we cannot usually give as much conscious attention to everything we do, as we can for a few hours of testing. Your mood screening scores were moderately elevated, with your responses suggesting you might be experiencing moderately low mood and moderate anxiety. Mood symptoms like this can also cause blips in cognitive functioning, so this might be something to target if you are noticing cognitive symptoms in daily life.

Thank you again for taking part in the cognitive assessment for this study, I hope it has been a useful process and that this feedback, in conjunction with the discussion of feedback over telephone, is helpful.

Yours sincerely

Luke Phelps
Project Lead
Neuropsychological Consequences of COVID-19: Long COVID and the role of 'Virtual Hospitals'

Appendix I: Questionnaire

Questionnaire for part two of the study "Neuropsychological Consequences of COVID-19: Long COVID and the role of "Virtual Hospitals""

Experience of COVID-19

1. What was your experience of illness from COVID-19 during the acute (immediate) stages?
    a. It may be helpful to describe the main symptoms that were present and what support you accessed at this time (from friends, professionals or other services).

2. How would you describe the impact COVID-19 had on your mental health and wellbeing at this time?

3. How would you describe the impact COVID-19 had on your cognitive ability at this time?

4. How did your experience of illness develop from then, to now?
    a. It may be helpful to describe any changes in symptoms or of different support (from friends, professionals or other services).

5. How would you describe the impact long COVID has on your mental health and wellbeing currently?

6. How would you describe the impact long COVID has on your cognitive ability currently?

7. What have the consequences of COVID-19 and long COVID been for you?

8. If you found/ find that fatigue was/ is a concern for you, how did this impact you?
    a. It may be helpful to describe how fatigue impacts on mental health, wellbeing, cognitive ability and/ or quality of life.

Appreciation for cognitive testing feedback

1. Based on the individual and group feedback summary provided, in your own words please describe how you appreciate these findings.

2. How does the individual and group feedback fit with how you experience your cognitive ability day-to-day?

3. What do you do to manage or cope with any difficulties you experience as a result of changes in cognitive abilities?

4. What was your experience of the testing session?

Appendix J: Excerpts from Integrated Research Application System application

A6-1. Summary of the study.

This study intends to report on the cognitive and emotional impact of long COVID across two groups that contracted COVID-19 during the first wave of the pandemic:
1. Group 1 includes participants that received support [redacted] "virtual hospital" that subsequently did not require support [redacted] new long COVID pathway.
2. Group 2 will include participants that did not seek or receive support during the acute stages of infection but that went on to present to the long COVID pathway.
This is to explore the hypothesis that:
• Support from the virtual hospital during the acute stages of infection from COVID-19 mediates potential for long COVID cognitive and emotional consequences. This study will aim to recruit 15-30 participants from each group and is a mixed methods study with quantitative and qualitative elements:
1. Firstly, both groups will be asked to complete neuropsychological assessment utilising a standardised battery of cognitive tests. Descriptive statistics and generalised linear modelling will be used to illustrate differences between groups.
2. Results from the first part of the study will be used to inform semi-structured interviews or questionnaires with participants during the second part of the study. This will include questions about experience of COVID-19 illness. Thematic analysis will be used to identify themes that support description of differences between groups. Content analysis may also be used to identify additional commonly reported symptoms of COVID-19 and long COVID. Existing hospital data from the previous study may also be used for this.
Provisional approval has been granted from R&D teams at [redacted]. This study is part of a doctoral qualification at University of Hertfordshire and is therefore anticipated to be completed by June 2022 with submission for publication to peer-reviewed journals soon after

A6-2. Summary of main issues.

Participants along with their contact details will be identified through existing patient databases at both [redacted] and sent a participant information sheet describing the study.
Those who wish to express an interest in taking part will be asked on the participant information sheet to contact Luke via email. The research team will have access to the names of participants who express an interest. It will be assumed that the email address potential participants email Luke to is the email address they wish to be contacted on. Consent will be sought by the research team, who have experience of assessing capacity in clinical practice. It is expected that all participants will have capacity to consent. Within the assessment, that will take place [redacted], each item of the consent form will be discussed with the participant. This will include stating that consent for the study includes an assessment of cognitive function that might highlight impairment, that the findings from each group will be shared within the second part of the study and published after the study has been completed. It will also mention that any interviews will be audio-recorded and that anonymised extracts from the interviews and/ or questionnaires may be published in the final project paper and papers for any academic journal(s). It will mention that information from existing hospital databases may be used in the study. The consent form will be signed and completed electronically. When completing the questionnaires or interviews, if a member of the research team feels concerned about participant risk to themselves or others (these issues may be physical, sexual, verbal, or emotional abuse), they have a duty of care to raise these concerns. The research team will always aim to discuss this breach of confidentiality with participants before sharing the information.
It is important to acknowledge that informed consent is not a one-off event but rather an ongoing process; therefore, participants will be reminded that they can withdraw participation during or up to 14 days after the assessment. If a participant becomes emotionally distressed during the assessment,

