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A Neuropsychological Profile of Post Covid-19 Syndrome: Chapter One. Post-Covid-19 Syndrome and Goal-Directed Behaviour: A Systematic Review of Standardized Neuropsychological Test Outcomes; Chapter Two. Exploration of the Outcomes and Experiences of Previously Hospitalised Patients with Post Covid-19 Syndrome: A Mixed Methods Approach

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Doctorate in Clinical Psychology

The University of Edinburgh, August 2023

Word Count: 23, 095

1.1 Acknowledgements

Firstly, I would like to thank all of the participants who took part in the study; your commitment to supporting the research and seeking to make a difference was humbling. I would also like to convey my deepest gratitude to Dr Maggie Whyte for her boundless support, patience and guidance from day one. I am forever inspired by your enthusiasm and wealth of knowledge, and a little bit in awe. Thank you, Maggie. Another huge thank you goes to my academic supervisor, Dr Vilas Sawrikar for his continued encouragement and passion for the project and swift and valuable feedback on drafts. His humour, patience and support during myriad problem-solving supervisions have been invaluable.

To the Department of Clinical Neuropsychology, thank you for putting up with me during this time! The kindness, patience and support extended to me by everyone in the department has been so very generous. I would like to thank Rowena Stewart for her expertise, advice and reassurance in the development of my systematic review. Huge thanks to Carol and Charlotte in the Ethics team for continual support and guidance. Thank you so much to Christine Campbell for co-reviewing my systematic review, despite just having given birth to wee Penny! Your efforts are inspiring, as is your compassion and kindness.

A personal thank you to my mum, dad, mummum and Josh for your endless love, support and encouragement in seeing me through my moments of despair, as well as my training during a pandemic! I cannot thank you enough for everything you do for me. Thank you to Anna and Ruth for your patience and never-ending support, I am incredibly lucky to have you as best friends. I would particularly like to thank my fellow crusts for your continued hilarity, bravery and remarkable support throughout this rollercoaster of an experience. I am truly privileged to know and share this journey with you. Here's to the next chapter.

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2.1 Lay Summary

COVID-19 began spreading worldwide in early 2020, becoming a global pandemic in March 2020. In 2023, people are still experiencing difficulties, including fatigue and problems with thinking, known as cognitive difficulties. Having ongoing symptoms is known as ‘long-COVID’ or post-COVID-19 syndrome (PCS). People with PCS often describe their cognitive difficulties as feeling mentally slow, hazy and having poor attention. Cognitive difficulties affect the ability to remember to carry out tasks, maintain concentration and have conversations with others, which impacts the daily lives of people with PCS.

Chapter one of this thesis involved summarising the existing research to understand if there is evidence of links between PCS and cognitive difficulties, especially those related to memory, attention and the ability to plan, organise and process complex information. This review also looked at whether other factors such as being in hospital with Covid-19, needing oxygen, increased anxiety and low mood affected thinking processes. The results showed that people with PCS had difficulties with their thinking across areas of memory, attention and complex information processing. Additionally, fatigue, depression and anxiety had a negative impact on peoples’ thinking abilities.

Chapter Two reviewed information gathered from PCS patients who had attended the Mental Health after Covid-19 Hospitalisation (MACH) service. The current project aimed to understand the types of everyday challenges that PCS patients who had been in hospital with Covid-19 were experiencing, based on their own reports. The clinical assessments of these patients’ thinking difficulties carried out by MACH were also analysed. The results showed that this group of patients experienced a range of challenges impacting their daily lives including carrying out everyday tasks, poorer mental-health and issues with their thinking,

two years after their initial infection with Covid-19. These difficulties were often upsetting and frustrating. Some individuals displayed poorer performance on tasks of attention, planning and organising than would have been expected. When their own reports of thinking difficulties were compared to the results of their clinical assessments, patients were seen to be aware of some of their difficulties.

The findings of both Chapters showed there are ongoing psychological and cognitive impacts of PCS on patients' daily lives two years' post infection. Research in the future with greater numbers of participants will allow a better understanding of the cognitive challenges PCS patients can expect to experience and enable clinical services to be adapted accordingly.

3.1 Portfolio Thesis Abstract

Purpose

Chapter one sought to determine whether there is evidence of impairments across the cognitive domains necessary for goal directed behaviour among individuals with post covid-19 syndrome (PCS) and the extent to which individual/ clinical variables were associated with such deficits. Impairments in these areas may underlie prevailing economic decline in this population. Chapter two sought to examine patients who were presenting with cognitive complaints to increase understanding of the neuropsychological profile of these individuals through their self-reported experiences, their objective cognitive assessments and the relationship between these two assessment areas.

Method

In Chapter one, a systematic search strategy was deployed across the following databases: PubMed/MEDLINE, Embase, AMED, PsychINFO, NeuroBITE, Google Scholar and ProQuest Dissertations & Theses. Methodological quality was assessed using the Newcastle-Ottawa Scale adapted for prospective cohort and cross-sectional studies. Chapter two applied thematic analysis to the subjective experiences of 21 PCS patients experiencing ongoing difficulties, alongside their objective cognitive function. Subjective and objective complaints were subsequently compared via correlational analyses.

Results

Chapter one: Of 5998 articles, 19 studies were included; on average, cross-sectional studies were rated as ‘moderate’ and cohort as ‘high’ quality. Impairments were observed across memory, attention and executive function. Individual and clinical differences impacted cognitive impairment variably; depression, anxiety and fatigue negatively so. Chapter two:

Thematic analysis identified four main themes related to the types of difficulties experienced; ‘functional consequences’, ‘cognitive changes’, ‘new-onset mental-health difficulties’ and ‘frequency of impact’. No significant differences were identified between the overall sample mean and the normative mean across cognitive domains assessed. However, a pattern of impaired individual test scores was observed across tests where PCS patients presented with primary attentional impairments with an executive component. Significant relationships were observed between subjective complaints of memory and objective cognitive assessments.

Conclusions

The findings of both chapters highlight the ongoing neuropsychological impact of PCS on patients’ daily lives, up to two years’ post infection. Further research with larger sample sizes and matched controls would support the identification of the cognitive impacts attributable to disease pathology, psychological, clinical variables and their relative contribution.

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Post-Covid-19 Syndrome and Goal-Directed Behaviour: A Systematic Review of Standardized Neuropsychological Test Outcomes

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Orcid ID: 0009-0009-3002-6635

Word Count: 11, 407

Prepared in the style for submission to *Brain, Behavior, and Immunity*

This research did not receive any specific grant from funding agencies in the public,
commercial, or not-for-profit sectors.

5.1 Systematic Review Abstract

Background: Approximately 80,000 people are economically inactive due to Post Covid-19 Syndrome (PCS) As cognitive domains of attention, executive function (EF) and memory are necessary for goal-directed behaviour (GDB), impairments across these domains may be contributing to this reduced workforce. It is unclear whether PCS is associated with cognitive dysfunction underlying GDB, with methodological issues present in the literature. A systematic review was conducted to establish whether impairments across domains of attention, EF and memory are evident using standardised neuropsychological assessments and to ascertain if individual differences influenced these impairments among PCS patients.

Methods: Systematic searches of databases were conducted up to October 13th, 2022. Databases searched: PubMed/MEDLINE, Embase, AMED, PsychINFO, NeuroBITE, Google Scholar and ProQuest Dissertations & Theses. Two reviewers independently assessed full-text articles according to pre-determined criteria. Methodological quality was assessed using the Newcastle-Ottawa Scale adapted for prospective cohort and cross-sectional studies. The review protocol is registered on PROSPERO (CRD42022359349).

Results: Of 5998 articles, 19 studies with 3083 participants were included (mean age = 51.4 years; time from diagnosis/ infection ranged from 3.4 to 10 months). Impairments were evident across memory, attention and EF. There was varying evidence of individual and clinical differences impacting cognitive impairment; depression, anxiety and fatigue negatively influenced cognitive function.

Conclusions: Cognitive domains necessary for GDB are impaired in PCS patients, indicating that services may offer rehabilitation interventions targeting GDB such as Goal Management Training to alleviate disability and increase well-being, supporting a return to the workforce.

Highlights:

- Cognitive impairments among PCS participants are evident across the domains of memory, attention and executive function.
- Fatigue, depression and anxiety exert a negative influence across these cognitive domains.
- The requirement for supplemental oxygen but not hospitalisation per se, negatively impacts cognitive function across the domains of memory and attention.

Keywords: Post Covid-19 Syndrome; Cognitive Impairment; Goal Directed Behaviour; Economic Inactivity; Neuropsychological Assessment; Covid-19

6.1 Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has resulted in 753 million infections and 6.81 million deaths globally as reported by the World Health Organisation (WHO, 2023). Multi-system manifestations of COVID-19 feature a range of mild to severe symptoms including fever, cough, loss of taste and smell, shortness of breath, pneumonia, and multi-organ dysfunction, including impact on the brain (Guan et al., 2020; Thakur et al., 2021). While most individuals in the community who contracted COVID-19 recovered to pre-morbid functioning, approximately 12% report ongoing symptoms; a condition known as Post-Covid-19 Syndrome or Condition (PCS) (European Centre for Disease Prevention and Control (ECDC, 2022)). PCS can be significantly debilitating, with considerable deleterious impacts on affected individuals' quality of life and ability to engage in the workforce (Malik et al., 2022).

The ability to function independently and indeed, engage in the workforce, requires complex cognitive processes to allow individuals to plan, organise, initiate, and maintain their behaviour in pursuit of a goal, integrating feedback and adapting behaviour as needed i.e., engage in goal-directed behaviour (GDB). Cognitive processes necessary for GDB include attention, executive functioning and to some extent, memory, while impairments in these domains can have detrimental effects on one's everyday functioning across environments (Benedictus et al., 2010; Biederman & Faraone, 2006; Biederman et al., 2007; Cullen & Weisz, 2011; Griffiths et al., 2014). Goal-management cognitive rehabilitation interventions to improve everyday functioning and reduce disability have been successfully deployed for use in numerous patient populations with impaired GDB and may be useful for PCS patients (Stamenova & Levine, 2019). However, research thus far has not clearly established whether PCS is associated with cognitive dysfunctions in GDB. The current study is a systematic review to synthesise the findings regarding cognitive impairments associated

with the cognitive subdomains necessary for GDB, including memory, attention and executive function (EF) within the context of PCS.

PCS refers to “symptoms persisting for more than 12 weeks and not explained by another diagnosis” (NICE-SIGN-RCGP, 2021; WHO, 2021). Across the literature, there are reports of over 50 ongoing symptoms which may fluctuate over time, including breathlessness, fatigue, anxiety, and cognitive dysfunction (Lopez-Leon et al., 2021; Michelen et al., 2021). Within a systematic review of 61 studies, the prevalence of any persistent symptom is reported to be 51% among PCS community samples, increasing to 67% among those hospitalised (ECDC, 2022), with some individuals reporting impacts up to 12 months’ post-infection (Alkodaymi et al., 2022). The underlying pathophysiology remains poorly understood, although research has indicated there may be direct and indirect effects on the central nervous system including neuroinflammation, encephalopathies (Helms et al., 2020; Nersesjan et al., 2021; Paterson et al., 2020) and stroke (Beyrouiti et al., 2020), all with potential contributions to cognitive functioning. Moreover, there are accounts of elevated cerebrospinal fluid antibodies and white matter changes in the brains of acute COVID-19 patients and low oxygen levels, again putting individuals at risk for developing cognitive impairments (Franke et al., 2021; Varatharaj et al., 2020). Irrespective of the mechanisms by which cognitive dysfunction may occur, COVID-19 appears to occasion long-term consequences on cognition, occupational and vocational functioning.

In terms of occupational functioning, a marked economic impact of PCS is emerging, specifically in relation to a reduced workforce with long-term sickness rising fastest among younger age groups (ONS, 2022). As of July 2022, approximately 80,000 people have withdrawn from the workforce due to PCS (Reuschke & Houston, 2022). Davis et al. (2021) reported that of 3,762 individuals with self-reported, persistent COVID-19 symptoms, two thirds experienced changes in their work schedule, 46% reduced their hours, while 23% were

no longer working. Critically, in this sample, less than 10% of individuals were hospitalised. Furthermore, in a systematic review of 13 articles, 13% reported employment consequences of PCS, with higher rates among those who were hospitalised (Nittas et al., 2022). It is clear that PCS individuals from both the hospitalised and community populations have experienced occupational functioning implications, suggesting that post-hospitalisation follow-up will not adequately capture all individuals requiring support. Specific and specialised healthcare services are needed (NICE-SIGN-RCGP, 2021; Norton et al., 2021) and some are in development to address this emerging and unique patient group (NHS England; NHS Scotland). The planning and development of such services requires an understanding of appropriate and effective management treatments and interventions.

Interventions targeting goal-directed behaviours such as Goal Management Training (Levine et al., 2012; Levine et al., 2000; I. Robertson, 1996) may be beneficial for PCS patients to improve functioning and meet occupational demands. It is proposed that the ability of an individual to carry out GDB demands significant input from executive attentional systems and memory in coordinating thought and action in line with one's values or aims (Miller & Wallis, 2009; Shallice & Cipolotti, 2018). Behaviours related to these cognitive systems include identifying and integrating relevant and complex information, initiating, planning, organising and adapting strategies to address everyday challenges (Hart & Evans, 2006; Wolf, 2010). Memory processes involved in GDB include the ability to learn new information, retain relevant information in short-term storages, retrieve germane memories and remember to carry out future tasks (Buschman & Miller, 2014). In this context, deficits in the integration of such processes can negatively impact daily functioning. It may be that impairments across these cognitive domains are contributing to the reduced occupational functioning seen among individuals with PCS and appropriate interventions targeting goal-

directed behaviours are required to remediate impairments in these areas and improve occupational functioning.

Research findings characterising the cognitive profile of PCS is however mixed, thus recognition of the cognitive domains to target in rehabilitation remain uncertain (Ceban et al., 2022). On the one hand, for instance, previous reviews suggest significant impairments in EFs, particularly within the executive element of attention (Ortelli et al., 2021). Impairments in executive attention, conceptualised as a “top-down” function governed by the ‘cognitive control network’, are thought to result in the fluctuating cognitive dysfunction and fatigue reported by PCS patients (Ladds et al., 2020; Petersen & Posner, 2012). Indeed, Ortelli, Benso, et al. (2022) recently reported a ‘global slowness’ through intraindividual variability analysis of reaction times on tasks of sustained attention and interference inhibition in PCS patients, implying dysfunction of the executive attentional system. In contrast to these findings, several studies have demonstrated normal cognitive function in PCS patients. For instance, in a sample of PCS patients with mild-moderate acute forms of the disease, few PCS patients demonstrated impaired performance on tests of EF and attention; and when compared to matched controls, no significant differences were found (Mattioli et al., 2021). Taken together, there is a high degree of heterogeneity in cognitive dysfunction across studies attempting to characterise the cognitive profile of PCS patients. It is imperative that research can equip healthcare services with accurate knowledge of the cognitive impairments associated with those experiencing PCS to facilitate streamlined treatments and interventions.

One potential reason for the mixed findings in previous reviews lies with the heterogeneous methods included to assess cognitive dysfunction. For instance, cognitive dysfunction implicated in PCS has largely been assessed using first-level screening tools including The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and the Mini State Mental Examination (Amalakanti et al., 2021; Del Brutto et al., 2021; Folstein et

al., 1975; Rass et al., 2021). While these widely available tools facilitate rapid and cost-effective *screening* of cognitive impairments, they do not offer a comprehensive analysis of cognitive functioning as provided by standardised neuropsychological testing. Moreover, these former screening tools were designed to detect global cognitive decline in emerging dementia among elderly populations, making their deployment less sensitive in identifying milder forms of cognitive dysfunction in other populations of varying ages and educational backgrounds. This lack of sensitivity may produce an under-representation of cognitive dysfunction relating to specific cognitive domains. In their study, Lynch et al. (2022) administered both the MoCA and a battery of standardised neuropsychological assessments to PCS participants. The authors applied thresholds of ‘low’ neuropsychological test performance as scoring “one or more standard deviations (SD) below age-matched population-based normative values on two or more neuropsychological tests” while ‘extremely low’ performance was determined by scores of two or more SD below normative scores on one or more tests. The sensitivity of the MoCA in detecting low and extremely low neuropsychological test performance was 50% and 68.8%, respectively. The authors concluded that the MoCA was not sufficiently sensitive in detecting mild or greater degrees of cognitive dysfunction among PCS populations. Currently, healthcare services lack a reliable picture of cognitive dysfunction of PCS, therefore a systematic review of the literature that synthesises standardised, sensitive, neuropsychological assessments is urgently needed.

To further understand reasons for the mixed findings, it is also important to consider how illness related factors such as disease severity, mechanical ventilation, delirium and being in ICU, may influence cognitive dysfunction (Boogaard et al., 2012; Hayhurst et al., 2020; Hopkins & Jackson, 2006; Wilcox et al., 2013). Previous research studies have shown that respiratory complications such as pneumonia and acute respiratory distress syndrome

(ARDS), characterised by severe hypoxemia, can impact cognitive function (Mikkelsen et al., 2012; Sasannejad et al., 2019). However, associations between respiratory complications and cognitive dysfunction have not always been found among PCS populations (Jaywant et al. (2021). Research also indicates that demographic factors including age and mental and physical comorbidities may moderate impact of PCS on cognitive function (Beydoun et al., 2014; Gunstad et al., 2010; Kloszewska et al., 2021; Mourao et al., 2016; Waldstein et al., 2019). To understand the nature of illness related factors in their influence of cognitive outcomes, a comprehensive systematic review summarising these factors will be beneficial. This will support healthcare teams in the development of their services; it is important to understand whether psychiatric or cognitive rehabilitation could be delivered as a primary treatment target.

In summary, the negative impact of cognitive dysfunction in the domains of memory, attention and EF can affect one's ability to function across occupational environments. However, it is unclear whether these cognitive subdomains are indeed impaired in the PCS population, with many results impacted by the use of screening tools. Furthermore, cognitive dysfunction has been associated with other contributing factors which may be linked to the reported deficits. To address the limitations evident in the literature, including pre-existing systematic reviews, the aims of the current systematic review were to: (i) synthesise findings in relation to cognitive impairments in the subdomains of memory, attention and EF in those with PCS, assessed via second-level measurements i.e., neuropsychological assessment; and (ii) report on individual differences relating to cognitive function which may include, although not limited to, neuropsychiatric difficulties, length of time on ventilation, severity of illness and other relevant comorbidities as available. The study sought to address the following research questions:

1. Is there evidence by objective measures of cognitive dysfunction among PCS individuals in the domains of memory, attention and executive function?
2. Which individual factors are associated with cognitive dysfunction among PCS individuals?