they will be reminded of this. It may be that more than the required number of participants express an interest in the study. It will be made clear on the Participant Information Sheet that the research team cannot guarantee that all participants who register their interest will be assessed. Participants will be asked if they would like to consent to both parts of the study. If more than the required number apply, it may be that a stratified sampling strategy will be used to match participants in the two groups by selecting participants that are diverse in terms of the clinically confirmed risk factors for long COVID: age and presence of two Long Term Conditions (LTCs). Race and gender may also be used depending interest in the study. Participant wellbeing: It is not anticipated that this research will cause significant distress. However, the research team is aware that participants may have been distressed by their experiences of COVID-19, and that talking about this may be difficult. The research team all have experience of managing distress through their training as clinical psychologists. Participants will be reminded that they only need to talk about what they feel able and willing to talk about, at a level of detail and a way that they feel comfortable with. Participants will also be reminded that they can take breaks if they need, or they can withdraw their participation at any point, without having to provide a reason. The research team will use their clinical experience and judgment to monitor participant distress during the interview and to manage this. If they have concerns at the end of the interview regarding the participants' emotional wellbeing, they will be reminded that they can speak to Dr. Parker, in addition to a list of contact details for further support. A distress protocol has been developed with clear guidance on how the researchers will respond to distress with participants and themselves as researchers.
Confidentiality: All data collected will be anonymized and kept confidential in compliance with the Data Protection Act 1998 and GDPR. Personal identifiable information about the participant and all third parties will be removed from the cognitive testing profiles and transcribed interviews. Any physical copies of personal identifiable information will be scanned and shredded. These files along with other electronical records such as recordings and interview transcripts will then be password protected, anonymised, and stored on an NHS encrypted laptop kept by Luke. Luke has a planned third year specialist placement at [redacted] and will acquire [redacted] via this placement. Records will be kept for five years after the study finishes, in line with University of Hertfordshire guidelines. After this time, they will be destroyed securely.
Face-to-face contact in light of COVID-19 restrictions: In the context of COVID-19, any face-to-face contact would be subject to and in line with restrictions set out by the Government, by the NHS Trust, and by the University at that point in time. This would include whether face to face contact was permitted at all (there are currently University restrictions on this for University members undertaking research, although this may change shortly). Covid-19 risk assessment has been completed.

A24. What is the potential for benefit to research participants?

All participants will be offered a brief neuropsychological feedback report and virtual session to discuss interpretation. There may be some indirect benefits as a result of participants feeling heard and valued when informing on their experience of Covid-19. The research will be contributing to a growing area of research which aims to improve provision of health care services and support available for patients with long covid.

A26. What are the potential risks for the researchers themselves? (if any)

In the context of the COVID-19, any face-to-face contact would be subject to and in line with restrictions set out by the Government, by the NHS Trust, and by the University at that point in time. This would include whether face to face contact was permitted at all (there are currently University restrictions on this for University members undertaking research, although this may change shortly), physical distancing guidelines, and advice on the use of PPE. Furthermore, Luke and Gaby both do not have any underlying health conditions that would put them at risk of more severe illness if they were to contract the virus. They have also received both doses of the vaccination. [redacted] clinical

spaces are continuously cleaned in line with infection control procedures and all staff take regular lateral flow tests. It is not expected that the researchers will be exposed to many risks. It is anticipated that it is unlikely that the study will lead to emotional distress in the research team, however, if this were to occur, there is support available from other members of the research team, as well as support from the University of Hertfordshire. The researchers will use selfcare strategies for the duration of the project. Luke will also make use of a reflective journal throughout.

A38. How will you ensure the confidentiality of personal data?

Every effort will be made to protect the identity of participants with personal details changed or removed where necessary to preserve their identity. As stated, Luke will not have access to personal data of potential participants until he receives expression of interest by the potential participant themselves via email. Personal identifiable information, including the consent form will only be accessed by Luke. All data collected will be anonymised and kept confidential in compliance with the Data Protection Act 1998 and GDPR. Personal identifiable information will be removed or changed from the transcribed interview. Participants will be invited to choose a pseudonym. Transcripts will be given participant codes by Luke.