7.1 Methods

7.1 Systematic review protocol

The protocol was registered a priori on PROSPERO (CRD42022359349) in September 2022. The current review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2021).

7.2 Search Strategy & Eligibility Criteria

In October 2022, the following databases were searched: MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily (1946-2022), EMBASE (1947-2022), PsychINFO (1806-2022), Allied and Complementary Medicine (AMED; 1985-2022), NeuroBITE (previously PsychBITE) and ProQuest Dissertations & Theses Global. The search terms were developed following consultation from the Librarian at the University of Edinburgh and included a combination of subject headings and keywords which were adapted to suit each database. The first twenty pages of Google Scholar, references of featured studies and relevant articles were also reviewed, and key authors contacted if necessary. The search strategy is presented in Table 1.

Table 1*Search Concepts*

Concept	Searches
COVID-19	Covid 19 or covid or severe acute respiratory syndrome coronavirus 2 or sars cov 2 or SARS-CoV-2 or SARS-CoV-2 infection or covid sequelae or covid 19 syndrome or covid syndrome or covid impairment or COVID 19 neurological syndrome
Post-Covid-19 Syndrome	Prolonged or persistent or enduring or linger* or recurrent or complications or long* haul* or longhaul* or long* tail* or longtail* or long duration or longduration or long lasting or longterm or long term or long or convalescent or chronic or post infect* or post acute or post-acute or postacute or post or after or recovery or sequelae or post-acute COVID-19 neurologic* syndrome or PCS or PASC
Cognition	Cogniti* or neurocogniti* or neuropsych*

7.2.1 Eligibility Criteria

In accordance with PRISMA guidance, eligibility criteria were created considering a Population, Exposure, Control, Outcome (PECO) framework (Page et al., 2021).

Population

Adult participants (aged 18+) with likely PCS. ‘Likely’ is used here as many studies to date have used different criteria to identify those with PCS. Current PCS definition asserts that symptoms cannot be explained by an alternative diagnosis (NICE-SIGN-RCGP, 2021). As such, participants with prior cognitive impairment and/or severe co-morbidities impacting cognitive function via e.g., dementia, neurological conditions, MCI, and subjective cognitive

impairment had to be excluded from studies. Post-mortem studies of PCS patients were also excluded.

Exposure

Participants with previously confirmed COVID-19 of any severity ascertained according to laboratory testing, ICD-10 linkage, and/or clinical diagnosis. To align with the NICE definition of PCS, symptoms had to persist since infection or diagnosis for at least 3-months. As such, the median or mean time was at least 3-months since COVID-19 diagnosis or infection and studies needed to demonstrate that symptoms arose and/or were exacerbated following infection i.e., persisting. This information could be derived via self-report and/or questionnaires administered to participants.

Comparison

Any comparison group as available including healthy controls and those with varying degrees of acute COVID-19 severity were included.

Outcome

Studies that reported scores on at least one standardised neuropsychological assessment tool related to cognitive subdomains of memory, attention and/or EF. Studies were excluded if they used only screening measures for assessing cognitive function such as the MoCA, MMSE and/ or non-standardised measures of assessment. Studies were also excluded if they reported inexact or incomplete quantitative data reported for primary outcomes such as descriptive ranges without numbers.

Study Design

Cohort studies, cross-sectional studies, case control studies, and dissertations/ theses were included. Studies which deployed a longitudinal design were included in the analysis if data at a time point >12 weeks post COVID-19 infection/ diagnosis were available to extract. Case series, case reports, qualitative studies, experimental studies, systematic reviews, book

chapters, editorials, abstracts, protocols, guidelines, case conferences, studies with a sample size <10 people were excluded. By virtue of the current topic, only studies published as defined by the beginning of the COVID-19 pandemic i.e., from 2019 onwards were included.

7.3 Search Process & Data Extraction

Searches were exported to Covidence where duplicates were removed. The lead reviewer screened 100% of *titles and abstracts* for relevance, while the second reviewer, CC, reviewed 13% of titles and abstracts. Subsequently, the full text of each article was assessed for screening against the eligibility criteria. The second reviewer independently reviewed 100% of the full text articles from the primary screening, with any disputes resolved through discussion between TS and CC. The study selection process is displayed in Figure 1.

Appropriate inter-rater agreement was observed for the screening of titles/ abstracts ($\kappa = .66$) and full-text screening ($\kappa = .93$) (Landis & Koch, 1977).

Study characteristics were extracted including study design, characteristics of the sample, time since diagnosis or infection to evaluation, cognitive measures utilised, main results and variables associated with ongoing symptoms, if applicable. The results of cognitive impairments were divided into memory, attention and EF domains. The tests used to measure each subdomain were categorised according to their original classification extracted from the study. If this was not explicitly stated, and a list of tests were reported without relating them to specific cognitive domains, the author categorised them according to tests classified by domains in the book 'Neuropsychological Assessment' by Lezak (2012).

7.4 Methodological Quality

The Newcastle-Ottawa Scale (NOS; (Wells et al., 2000)) was modified from the study by Ceban et al. (2022) and utilised for cross-sectional and prospective cohort studies. The adapted methodological quality criteria for cross-sectional and cohort studies are provided in Appendix A. Methodological quality was rated as follows: 'High'=7-8 stars, 'Moderate'=5-6

stars, 'Low'=4 or fewer stars. TS and CC independently rated 100% of the articles for methodological quality. Near perfect inter-rater agreement was observed ($\kappa = .98$) (Landis & Koch, 1977). Studies were rated according to the prospective cohort NOS whereby the design was inexplicit. Studies were penalised for failing to include a non-exposed cohort in those instances. Furthermore, the comparability rating required studies to be matched in the design and/or confounders to be adjusted for in the analysis. According to the NOS guidelines, the most important sociodemographic factor among age and sex should be controlled for. Given that PCS is an emerging patient group, it was felt that both factors would be equally important to control/ adjust for. Studies were awarded points if they compared data to assessment-specific normative means which control for age and sex and penalised if those measures didn't offer normative data for both age and sex.

7.5 Synthesis of Results

A narrative synthesis of the results was carried out. It was deemed inappropriate to conduct a quantitative synthesis (meta-analysis) given the lack of homogeneity across the studies' clinical and methodological variables. Variation included different source populations and settings (hospital (ICU, ward level, community)), acute disease severity, assessment methods used to assess each cognitive domain, levels of impairment assessed and data analysis i.e., use of control groups (Deeks et al., 2022).

8.1 Results

The literature search yielded 5,998 articles. Following de-duplication, 3797 titles and abstracts were screened, resulting in 145 articles for the full-text review as shown in Figure 1.