Appendix K: Email from Health Research Authority regarding amendments

23/08/21
Thank you for submitting the above application for review.
This review is comprised of an Assessment to check compliance with the UK Study-wide governance criteria, as well as relevant additional nation specific areas of review, details of which can be found here. I have now undertaken an assessment of your application. Please would you provide me with the following information

- Please clarify if both NHS sites will undertake the same activities as the IRAS form states that CLCH will only do the neurological assessments. If this is correct please change your Organisation Documents to reflect this and return to me by email. Please note that if both sites are undertaking the same activities a PI will be required at sites (please change Q8 OID). If only CLCH will be undertaking the neurological assessments a PI would be required at CLCH and local collaborator at WHHT.
- As above if sites are undertaking different activities please udate your schedule of events and return to me by email.
- The IRAS form states that audio recordings will be deleted at the end of the study, if being transcribed please clarify why these cannot be deleted once transcribed?
- The data collected in the previous study (IRAS 283888) looks to be done under the COPI notice which expires at the end of Sept 2021. Please confirm that this data is now anonymised, and you will only receive anonymised data

Please provide a response by 28 August 2021. Please contact me if you think you will not be able to submit any information by this date.
As you have submitted to a REC in Scotland, the below updates should be submitted to the REC as part of your response the REC opinion, if the REC issue a Favourable opinion at first review, please email these back to me instead.

- Please supply a copy of the template email that will be sent to potential participants
- The Final paragraph of the PIS states ‘Withdrawal from the study would have no impact on your job role.’ This should be documented as 'on the care you receive’ rather than ‘on your job role’
- The Consent form indicates that GPs will be informed of participation in the study, however no GP letter has been received. Please submit.
- Please update the PIS to include further information on the activities involved for the participant, i.e how long they will take, where they be undertaken etc.
- Please submit an updated copy of the sponsor insurance certificate.
- Please change any reference to the Data Protection Act 1998 to the Data Protection Act 2018 in your Protocol and any patient facing documentation.
- Please update your ICF to include specific consent for audio/video recording of interviews.
- in order for your PIS to be GDPR compliant, please update with the HRA GDPR Transparency wording available at:Transparency wording for all sponsors - Health Research Authority (hra.nhs.uk)

Health Research Authority
E. approvals@hra.nhs.uk
W. www.hra.nhs.uk

Appendix L: Email responding to Research Ethics Committee regarding further information

16/08/21

As requested, I've made the following changes and uploaded the required documents:

Findings	Applicant Response
Date completed: 10 August 2021	Date completed: 13 August 2021
IRAS A6-2 *It is expected that all participants will have capacity to consent, however, the British Psychological Society have provided guidance on completing research with those that cannot consent to their own participation and this guidance will be followed as and when needed.* **Please note as a REC we are unable to review any application that may have participants to lose capacity at any point of the study. Please confirm whether your study will include adults with incapacity.**	I can confirm that this study will not require recruitment of adults that do not have the capacity to consent to take part.
IRAS A13 – Please provide the following supporting documents as mentioned in the IRAS form. Test Of Memory Malingering (TOMM), Test Of Premorbid Function (TOPF), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Line orientation, Wechsler Adult Intelligence Scale (WAIS-IV): - Similarities, Matrix Reasoning Digit Span Coding Behavioural Assessment of the Dysexecutive Syndrome (BADS): Zoo map, Delis[1]Kaplan Executive Function System (D-KEFS): Trail Making Task, Stroop, Kaplan Baycrest Neurocognitive Assessment (KBNA): Sequences, Spatial Location, Word lists, Complex Figure, Clock Drawing, Verbal Fluency Picture Naming and Recognition, Practical Problem Solving, Conceptual Shifting the Graded Naming Test (GNT). The Patient Health Questionnaire 9 (PHQ-9), Generalised Anxiety Disorder 7 (GAD-7) Post-Traumatic Stress Disorder Checklist for DSM[1]5 (PCL-5) The European Brain Injury Questionnaire (EBIQ)	I've attached screenshots and links from the psychometric tests in one word file and have attached PDF copies of the four questionnaires that will be used. Will this be ok or will you need me to upload any of these to IRAS/ require further information?
IRAS A36 – please confirm in the applicant response column of this form that you are aware of the following IRAS guidance on the storage of personal data on laptops: *Use of laptops and other portable devices is to be avoided. Where it is necessary for them to be used, data must be encrypted and the data uploaded onto a secure server or desktop as soon as possible and the data removed from the portable device as soon*	I can confirm that I am aware of the IRAS guidance on the storage of data on laptops. I have been accepted on to a placement at the trust and will be issued with a trust encrypted laptop.

as possible and using appropriate data destruction software.	
IRAS A54 Scientific Review –Please provide any written comments from the reviewers (eg completed Peer Review Form or correspondence) if available.	I've attached the initial University of Hertfordshire proposal feedback form to the checklist section on IRAS. I've also attached to this email.

Findings related to supporting documentation	Applicant Response:
Date completed: 10 August 2021	Date completed:
1. Please confirm the version number/dates for the following documents: Invitation letter – Document has Version 0.2, Checklist has version Provisional Interview/ Questionnaire Questions – Document has V0.1 14 July 2021 Checklist has – V1 03 August 2021 Distress Protocol – Document – 03 August 2021 V0.1. Checklist – 03 August 2021 V1 Consent Form – Document – 09 August 2021 V0.2 Checklist 09 August 2021 V2 Participant Information Sheet – Document – 09 August 2021 V0.2 Checklist – 09 August 2021 V2 Protocol – Document – 14 July 2021 V0.1 Checklist – 14 July 2021 V1 Luke Phelps CV – Document – 06 August 2021 Checklist -08 August 2021	I can confirm that the: Invite letter is version 2 - 9/8/21 Provisional interview/ questionnaire is version 1 - 3/8/21 Distress protocol is version 1 3/8/21 Consent form was version 2 9/8/21 (VERSION 3 uploaded 13/8/21 with requested amendments made) Participant Information Sheet is version 2 9/8/21 (VERSION 3 uploaded 13/8/21 with requested amendments made) Protocol is version 1 14/7/21 Luke Phelps CV is version 1 6/8/21 Apologies for this. Would you require me to reupload the documents to IRAS with this information corrected or does this suffice?
Consent Form – Please insert a point for the consent to Audio or video recording the interviews.	Amendment made and uploaded to IRAS. Attached to this email also.
Participant Information Sheet – Please insert the heading ‘Who has reviewed the study’ under the heading please insert The North of Scotland Research Ethics Committee 2.	Amendment made and uploaded to IRAS. Attached to this email also.

Please do let me know if these are ok or if you might require any further information.

Best wishes,
Luke

Appendix M: Health Research Authority Approvals Letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Keith Sullivan
Doctorate in Clinical Psychology
Health Research Building, College Lane Campus
University of Hertfordshire
AL10 9AB

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

21 September 2021

Dear Dr Sullivan

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Neuropsychological Consequences of COVID-19: Long COVID and the role of "Virtual Hospitals"**
IRAS project ID:	**300361**
Protocol number:	**To be confirmed**
REC reference:	**21/NS/0114**
Sponsor	**University of Hertfordshire**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Appendix N: Email confirmation of Capacity and Capability

10/11/2021
Please find attached the Confirmation of Capacity & Capability (CCC), as well as the updated Organisational Information Document as confirmation of site participation.

Please ensure you read the investigator's and sponsors' responsibilities outlined in Appendix 1 in attached (CCC Letter). A breakdown of the monthly recruitment should be provided to ** within the 1st week of each month for the preceding months recruitment.

Please inform the R&D Office of the actual the Green light date to commence study activities.

If you wish to discuss further, please do not hesitate to contact me.

Many thanks,

8 www.clch.nhs.uk/about-us/research

Appendix O: University of Hertfordshire Ethical Approval and Sponsorship

University of Hertfordshire UH

University of Hertfordshire
Higher Education Corporation
Hatfield, Hertfordshire
AL10 9AB

Telephone +44 (0) 1707 284000
Fax +44 (0) 1707 284115
Website www.herts.ac.uk

John M Senior
BSc MSc DSc PGCE CEng FIET FRSA FHEA
Professor of Communication Networks
Pro Vice-Chancellor (Research and Enterprise)

Dr Keith Sullivan
Senior Research Fellow
School of Life and Medical Sciences
University of Hertfordshire
Health Research Building, College Lane Campus
Hatfield Herts AL10 9AB

10 December 2021

Dear Keith

Re: **UNIVERSITY OF HERTFORDSHIRE SPONSORSHIP IN FULL for the following:**
RESEARCH STUDY TITLE: "Neuropsychological Consequences of COVID-19: Long COVID and the role of "Virtual Hospitals""
NAME OF CHIEF INVESTIGATOR (Supervisor): Dr Keith Sullivan
NAME OF INVESTIGATOR (Student): Luke Phelps
UNIVERSITY OF HERTFORDSHIRE ETHICS PROTOCOL NUMBER: LMS/PGT/NHS/02967
IRAS REFERENCE: 300361

This letter is to confirm your research study detailed above has been reviewed and accepted and I agree to give full University of Hertfordshire sponsorship, so you may now commence your research.

As a condition of receiving full sponsorship, please note that it is the responsibility of the Chief Investigator to inform the Sponsor at any time of any changes to the duration or funding of the project, changes of investigators, changes to the protocol and any future amendments, or deviations from the protocol, which may require re-evaluation of the sponsorship arrangements.

Permission to seek changes as outlined above should be requested from myself before submission to the Health Research Authority (HRA) Research Ethics Committee (REC) and I must also be notified of the outcome. It is also essential that evidence of any further NHS Trust or other site permissions is sent as soon as they are received. Copies of annual reports and the end of study report as submitted to the HRA also need to be provided. Please do this via email to research-sponsorship@herts.ac.uk

Please note that University Sponsorship of your study is invalidated if this process is not followed.

In the meantime, I wish you well in pursuing this interesting research study.