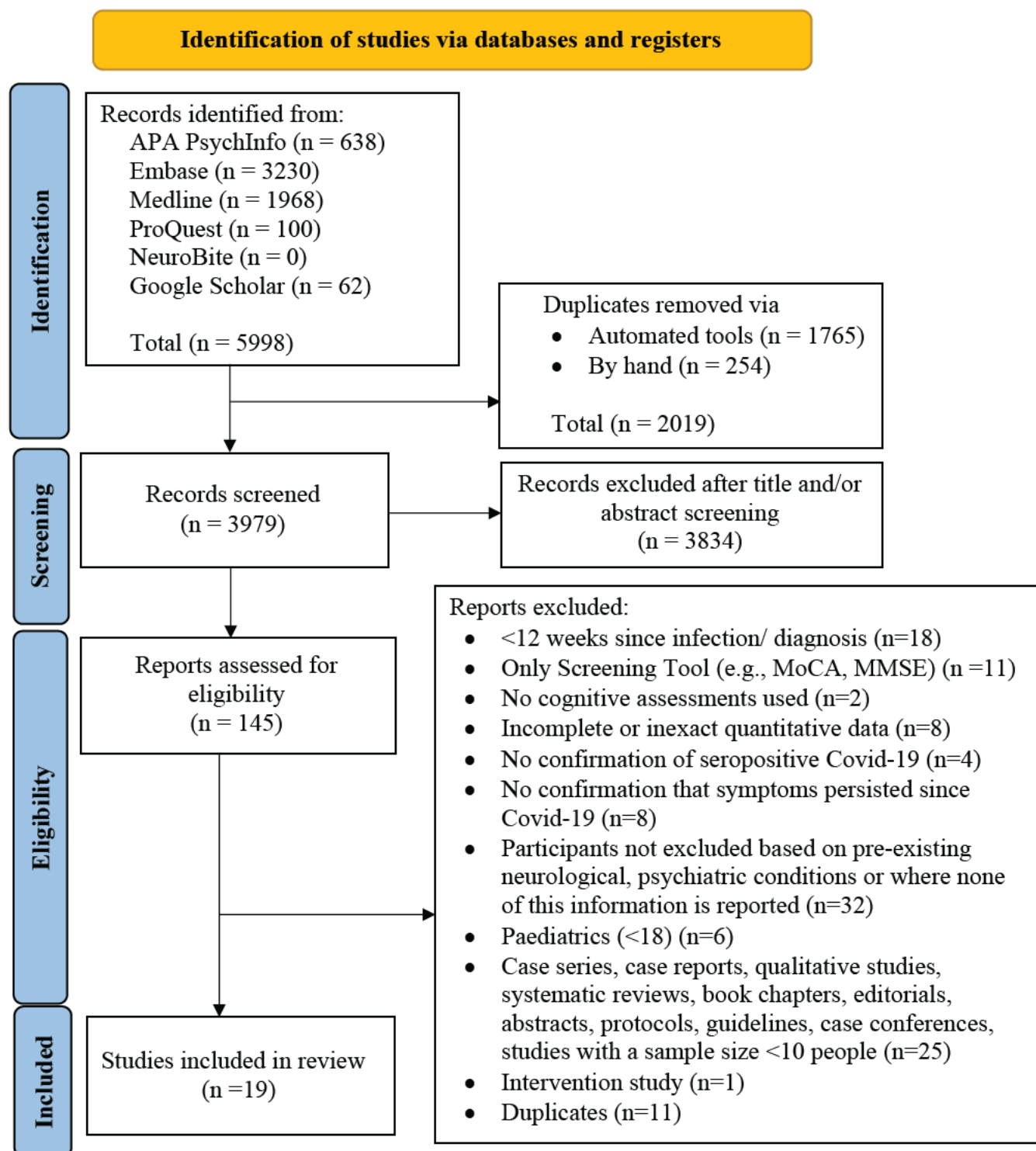


Figure 1: PRISMA Flow Diagram of Study Selection & Screening Process

8.1 Study Characteristics

Nineteen studies were conducted across nine countries, including Spain ($n=5$), Italy ($n=3$), USA ($n=3$), Sweden ($n=2$), Switzerland ($n=2$), Brazil ($n=1$), France ($n=1$), Argentina ($n=1$) and Germany ($n=1$). A total of 3,083 PCS patients were included in analyses. Sample sizes ranged from 20 to 614, with an average of 94.8 participants. On average, females comprised 52.8% of participants. The average age of PCS participants was 51.4 years, ranging from 40.9 to 60.8 years. Time from diagnosis or infection ranged from 3.4 to 10 months, with the mean being 6.4 months. The analysis included 12 prospective cohort (Birberg Thornberg et al., 2022; Cecchetti et al., 2022; Crivelli, Calandri, et al., 2022; Dressing et al., 2022; García-Molina et al., 2022; García-Sánchez et al., 2022; Hellgren et al., 2021; O'Connor et al., 2022; Ortelli, Benso, et al., 2022; Ortelli, Ferrazzoli, et al., 2022; Voruz, Cionca, et al., 2022; Voruz, de Alcantara, et al., 2022) and 7 cross-sectional studies (Albu et al., 2021; Braga et al., 2022; Calabria et al., 2022; Delgado-Alonso et al., 2022; Dondaine et al., 2022; Ferrando et al., 2022; Krishnan et al., 2022).

Various sample types were included; most studies included participants who were previously hospitalised (94.7%), while one study featured those never hospitalised. Of the 1,008 individuals hospitalised, 357 were reported to require care in ICU, with 110 requiring mechanical ventilation.

The manner in which impaired test scores were defined across studies differed; 4 studies applied an impairment threshold of z-scores of $<1.5SD$ and 2 studies utilising a criterion of $<2SD$ from the normative mean (Ferrando et al., 2022; Hellgren et al., 2021). One study displayed results according to both criteria (Birberg Thornberg et al., 2022). Six studies incorporated healthy control groups in their analyses, while others subdivided PCS participants by the requirement of oxygen therapy during hospital admission (Dondaine et al., 2022), by acute disease severity and/or by the requirement for hospitalisation (Albu et al.,

2021; Birberg Thornberg et al., 2022; Braga et al., 2022; Calabria et al., 2022; García-Molina et al., 2022; O'Connor et al., 2022; Voruz, de Alcantara, et al., 2022). Patients were also categorised as anosognosic/ nosognosic (Voruz, Cionca, et al., 2022) and whether or not they sought care for their symptoms (Ferrando et al., 2022). Detailed study characteristics are displayed below in Table 2.

Table 2*Study Characteristics*

Study; Country	Design	Sample Type	Demographics Covid Age (M); Sex (female n, (%)); Education (years)	Demographics Control Group Age (M); Sex (female n, (%)); Education (years)	Covid Group <i>n</i>	Control Group (healthy control unless otherwise stated) <i>n</i>	Evaluation timeline, months
Albu et al. (2021) Spain	Cross- sectional	Hospitalised patients referred for neuro- rehab	ICU Age 61.5 Sex 3 (18.75) Education: -	Non-ICU Age 43.5 Sex 8 (57) Education: -	ICU: 16	Non-ICU: 14	3.4
Birberg Thornberg et al. (2022) Sweden	Cohort	Hospitalised	Age 57.7 Sex 51 (38.3) Education 9 = 18.8% 9-12 = 40.6% >12 = 40.6%		ICU: 36	Non-ICU: 97	4.6
Braga et al. (2022) Brazil	Cross- sectional	Hospitalised and non- hospitalised patients self-seeking rehab. Hospitalised patients: Ward, ICU and OTI	Age 47.6 Sex 451 (73) Education 5-8 = 5% 9-11 = 6% 12-15 = 35% 16+ = 54%		Hospitalised: 206	Non- Hospitalised: 408	8

Study; Country	Design	Sample Type	Demographics Covid Age (M); Sex (female n, (%)); Education (years)	Demographics Control Group Age (M); Sex (female n, (%)); Education (years)	Covid Group <i>n</i>	Control Group (healthy control unless otherwise stated) <i>n</i>	Evaluation timeline, months
Calabria et al. (2022) Spain	Cross-sectional	Hospitalised and non-hospitalised	Age 51.7 (20-88) Sex 87 (64) Education 5-8 = 5% 9-11 = 6% 12-15 = 35% 16+ = 54%		136 (Hospitalised: 59 (ICU 24); Non-Hospitalised: 77)		8.3
Cecchetti et al. (2022) Italy	Cohort	Previously hospitalised	Age: 60.8 ± 12.6 Sex: 13 (27) Education: 11.1 ± 3.9		33	49	10
Crivelli et al. (2022) Argentina	Cohort	Hospitalised and non-hospitalised outpatients	Age: 50 (43-63) Sex: 22 (49) Education: 17 (15- 18)	Age: 57 (46-64) Sex: 20 (44) Education: 17 (15 - 18)	45	45	4.7
Delgado-Alonso et al. (2022) Spain	Cross-sectional	Hospitalised and non-hospitalised outpatients attending general neurology consultations	Age 51.06 Sex 37 (74) Education 13.58 ± 4.01		50	50	9.4

Study; Country	Design	Sample Type	Demographics Covid Age (M); Sex (female n, (%)); Education (years)	Demographics Control Group Age (M); Sex (female n, (%)); Education (years)	Covid Group <i>n</i>	Control Group (healthy control unless otherwise stated) <i>n</i>	Evaluation timeline, months
Dondaine et al. (2022) France	Cross-sectional	Previously hospitalized having received oxygen therapy (“O ₂ +”) and pneumonia-free outpatient COVID-19 patients not having received oxygen therapy (“O ₂ -”)		Age O ₂ + = 52.19 O ₂ - = 43.90 Sex O ₂ + = 15 (48.3) O ₂ - = 21 (67.7) Education O ₂ + = 14.35 O ₂ - = 14.84	O ₂ +: 31	O ₂ -: 31	O ₂ +: 4.6 O ₂ +: 5
Dressing et al. (2022) Germany	Cohort	Hospitalised and non-hospitalised outpatients	Age 53.6 (24-75) Sex 20 (64) Education 13.6 (8-18)		31		6.65
Ferrando et al. (2022) USA	Cross-sectional	Hospitalised and non-hospitalised outpatients	Care-Seeking (CS): Age: 48.1 Sex: 25 (78) Education: 15.8	Non-care seeking (NCS): Age: 33.7 Sex: 16 (57) Education: 1 6.4	CS: 32	NCS: 28	CS: 8.2 NCS: 5.6

Study; Country	Design	Sample Type	Demographics Covid Age (M); Sex (female n, (%)); Education (years)	Demographics Control Group Age (M); Sex (female n, (%)); Education (years)	Covid Group <i>n</i>	Control Group (healthy control unless otherwise stated) <i>n</i>	Evaluation timeline, months
García-Molina et al. (2022) Spain	Cohort	Hospitalised and non-hospitalised outpatients referred for neurorehabilitation; Control group were Covid-19+ cases with normal NP results.	Covid Age: 49.7 Sex: 55 (60.4) Education: ≤7 = 15.4% 8-12 = 27.5% >12 = 57.1%	Control Age: 54.69 Sex: 17 (53.1) Education: ≤7 = 12.5% 8-12 = 34.4% >12 = 53.1%	Covid: 91	Control: 32	Covid: 7.4 Control: 8.5
García-Sánchez et al. (2022) Spain	Cohort	Hospitalised and non-hospitalised outpatients	Age 51.1 (22-78) Sex 41 (63) Education 14.4		63		6.1
Hellgren et al. (2021) Sweden	Cohort	Hospitalised patients	Age 59 (51-66) Sex 7 (20) Education ≤9 = 28.5% 9-12 = 42.8% >12 = 28.5%		35		5