Yours sincerely

Professor J M Senior
Pro Vice-Chancellor (Research and Enterprise)

Appendix P: Letter to GP

Luke Phelps
Trainee Clinical Psychologist
Mob: **
Email: **
Health Research Building
University of Hertfordshire
Hatfield
AL10 9PN

Dear **

Re: **

Subject: Patient taking part in study - Neuropsychological Consequences of COVID-19: Long COVID and the role of "Virtual Hospitals"

I am contacting you to inform you that ** is taking part in a research study sponsored by the University of Hertfordshire. This study involves Neuropsychological assessment to explore differences between groups of patients that attended [redacted] "virtual hospital" and [redacted]. After assessment, participants will be provided with a brief assessment summary and will be asked to complete a short questionnaire regarding their experience in relation to the assessment findings.

We also provide a debrief containing information about who to contact if they feel distressed (including you as their GP) once they have participated in the study activity.

Please find enclosed a copy of the Participant Information Sheet your patient has received.

If you have any questions about the study, please contact me at the address given above.

Best wishes,

Luke Phelps
Trainee Clinical Psychologist
Principal Investigator

Appendix Q: Distress Protocol

Distress Protocol fordata collection

This document sets out the protocols for managing distress arising in the contextof this research project, including distress to participants and the research team.

The research team includes:

The project lead and primary researcher from the University of Hertfordshire DClinPsy course
(Luke Phelps, Trainee Clinical Psychologist)

The project internal supervisor from the University of Hertfordshire DClinPsy course
(Dr Keith Sullivan, Senior Research Fellow)

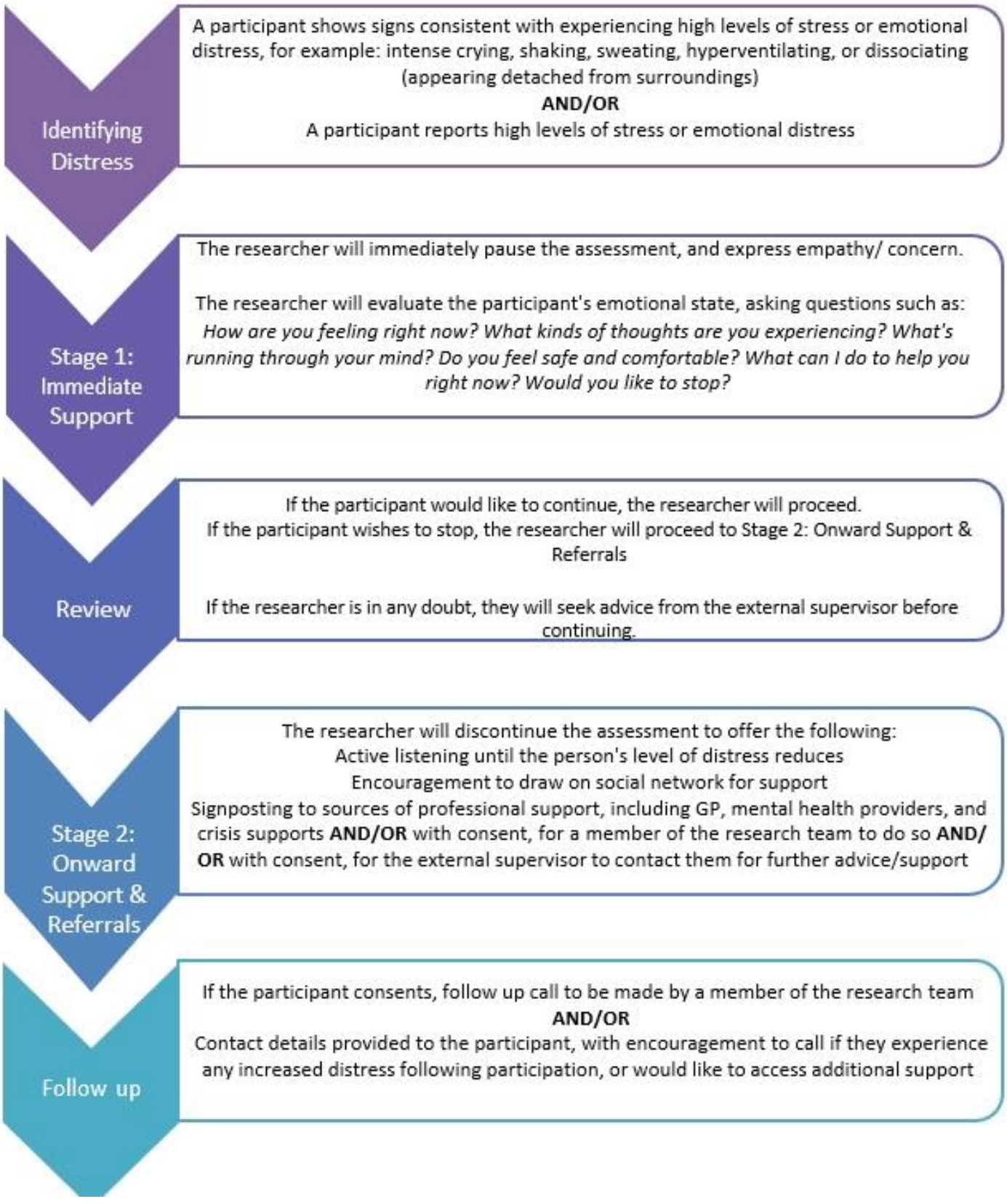
The project external supervisor from Central London [redacted]
(Dr Gaby Parker, Consultant Clinical Neuropsychologist)

The project consultant from the University of Exeter
(Dr Huw Williams, Professor in Clinical Neuropsychology)

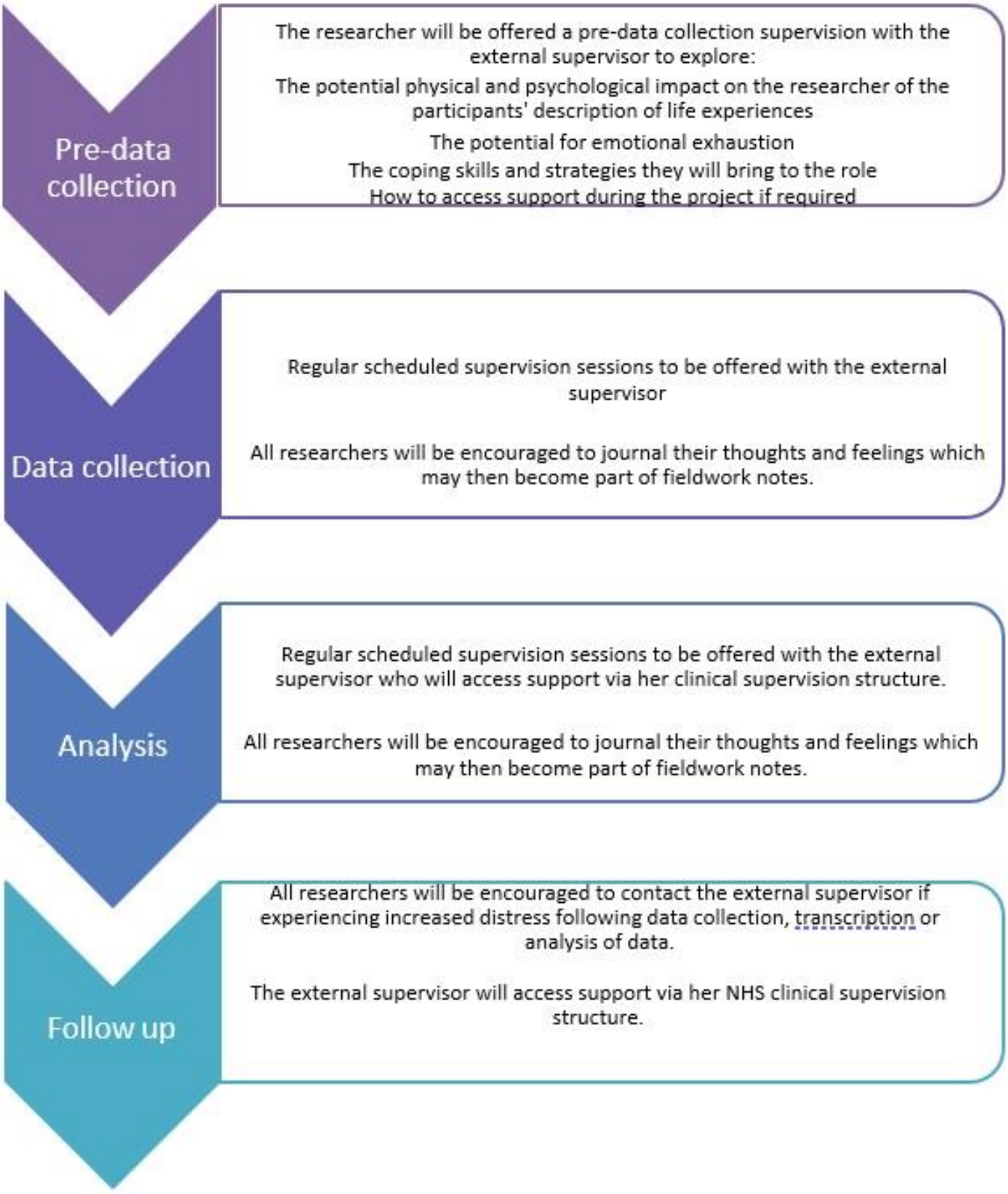
For the purposes of this document, 'Research Team' or

'Researcher'encompasses all colleagues listed above.