Study; Country	Design	Sample Type	Demographics Covid Age (M); Sex (female n, (%)); Education (years)	Demographics Control Group Age (M); Sex (female n, (%)); Education (years)	Covid Group <i>n</i>	Control Group (healthy control unless otherwise stated) <i>n</i>	Evaluation timeline, months
Krishnan et al. (2022) USA	Cross- sectional	Hospitalised and non- hospitalised outpatients	Age 44.75 (25- 65) Sex 18 (90) Education 15.2 (10-19)		20		5.5
O'Connor et al. (2022) USA	Cohort	Hospitalised and non- hospitalised outpatients (clinic and via advertisement)	Long-Covid (LC) Age: 47.91 Sex: 8 (72.7) Education: <12 = 0 >12 = 11	Covid Age: 44.64 Sex: 4 (28.6) Education: <12 = 2 >12 = 12 HC Age: 48.25 Sex: 9 (45) Education: <12 = 0 >12 = 20	LC 11	Covid: 14 HC: 20	LC 11.2 Covid: 5.2
Ortelli, Benso, et al. (2022) Italy	Cohort	Hospitalised and non- hospitalised	Age: 48.4 Sex: 21 (28.4) Education: 14.3	Age: 44.2 Sex: 12 (41.4) Education: 14.8	74	29	4.1
Ortelli, Ferrazzoli, et al. (2022) Italy	Cohort	Non-hospitalised	Age: 49.7 Sex: 50 (74.5) Education: 14.1	Age: 46.4 Sex: 11 (50) Education: 14.3	77	22	3.6

Study; Country	Design	Sample Type	Demographics Covid Age (M); Sex (female n, (%)); Education (years)	Demographics Control Group Age (M); Sex (female n, (%)); Education (years)	Covid Group <i>n</i>	Control Group (healthy control unless otherwise stated) <i>n</i>	Evaluation timeline, months
Voruz, de Alcantara, et al. (2022) Switzerland	Cohort	Hospitalised (moderate-severe) and non-hospitalised (mild)	Mild Age 54.86 Sex 34.7 Education 11-12 Moderate Age 55.85 Sex 35.4% Education 11-12 Severe Age 62.08 Sex 20.8% Education 11-12		Mild 49 Moderate 48 Severe 24		7.3
Voruz, Cionca, et al. (2022) Switzerland	Cohort	Hospitalised	Anosognosic (A) Age: 56.58 Sex: 7 (26.9) Education: 11- 12	Nosognosic (N) Age: 56.49 Sex: 30 (39.4) Education: 11-12	A 26	N 76	7.5

8.2 Methodological Quality

Table 3 displays the methodological quality ratings for seven studies according to the NOS criteria adapted for cross-sectional studies. A maximum of 9 stars could be awarded where 7-9 stars equated to 'High' quality, 5-6 stars was 'Moderate' and fewer than 4 stars was 'Low' quality. Studies were rated on average as 'moderate' ($M = 5.86$) according to the NOS criteria. All samples were largely representative of the PCS population. Only 1 study reported on the response rate between respondents and non-respondents (Delgado-Alonso et al., 2022). No study reported a pre-determined sample size calculation.

Table 3*Cross-Sectional Studies Methodological Quality as per adapted NOS quality rating*

Study	Selection				Comparability		Outcome		Total /9	Quality Rating
	1	2	3	4	1	2	1	2		
Albu et al. (2021)	*			**			*	*	5/9	Moderate
Braga et al. (2022)	*			**			*	*	5/9	Moderate
Calabria et al. (2022)	*			**		*	*	*	6/9	Moderate
Delgado-Alonso et al. (2022)	*		*	**	*		*	*	7/9	High
Dondaine et al. (2022)	*			**	*	*	*	*	7/9	High
Ferrando et al. (2022)	*			**		*	*	*	6/9	Moderate
Krishnan et al. (2022)	*			**			*	*	5/9	Moderate

Note: A study can be awarded a maximum of one star () for items 1-3 for Selection and the Outcome categories. A maximum of two stars (**) can be given for item 4 in Selection, and Comparability.*

Table 4 displays the methodological quality ratings for 12 studies rated according to the NOS adapted for prospective cohort studies. Studies were on average ‘high’ (M= 7.0). Studies were frequently penalised for lacking a non-exposed group or failing to detail the recruitment source of the non-exposed group. There is potential overlap of participants between two sets of studies (Birberg Thornberg et al., 2022; Hellgren et al., 2021) and (Voruz, Cionca, et al., 2022; Voruz, de Alcantara, et al., 2022) as both recruited from the same databases/ hospitals as each other. There are no reports in the studies indicating there is no overlap.

Table 4*Cohort Studies Methodological Quality as per adapted NOS quality rating*

Study	Selection				Comparability		Outcome			Total /9	Quality Rating
	1	2	3	4	1	2	1	2	3		
Birberg Thornberg et al. (2022)	*		*	*		*	*	*	*	7/9	High
Cecchetti et al. (2022)	*	*	*	*	*	*	*	*	*	8/9	High
Crivelli, Calandri, et al. (2022)	*		*	*	*	*	*	*	*	8/9	High
Dressing et al. (2022)	*		*	*		*	*	*	*	7/9	High
García-Molina et al. (2022)	*		*	*			*	*	*	6/9	Moderate
García-Sánchez et al. (2022)	*		*	*			*	*	*	6/9	Moderate
Hellgren et al. (2021)	*		*	*			*	*	*	6/9	Moderate
O'Connor et al. (2022)	*	*	*	*	*	*	*	*	*	9/9	High
Ortelli, Benso, et al. (2022)			*	*	*		*	*	*	6/9	Moderate
Ortelli, Ferrazzoli, et al. (2022)		*	*	*	*		*	*	*	7/9	High
Voruz, Cionca, et al. (2022)	*		*	*	*		*	*	*	7/9	Moderate
Voruz, de Alcantara, et al. (2022)	*		*	*	*		*	*	*	7/9	Moderate

NB: A study can be awarded a maximum of one star () for each numbered item within the Selection and Outcome categories. A maximum of two stars (**) can be given for Comparability.*

8.3 Narrative Synthesis

8.3.1 Memory

Sixteen studies assessed memory as can be seen in Table 5 whereby results are presented as a percentage of the participants with impairments unless otherwise stated. All 11 studies which reported percentages of participants with impairments revealed impairments ranging from 6% to 75% (Albu et al., 2021; Birberg Thornberg et al., 2022; Calabria et al., 2022; Cecchetti et al., 2022; Delgado-Alonso et al., 2022; Dondaine et al., 2022; Dressing et al., 2022; García-Sánchez et al., 2022; Hellgren et al., 2021; Krishnan et al., 2022; Voruz, de Alcantara, et al., 2022). The study by Cecchetti et al. (2022) which reported the lowest level of impairment at 6%, included a small sample size of 33 and participants with the longest time since infection at 10 months. The quality of this study was awarded a 'High' rating of eight out of nine marks. Across studies, verbal learning commanded the highest level of impairment, followed by delayed verbal recall. Albu et al. (2021) reported that 75% of those in ICU ($n = 14$) demonstrated impairments on measures of verbal learning compared to 58% of those who were hospitalised at ward level. Indeed, higher levels of impairment were reported in previously hospitalised samples among other studies (Birberg Thornberg et al., 2022; Dondaine et al., 2022; Hellgren et al., 2021). Similarly, higher levels of impairment were reported in previously hospitalised samples across tests of delayed verbal recall (Albu et al., 2021; Birberg Thornberg et al., 2022; Hellgren et al., 2021). Notably, the two studies using an impairment criterion of 2SD below the normative mean revealed impairments (Birberg Thornberg et al., 2022; Hellgren et al., 2021), particularly on tests of verbal learning, in line with other studies. There were lower rates of delayed visual recall among studies; studies using the same measurement tool for delayed visual recall demonstrated similar impairments. For example, impairments ranged from 10-13% in studies using the Brief Visuospatial Memory Test (BVMT) (Dressing et al., 2022; Krishnan et al., 2022), while

two studies using the Rey-Osterrieth Complex Figure Test (ROCFT) revealed impairments of 16% (Delgado-Alonso et al., 2022) and 16.9% (Calabria et al., 2022).

Of the five studies which analysed their results using a comparison group, four revealed significantly worse memory performance in the PCS sample (Crivelli, Palmer, et al., 2022; Ferrando et al., 2022; García-Molina et al., 2022; Voruz, Cionca, et al., 2022). Two of these studies compared performance to other COVID-19 patients rather than healthy controls. For example, Ferrando et al. (2022) reported significantly worse performance on verbal learning tasks in ‘care-seeking’ participants compared to those who were ‘non-care seeking’, while Voruz, Cionca, et al. (2022) reported similar deficits in anosognosic v nosognosic patients. One study found no significant difference between PCS and a comparison group of healthy controls across memory tasks (O'Connor et al., 2022). The quality of this study was deemed to be ‘High’ with full marks awarded. A further important aspect is that time since infection in this study was one of the highest at 8.2 months.