Distress Protocol 1: Managing distress arising during research (Participants) Modified from: Draucker CB, Martsolf DS and Poole C (2009). Developing Distress Protocols for Research on Sensitive Topics. *Archives of Psychiatric Nursing* 23 (5) pp 343-350)



Distress Protocol 2: Managing distress arising during research (Researchers) Drawing on: Taylor, J, Bradbury-Jones C, Breckenridge, JP, Jones, C & Herber, OR (2016). Risk of vicarious trauma in nursingresearch: a focused mapping review and synthesis. Journal of Clinical Nursing, 25(19-20), 2768-2777.



Appendix R: EbE suggestions and changes to study

Suggestion	Change
To send feedback questionnaire via email as it was created in word and could be edited in the same file and sent back, rather than printed and posted.	Decided to build on this suggestion to send all communications, including study information, consent forms, voucher codes, feedback letters and feedback questionnaires by one method, email.
During various team meetings, suggestions for clarity on jargon used to aid his own understanding if the study findings and feedback being provided.	This aided the research teams thinking on what information was being presented to participants of the research, during the feedback session, letter and questionnaire. Various terms changed and specific descriptions provided for key terms.
Whilst reviewing feedback questionnaire and letter, various suggestions to format, layout and language used.	Main change was made to the order in which questions were presented, asking in order of what initial illness experience was, current illness experience and finally appreciation for cognitive test findings. Other changes to format and language also.
Advised on how presenting feedback that COVID-19 had perhaps caused identifiable cognitive deficit would feel.	No specific changes, but confirmation that the approach used to provide feedback felt appropriate and emphasised that the research had individual value to participants in the form of validation of symptoms.
During member checking of themes, main suggestion was confirmation that each of the themes made sense based on the questions asked and felt familiar to his experience. Individual quotes appeared to be captured by broader sub-themes and themes.	No changes made. However, at this point in the research there was option to attempt thematic analysis again to see if themes could be generated that felt less deductive. The feedback instead supported decision to stick with the identified themes, as these seemed to capture appropriately the experiences of participants.
Supported research team formulation of cognitive test findings. Advice provided on whether the broad findings felt related to participants subjective reports found in questionnaire feedback, as well as commenting on own experience.	No changes.

Appendix S: Example of thematic analysis spreadsheet transcripts

ID	Group	Participa	Partcipant	Questi	Quote	Initial 1	Initial 2	Coding 1	Coding 2	Coding 3	Coding 4	Symptom	Emotional	Recovery	Assessme
1	VH	VH4	1	1	headache (first 24 hours only)	Symptom		Naming the health impact				1			
2	VH	VH4	1	1	breathlessness that limited exercise tolerance	Symptom		Exertion				1			
3	VH	VH4	1	1	severe fatigue	Symptom		Fatigue symptom				1			
4	VH	VH4	1	1	Effectively bed bound for two weeks	Impact		Naming the health impact	Fatigue symptom	Loss and restriction		1	1		
5	VH	VH4	1	1	Also cardiac arrythmia (multiple ectopic beats)	Symptom		Naming the health impact				1			
6	VH	VH4	1	1	impaired concentration	Symptom		Cognitive symptom				1			
7	VH	VH4	1	1	Accessed nhs website for advice	Navigating		Recovery						1	
8	VH	VH4	1	1	Called a friend (a GP) who phoned me twice a day to check I wasn't getting worse	Navigating		Recovery						1	
9	VH	VH4	1	1	Two visits to WGH ED once because breathlessness was worsening and later in illness because of chest pain	Navigating		Recovery						1	
10	VH	VH4	1	1	NHS 111 advices excluding pulmonary embolus.	Navigating		Recovery						1	
11	VH	VH4	1	2	I was too unwell to function normally	Impact		Loss and restriction	Naming the health impact			1	1		
12	VH	VH4	1	2	finding it very hard to concentrate so did nothing other than be ill or about three weeks	Impact		Cognitive symptom				1			
13	VH	VH4	1	2	I was quite scared a few times but didn't have the energy to worry too much!	Impact	Experience	Fear and uncertainty	Fatigue symptom			1	1		
14	VH	VH4	1	3	It was hopeless – couldn't concentrate on anything.	Experience		Cognitive symptom	Affect			1	1		
15	VH	VH4	1	3	Got through the days by dozing in bed and listening to the radio.	Experience		Affect	Adapting				1	1	
16	VH	VH4	1	3	Soon lost track of time	Experience		Affect					1		
17	VH	VH4	1	4	After about three weeks I started to get up a bit more but energy reserves were seriously limited.	Experience	Symptom	Exertion				1			
18	VH	VH4	1	4	I spent a lot of the next few months lying in the garden	Impact		Loss and restriction					1		
19	VH	VH4	1	4	Gradually started to walk a bit more, but very limited exercise tolerance due to fatigue rather than breathlessness.	Impact	Symptom	Exertion	Loss and restriction			1	1		
20	VH	VH4	1	4	Noticed that concentration and memory had been affected.	Symptom		Cognitive symptom				1			
21	VH	VH4	1	4	Had a few tests (echocardiogram, 24 hours tape) as a result of attending WGH ED and being referred to hospital at home.	Navigating		Recovery						1	
22	VH	VH4	1	4	GP prescribed inhalers at one stage for ongoing breathlessness (didn't help)	Navigating	Symptom	Naming the health impact	Recovery			1		1	
23	VH	VH4	1	5	It took a very long time to get physically fit again (at least 18 months) and recover stamina.	Impact	Symptom	Exertion	Recovery	Loss and restriction		1	1	1	
24	VH	VH4	1	5	I'm not sure if the latter is still completely normal, which makes me a little concerned and cautious.	Symptom	Experience	Fear and uncertainty	Recovery				1	1	
25	VH	VH4	1	5	Mental health is ok, though I have developed much worse insomnia than I've ever had before and have wondered several times if this is a result of Covid.	Experience	Symptom	Fatigue symptom	Fear and uncertainty			1	1		
26	VH	VH4	1	6	I have gradually recovered from the poor concentration and that seems to be normal now.	Symptom		Cognitive symptom				1			
27	VH	VH4	1	6	I'm not sure that the memory impairment has completely resolved.	Symptom		Cognitive symptom				1			
28	VH	VH4	1	6	I have to try a lot harder to remember things and deploy lots of strategies that I didn't used to have to use.	Coping		Adapting						1	
29	VH	VH4	1	7	I feel I lost a year of 'ordinary' life.	Impact		Loss and restriction					1		
30	VH	VH4	1	7	Covid affected virtually all normal activities somehow, even though I got better at adapting and getting through normal life.	Impact	Experience	Recovery	Adapting					1	