Table 5*Results: Memory*

Study; Country	Memory Domain	Cognitive Assessments	Results (% Impaired)	Variables associated with ongoing symptoms
Albu et al. (2021); Spain	Verbal Memory	RAVLT-Immediate RAVLT-Delayed RAVLT-Recognition	<u>ICU; Non-ICU¹</u> 75%; 58% 62%; 58% 30%; 17%	No association between ICU admission and objective assessments.
BirbergThornberg et al. (2022); Sweden	Immediate Memory Delayed Memory	RBANS List Learning Story Memory RBANS List Recall Story Recall List Recognition Figure Recall	<u><1.5SD; <2D</u> 29.6%; 16.8% 17.1%; 10.1% 20.3%; 13.8% 24.8%; 8.8% N/A 15.2%; 8% N/A 11.4%; 9.1%	No significant differences between ICU and non-ICU on memory, or any other cognitive indices; No association between higher WHO CPS grade and severity of cognitive impairment; Level of education predicted delayed memory; No association between subjective cognitive complaints and objective tests; No differences in cognitive assessments between patients with/without anxiety or depression.
Calabria et al. (2022); Spain	Verbal Memory ² Visual Memory ²	RAVLT-Immediate RAVLT-Delayed ROCFT-Delayed	32.3% 28.7% 16.9%	Hospitalisation was not related to the prevalence and severity of cognitive impairments.
Cecchetti et al. (2022); Italy	Overall memory impairment ³ Verbal Memory	DSF: RAVLT-Immediate:	<u>Covid; HC (M, SD)</u> 6% 4.9; 6.0 35.8; 49.7	

Study; Country	Memory Domain	Cognitive Assessments	Results (% Impaired)	Variables associated with ongoing symptoms
	Visual Memory	RAVLT-Delayed: ROCFT:	7.1; 11.4 0.4; 0.76	
Crivelli et al. (2022); Argentina	Verbal Memory Visual Memory	RAVLT-Immediate: RAVLT-Delayed: BCFT:	<u>Covid; HC (M, SD)</u> 43 (13)*; 50 (9) 8.2 (3.5)*; 10.2 (2.9) 10.50 (3.25)*; 12.27 (2.65)	Significant differences b/w groups' impaired ⁴ scores on memory ($p=0.016$, Cohen's $d=0.73$). Cognitive impairment ⁴ was not associated with severity of illness (determined by WHO severity scale). Anxiety (HADS) was a predictive factor of cognitive impairment.
Delgado-Alonso et al. (2022); Spain	Verbal Memory Visual Memory	FCSRT-Delayed ROCFT-Delayed FGT-Learning FGT-Delayed Free (5min) FGT-Delayed Free(30min) FGT-Recognition	<u>Covid; HC⁴</u> 24% 16% 20%; 0% 20%**; 4% 16%*; 4% 20%**; 2%	Effect sizes were small meaning the cognitive deficit was overall small. Anxiety was weakly associated with memory tasks.
Dondaine et al. (2022); France	Verbal Memory ⁵	FCSRT-Immediate FCSRT-Delayed	18%-24% 23%	Those who received O ₂ therapy had greater memory impairments in cue efficiency index and total recall.
Dressing et al. (2022); Germany	Verbal Memory ⁴ Visual memory ⁴	HVLT-Learning HVLT-Delayed HVLT-Recognition BVMT-Learning BVMT-Delayed BVMT-Recognition	10% 23% 13% 23% 13% 26%	

Study; Country	Memory Domain	Cognitive Assessments	Results (% Impaired)	Variables associated with ongoing symptoms
Ferrando et al. (2022); USA	Immediate Memory Delayed Memory	RBANS RBANS	CS; NCS (M, SD) ⁶ 87.7(17.1)***; 94.3(11.5) 89.6(14.8)***; 97.0(12.8)	Severity of acute Covid-19 illness was associated with cognitive impairment. Depression was predictive of “extremely low” ⁶ test scores.
García-Molina et al. (2022); Spain	Verbal Memory	RAVLT-Immediate: RAVLT-Delayed: RAVLT-Recognition:	Covid; Control (M, SD) 41.29 (10.11)*; 45 (8.06) 7.69 (2.59)*; 9.22 (2.74) 11.69 (2.79)*; 12.5 (3.19)	
García-Sánchez et al. (2022); Spain	Verbal Memory	Distribution of test scores (% test scores) ⁷		No correlations found between anxiety subscale of HADS and cognitive function.
		DSF <8 9–24 >25 RAVLT-Immediate <8 9–24 >25 RAVLT-Delayed <8 9–24 >25 RAVLT-Recognition <8 9–24 >25		
	Visual Memory			

Study; Country	Memory Domain	Cognitive Assessments	Results (% Impaired)	Variables associated with ongoing symptoms
		ROCFT-Delayed <8 9–24 >25	13 (20.63%) 18 (28.57%) 32 (50.79%)	
Hellgren et al. (2021); Sweden	Immediate Memory ⁶ Delayed Memory ⁶	RBANS RBANS	25% 19%	No significant differences between normal and abnormal MRI groups re frequency of patients with cognitive impairments or with fatigue; No association between RBANS total score, time in hospital or scores on WHO CP-Scale.
Krishnan et al. (2022); USA	Verbal Memory ⁴ Visual Memory ⁴	LM-Immediate LM-Delay LM-Recognition RAVLT-Immediate RAVLT-Recognition BVMT-Learning BVMT-Delayed BVMT-Recognition	15% 10% 0% 10% 5% 15% 10% 20%	50% non-hospitalised and 63% of hospitalised patients demonstrated cognitive impairments on 3 or more measures. 40% moderate-severe anxiety (BAI); 35% moderate-severe depression (BDI-II); 85% (n=13) fatigue (FSS)
O'Connor et al. (2022); USA	Verbal Memory	AVLT	<u>Long-COVID vs. No-COVID</u> $\beta = -0.67$	No significant differences between Long-Covid and Covid groups on memory.
Voruz, Cionca, et al. (2022); Switzerland	Verbal Memory	GB-Immediate: GB-T1-T3 Free: GB T1-T3 Total:	<u>Anosognosic; Nosognosic</u> <u>(M, SD)</u> 15.53 (± 0.76); 15.87 (± 0.47)** 8.50 (± 6.59); 32.37 (± 6.18)*	

Study; Country	Memory Domain	Cognitive Assessments	Results (% Impaired)	Variables associated with ongoing symptoms
	Visual Memory	GB-Delayed Free: GB-Delayed Total: DSF: ROCFT-Immediate: ROCFT-Delayed:	44.00 (±3.45); 46.05 (±2.81)*** 10.81 (±2.77); 12.96 (±2.25)** 14.88 (±1.56); 15.75 (±0.61)** 8.12 (±2.07); 8.17 (±2.16) 17.10 (±6.77); 19.43 (±6.30) 21.92 (±7.74); 24.22 (±6.53)	
Voruz, de Alcantara, et al. (2022); Switzerland	Memory (8-tests) ^{8,9}	Total ≥5 low test-scores Mild ≥2 low scores Moderate ≥5 low scores Severe ≥2 low scores	3.31% 10.20% 6.25% 25%	

¹= no details given regarding analysis to define “% of patients with altered cognitive tests”; ² = Cognitive impairment of T-scores <36; ³= Cognitive impairment was defined by a performance lower than the assessment-specific normative values in at least two tests within the same domain; ⁴ = Cognitive impaired classified as z score of <1.5 SD below assessment-specific normative data; ⁵ = Cognitive impairment defined as T-score of <35, corresponding to 1.5SD from normative mean; ⁶ = Cognitive impairment defined as z-score of <2SD from assessment-specific normative mean; ⁷ = Scores defined according to Guilmette et al. (2020) Pc < 8 as below average and exceptionally low score, Pc 9–24 as low average score and Pc > 25 as average or above; ⁸ = the percentage of the normative population who would exhibit one or more, two or more, three or more, or four or more abnormally low scores, applying a conservative threshold < 5th percentile which is equal to <1.67SD from normative mean; ⁹ = Cumulative percentages of patients significantly above the estimated percentage for the normative population after false detection rate (FDR) correction.

Abbreviations: AVLT: Auditory Verbal Learning Test; BAI: Beck Anxiety Inventory; BCFT: Benson’s Complex Figure Test; BDI-II: Beck Depression Inventory- Second Edition; BVMT: Brief Visuospatial Memory Test; Digit Span-2: Subtest (WMS); DSF: Digit Span Forwards; FCSRT: The Free and Cued Selective Reminding Test; FGT: Figural Memory Test (Vienna Test System); FSS: Fatigue Severity Scale; GB: Grober and Buschke; HADS: Hospital Anxiety and Depression Scale; HVLT: Hopkins Verbal Learning Test-Revised; LM: Logical Memory (WMS); ; RAVLT: Rey Auditory Verbal Learning Test; RBANS; Repeatable Battery for Assessment of Neuropsychological Status; ROCFT: Rey-Osterrieth Complex Figure Test.

Significance levels * = p<0.05; ** = p<0.01; *** = p<0.001.

8.3.2 *Attention*

Seventeen studies assessed attention overall as can be seen in Table 6 whereby results are presented as a percentage of the participants with impairments unless otherwise stated. Of ten studies that reported percentages of participants with attentional impairments, nine studies revealed impairments of attention ranging from 5% to 41.2% (Albu et al., 2021; Birberg Thornberg et al., 2022; Calabria et al., 2022; Delgado-Alonso et al., 2022; Dondaine et al., 2022; García-Sánchez et al., 2022; Hellgren et al., 2021; Krishnan et al., 2022; Voruz, de Alcantara, et al., 2022). The only study to report 0% of participants with impairments was that of Dressing et al. (2022) which was rated as being of 'High' quality. The test used in this study was the Digit-Span Forwards (DSF). An evident commonality among those studies with no-to-minimal impairments observed were the tests used including the Digit-Span Forwards and Coding tests (Albu et al., 2021; Dressing et al., 2022; Hellgren et al., 2021; Krishnan et al., 2022). However, these four studies also had the smallest sample sizes, ranging from 20-35. There were differences in measures used including computerised tests (d2 Test of Attention) and those commonly used within ADHD research (CPT-II & CPT-3). Higher rates of impairment were found among studies using CPT-II & CPT-3 (Calabria et al., 2022; Dondaine et al., 2022; García-Sánchez et al., 2022; Krishnan et al., 2022). Studies consistently reported impairments across sustained and selective attention, particularly on tasks involving an EF aspect such as Stroop and the Eriksen Flanker Task.

Among the seven studies to analyse their results using a comparison group, five revealed significantly worse attentional performance in the PCS sample (Crivelli, Calandri, et al., 2022; Ferrando et al., 2022; Ortelli, Benso, et al., 2022; Ortelli, Ferrazzoli, et al., 2022; Voruz, Cionca, et al., 2022). Among four of the studies where significant differences were found, healthy controls were used as comparators (Crivelli, Calandri, et al., 2022; O'Connor et al., 2022; Ortelli, Benso, et al., 2022; Ortelli, Ferrazzoli, et al., 2022). In one study, only

performance on a measure of sustained attention was significantly different between PCS participant and controls, while performance on divided attention was not significantly different (Voruz, Cionca, et al., 2022).

Table 6*Results: Attention*

Study; Country	Cognitive Assessment	Results (% Impaired)	Variables associated with ongoing symptoms
Albu et al. (2021); Spain	DSF	<u>ICU; Non-ICU¹</u> 18%; 5%	
Birberg Thornberg et al. (2022); Sweden	RBANS Attention-Index Digit-Span Coding	<u><1.5SD; <2D</u> 31.0%; 17.1% 23.7%; 19.8% 36.2%; 26.9%	
Calabria et al. (2022); Spain	CPT-II ² Omissions Commissions Variability Hit RT Detectability Perseveration Hit SE Hit RT ISI Change	36.8% 21.3% 41.2% 36.1% 19.8% 41.2% 27.2% 31.6%	Fatigue was predicted by depression, apathy, anxiety and working memory and sustained attention; the greater the cognitive deficits, the greater the total fatigue scores.
Crivelli et al. (2022); Argentina	TMT-A: DSF: DSB: WAIS-Coding:	<u>Covid; HC (M, SD)</u> 47 (25)***; 29 (7) 5.89(1.30)***; 6.89 (0.93) 4.04 (1.19)***; 5.09 (0.95) 11.8 (3.7)**; 13.5 (2.9)	Significant differences b/w groups' impaired ³ scores on attention ($p < 0.001$, Cohen's $d = 1.2$).
Delgado-Alonso et al. (2022); Spain	TMT-A Cognitrone-Time Cognitrone-Correct Rejection WAF-Intrinsic Alertness (visual)	<u>Covid; HC³</u> 8%** 10.6; 6.2% 14.9%; 4.2% 22.4%*; 6%	

Study; Country	Cognitive Assessment	Results (% Impaired)	Variables associated with ongoing symptoms
	WAF-Crossmodal Divided Attention WAF-Unimodal Selective Attention WAF Visual vigilance WAF Smooth pursuit eye movements	8.3%; 6.1% 21.7%*; 6.2% 4.3%**; 4.3% 21.7%*; 6.2%	
Dondaine et al. (2022); France	CPT-3 ² Detectability Omissions Commissions Preservations Hit RT Hit RT ISI Change Hit RT Block Change DSCT	16% 13% 34% 13% 13% 8% 11% 5%	
Dressing et al. (2022); Germany	TMT-A ³ DSF ³	10% 0%	
Ferrando et al. (2022); USA	RBANS	<u>CS; NCS (M, SD)</u> ⁴ 92.6 (14.9)**; 103.6 (15.5)	
García-Molina et al. (2022); Spain	DSF	<u>Covid; Control (M, SD)</u> 5.79 (1.06); 5.75 (1.19)	
García-Sánchez et al. (2022); Spain	Distribution of test scores, M, range (M%) ⁵ CPT-II <8 9–24 >25	18.66, 10-33 (29.62%) 16.25, 1-29 (25.79%) 28.08, 14-42 (44.58%)	
Hellgren et al. (2021); Sweden	RBANS Attention ⁴	9%	

Study; Country	Cognitive Assessment	Results (% Impaired)	Variables associated with ongoing symptoms
Krishnan et al. (2022); USA	TMT-A ³ Digit Span-2 ³ Coding ⁶ Symbol Search ⁶ CPT-3 ² : Omissions Commissions Hit RT Hit RT ISI Change Hit RT Block Change	20% 5% 5% 6% 7% 0% 21% 36% 21%	
O'Connor et al. (2022); USA	<u>d2 Test-of-Attention</u> Correct-Items: Sustained Attention: <u>EFT</u>	Long-COVID vs. No-COVID: $\beta = -0.82$ $\beta = -0.69$ $\beta = -0.50$	No significant differences between Long-Covid and Covid groups on attentional tasks.
Ortelli, Benso, et al. (2022); Italy	SAT: Stroop-Reading: Stroop-Colour:	<u>Covid; HC (M, SD)</u> 428.6; 323.5*** 1156.5; 858.5*** 879.3; 726.9***	Significant association between sustained attention (SAT) and fatigue (FSS) (p=0.006) and depression (BDI-II) (p=0.005).

Study; Country	Cognitive Assessment	Results (% Impaired)	Variables associated with ongoing symptoms
Ortelli, Ferrazzoli, et al. (2022); Italy	Sustained Attention Task: Executive-Attention Stroop-Word Naming: Stroop-Colour: Stroop-Reading: Stroop-Inhibition: Navon Task-Total: Navon Task-Congruent Condition: Navon Task-Incongruent Condition:	<u>Covid; HC (M, SD)</u> 421.2 (170.6); 324.7 (41.7)*** 1114.1(314.6); 886.3 (165.7)** 865.5 (155.0); 760.8 (94.8)** 1007.7 (214.1); 878.9 (136.7)* 177.5 (203.0); 66.5 (110.0)* 1055.9 (253.3); 871.3 (185.3)** 994.6 (238.9); 827.1 (157.5)** 1092.7 (268.4) 907.7 (211.7)**	Overall, patients demonstrated slower RTs <i>and</i> greater intra-individual variability in RTs indicative of global slowing and increased fluctuation in response time. Significant association between sustained attention (SAT) and fatigue (FRS $p = 0.029$ & FSS $p = 0.003$).
Voruz, de Alcantara, et al. (2022); Switzerland	TAP (10-tests) ^{7,8} Total ≥ 3 low scores Mild ≥ 2 low scores Moderate ≥ 2 low scores Severe ≥ 2 low scores	7.50% 12.24% 17.02% 12.5%	
Voruz, Cionca, et al. (2022); Switzerland	Sustained Attention: TAP-Item Omissions: TAP-False Alarms: Divided Attention: TAP-Total Omissions: TAP-Total False-Alarms:	<u>Anosognosic; Nosognosic (M, SD)</u> 13.36 (± 9.88); 11.64 (± 9.77) 18.84 (± 27.93); 6.29 (± 9.43)* 1.96 (± 2.37); 1.84 (± 1.99) 1.88 (± 2.55); 0.84 (± 1.41)	

¹= no details given regarding analysis to define “% of patients with altered cognitive tests; ² = CPT-II & CPT3 scores >60 are clinically significant impaired; ³ = Cognitive impaired classified as z score of <1.5 SD below assessment-specific normative data; ⁴= Cognitive impairment defined as z-score of <2SD from assessment-specific normative mean; ⁵ = Scores defined according to Guilmette et al. (2020) Pc < 8 as below average and exceptionally low score, Pc 9–24 as low average score and Pc > 25 as average or above; ⁶= Subtests from the WAIS-IV; ⁷ = the percentage of the normative population who would exhibit one or more, two or more, three or more, or four or more abnormally low scores,

applying a conservative threshold < 5th percentile which is equal to <1.67SD from normative mean; ⁸ = Cumulative percentages of patients significantly above the estimated percentage for the normative population after false detection rate (FDR) correction.

Abbreviations: BDI-II: Beck Depression Inventory- Second Edition; CPT-3: Connors Continuous Performance Test- Third Edition; CPT-II: Connors' Continuous Performance Test-Second Edition; Digit Span-2: Subtest (WMS); Digit-Span: Subtest (RBANS); DSB: Digit Span Backwards; DSF: Digit Span Forwards; EFT: DSCT: Digit Symbol Coding Test; EFT: Eriksen Flanker Test (Flanker Inhibitory Control and Attention Task); FRS: Fatigue Rating Scale; FSS: Fatigue Severity Scale; HADS: Hospital Anxiety and Depression Scale; RBANS; Repeatable Battery for Assessment of Neuropsychological Status; SAT: Sustained Attention Task; Stroop: Stroop Task; TAP: Test of Attentional Performance; TMT-A: Trail Making Test Part-A; WAF: WAF battery.

Significance levels * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

8.3.3 *Executive Function*

Eighteen studies assessed EF as can be seen in Table 7 whereby results are presented as a percentage of the participants with impairments unless otherwise stated.. Eleven studies that reported percentages of participants revealed EF impairments (Albu et al., 2021; Birberg Thornberg et al., 2022; Calabria et al., 2022; Cecchetti et al., 2022; Delgado-Alonso et al., 2022; Dondaine et al., 2022; Dressing et al., 2022; García-Sánchez et al., 2022; Krishnan et al., 2022; Voruz, de Alcantara, et al., 2022). The Trail Making Test-B (TMT-B) was the most frequently used measure to assess EF, and impairments on this test were highest among hospitalised samples (Birberg Thornberg et al., 2022; García-Sánchez et al., 2022).