Appendix T: Number of quotes per participant per question on the feedback questionnaire

	Question												
Participant	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total**
VH3	7	1	1	1	1	1	1	1			1	1	**16**
VH4	10	3	3	6	3	3	4	2	1		1	3	**39**
VH5	1	3	2	2	3	2	2	2	2	2	3	1	**25**
VH6	6	3	3	4	2	1	1	3	2	3	2	1	**31**
VH7	9	1	1	2	2	1	1	3	2	1	2	1	**26**
VH9	4	4	1	1	3	3	3	2	3	2	4	3	**33**
LC3	12	12	8	15	12	9	7	10	7	2	8	7	**109**
LC4	2	1	1	8	1	1	2	1	1	1	2	1	**22**
LC5	5	5	6	50	6	6	5	8	2	6	3	8	**110**
LC6	7	3	2	6	2	5	5	3	3	3	4	2	**45**
LC8	4	2	2	2	2	2	1	2	2	1	2	3	**25**
LC9	11	2	1	7	3	5	7	9	2	3	6	4	**60**
LC10	3	1	1	2	5	1	1	4	2	1	1	1	**23**
Total	**81**	**41**	**32**	**106**	**45**	**40**	**40**	**50**	**29**	**25**	**39**	**36**	**564**

Appendix U: Extracts from research diary

October

3rd

Feeling motivated that IRAS is now complete but at the same time frustrated capability and capacity is taking it's time. Hoping to have started recruitment during teaching block and have things booked in for start of placement in November. Plan to speak to internal, external, consultant and EbE supervisor once everything has been approved to complete annual review and to discuss their roles moving forward. I'm aware that my external supervisor has had time off and concerned how busy she might be upon returning and how this may influence her capacity to complete the 30 assessments. Generally, concerned this is a large number for us to do regardless (following on from concerns previously that I had after sitting down and practicing the battery) and how much placement time this may take. Plan to review this in the annual meeting also to discuss. Hoping this eases anxiety. Due to start Systematic Review also now that all academic work is out the way!

November

1st

Long delay receiving the PIC so unfortunately haven't been able to start yet, but hopefully soon! Spoken to Gaby upon starting placement and feeling reassured that we will be able to get all testing done. I think, though, that as the project progresses, I am becoming more aware of how much there will be to cover in the thesis, and that there is a lot of analysis (including the thematic analysis) to complete before even considering write up. Meetings arranged now with Huw for December, goal for initial systematic review to be completed by then. Also arranged with the EbE so hopefully their input will help me in considering how I will go about conducting the research and analysing data. I think I feel that I neglected EbE a bit during the development of the study and am curious to see how this may impact on its progress. I wonder if the fact that the study attempted to account for many different viewpoints on what would be helpful has ended up making it too comprehensive and not specific enough?

March

6th

Most feedback interviews are finished now and due to start collecting feedback questionnaires. Most participants appear to have found the research useful which is reassuring to hear, although there were some that commented about the length of testing and feeling tired in the days following. I'm intrigued to see if this comes out for many in the feedback questionnaires. Had a research team meeting which was useful in finalising thoughts for how to present the cognitive testing data in the thesis and also spoke about how this relates to the systematic review. A provisional comparison seems to suggest findings aren't too unexpected, which is reassuring.