The prevalence of impairment appeared to be more frequent among those tests which were influenced by processing speed, a cognitive subdomain not analysed in this review i.e., were timed. These tests include Phonemic Fluency, Stroop-Test and Trail-Making Tests (TMT-A, TMT-B); whereas tests of EF without significant processing speed influence included Similarities, Wisconsin Card Sorting Task (WCST) and non-timed facets across fluency tasks such as DKEFS-Category-Switching. Ten studies that assessed EF with a processing speed influence reported impairments ranging from 2% to 64% (Albu et al., 2021; Birberg Thornberg et al., 2022; Calabria et al., 2022; Cecchetti et al., 2022; Delgado-Alonso et al., 2022; Dondaine et al., 2022; Dressing et al., 2022; García-Sánchez et al., 2022; Krishnan et al., 2022; Voruz, de Alcantara, et al., 2022). Tests of phonemic fluency were most consistently reported as impaired regardless of thresholds of impairment defined within the study i.e., 1.5SD, 2SD below the normative mean, the highest being 64% on a Spanish version of FAS fluency task (Albu et al., 2021). However, no details were reported concerning impairment threshold applied in this study as well as this study being rated as ‘Moderate’ quality. Three studies did not reveal impairment on *some* tests (Dondaine et al., 2022; Dressing et al., 2022; Krishnan et al., 2022). These tests included the Trail Making

Test-A (TMT-A) which is used as a measure of attention in other studies (Dondaine et al., 2022); Digit-Span Backwards (DSB), Trail Making Test-B (TMT-B) and a German version of the Colour-Word Interference Test (FWIT) (Dressing et al., 2022); and, Colour Word Interference Tests (CWIT), which involve aspects of inhibition (Krishnan et al., 2022).

Of the seven studies which assessed EF without significant influence of processing speed ability, six studies reported impairments ranging from 5% to 16.3% (Albu et al., 2021; Delgado-Alonso et al., 2022). The highest prevalence of impairment was 16.3% on the Tower of London task (Delgado-Alonso et al., 2022). The authors reported that compared to controls, the frequency of impairment among PCS patients was at least three times more frequent on tests of inhibition.

Where a percentage of impairment was not available (n=6), four studies analysed their results using a comparison group which revealed significantly worse EF performance in the PCS sample (Crivelli, Calandri, et al., 2022; Ferrando et al., 2022; García-Molina et al., 2022; Voruz, Cionca, et al., 2022). One study used healthy controls as comparators, (Crivelli, Calandri, et al., 2022), while the other three utilised COVID-19 participants in control analyses (Ferrando et al., 2022; García-Molina et al., 2022; Voruz, de Alcantara, et al., 2022).

Table 7*Results: Executive Function*

Study; Country	Cognitive Assessment	Results (% Impaired)	Variables associated with ongoing symptoms
Albu et al. (2021); Spain	Working memory: DSB Executive control: PMR	<u>ICU; Non-ICU¹</u> 5%; 15% 62%; 64%	
BirbergThornberg et al. (2022); Sweden	CWIT-Inhibition CWIT-Inhibition/ Switching D-KEFS EF Composite Score	<u><1.5SD; <2D</u> 12.4%; 8.8% 12.8%; 11.9% 10.6%; 7.1%	No significant differences between ICU and non-ICU on EF tasks, or any other cognitive indices; Level of education predicted EF indices
Braga et al. (2022); Brazil	DKEFS Phonemic Fluency	M z-score -0.63 ±0.99	No association between anxiety and depression scores nor severity of COVID-19 symptoms with objective cognitive tests; No differences between hospitalised and non-hospitalised patients on objective cognitive tests.
Calabria et al. (2022); Spain	TMT-A ² TMT-B ² Stroop-Reading ² Stroop-Colour ² Stroop-Inhibition ²	16.7% 23.5% 28% 38.6% 24.2%	Fatigue was predicted by depression, apathy, anxiety and working memory the greater the cognitive deficits, the greater the total fatigue scores.

Study; Country	Cognitive Assessment	Results (% Impaired)	Variables associated with ongoing symptoms
Cecchetti et al. (2022); Italy	Overall executive impairment ³ SDMT: DSB: TMT-A: TMT-BA: Cognitive Estimations: Phonemic Fluency:	<u>Covid; HC</u> 3% 41.8; N/A 3.7; 4.7 42.6; 33.5 75.9; 70.8 4.7; N/A 31.9; 36.3	
Crivelli et al. (2022); Argentina	TMT-B: WCST-Categories: WCST-Preservative:	<u>Covid; HC</u> 107 (76)***; 62 (22) 5.59 (1.04)*; 6.00 (0.00) 2.94 (4.63)**; 0.89 (1.29)	Significant differences b/w groups' impaired ⁴ scores on executive functions ($p < 0.001$, Cohen's $d = 1.4$).
Delgado-Alonso et al. (2022); Spain	TMT-B ⁴ TOL ⁴ N-Back Verbal Test ⁴ INHIB ⁴	10%** 16.3% 14%** 32%**	Subjective mental ability, fatigue and olfactory dysfunction were moderately associated executive function tasks; Anxiety was weakly associated with executive function tasks; Depression was weakly associated only 1 attentional task and 1 executive function task.
Dondaine et al. (2022); France	TMT-A ⁵ TMT-B ⁵ Digit Span-2 ⁵ Phonemic Fluency ⁵ Semantic Fluency ⁵	0% 2% 11% 6% 9%	

Study; Country	Cognitive Assessment	Results (% Impaired)	Variables associated with ongoing symptoms
Dressing et al. (2022); Germany	DSB ⁶ Phonemic Fluency ⁶ Semantic Fluency ⁶ FWIT ⁶ TMT-B ⁶	0% 6% 6% 0% 0%	
Ferrando et al. (2022); USA	TMT-A: TMT-B: Phonemic-Fluency: Semantic Fluency: Stroop:	<u>CS; NCS (M, SD)</u> ⁶ 46.2(12.2); 48.6(11.0) 43.1(9.8)***; 48.4(11.6) 45.4(9.5)**; 50.4(10.7) 47.8(9.5)*; 51.0(11.8) 43.6(9.2)***; 54.6(12.1)	
García-Molina et al. (2022); Spain	DSB: Phonemic Fluency:	<u>Covid; Control (M, SD)</u> 4.31 (1.05); 4.34 (0.86) 35.86 (11.35)*; 41.59 (14.65)	
García-Sánchez et al. (2022); Spain	Distribution of test scores (% test scores) ⁷ DSB <8 9–24 >25 TMT-A <8 9–24 >25 TMT-B <8 9–24 >25	 6 (9.52%) 7 (11.11%) 50 (79.37%) 8 (12.70%) 15 (23.81%) 40 (63.49%) 12 (19.67%) 17 (27.87%) 32 (52.46%)	Multiple-domain impairment (60.3%) was more common than single-domain impairment (39.7%). Multiple-domain impairments most frequent among attention and executive function (9.5%). Attentional impairments most common single-domain impairment (19%) while executive function was less common (4.8%).

Study; Country	Cognitive Assessment	Results (% Impaired)	Variables associated with ongoing symptoms
	Stroop-Colour <8 9–24 >25 Stroop-Inhibition <8 9–24 >25	20 (32.79%) 10 (16.39%) 31 (50.82%) 14 (22.95%) 9 (14.75%) 38 (62.30%)	No correlation found between attention/ executive function with hospitalisation and disease duration.
Krishnan et al. (2022); USA	Phonemic Fluency ⁴ TMT-B ⁴ Matrix Reasoning ⁸ Similarities ⁸ CWIT-Inhibition ⁴ CWIT-Inhibition/ Switching ⁴ WCST ⁴ : Total Errors Perseverative Conceptual Responses Categories SL Errors	16% 5% 5% 0% 11% 0% 11% 16% 11% 11% 16%	
Ortelli, Benso, et al. (2022); Italy	Stroop-Inhibition:	<u>Covid; HC (M, SD)</u> 277.2; 131.6	

Study; Country	Cognitive Assessment	Results (% Impaired)	Variables associated with ongoing symptoms
Voruz, de Alcantara, et al. (2022); Switzerland	Executive Function (11-tests) ^{9,10} Total ≥ 4 low scores Mild ≥ 2 low scores Moderate ≥ 4 low scores Severe ≥ 2 low scores	6.61% 16.33% 12.5% 29.17%	
Voruz, Cionca, et al. (2022); Switzerland	Stroop-Inhibition Working Memory (WM) MEM III: Visuospatial WM ⁵ : TAP-WM Omissions: TAP-WM False-Alarms: Mental Flexibility TMT-BA: Phonemic Fluency: Semantic Fluency:	<u>Anosognosic; Nosognosic (M, SD)</u> 51.43 (± 19.47); 49.93 (± 22.01) 8.12 (± 2.07); 8.38 (± 1.87) 7.50 (± 1.73); 7.72 (± 1.82) 2.38 (± 3.02); 2.25 (± 2.03) 3.85 (± 6.04); 3.04 (± 3.31) 77.46 (± 75.42); 49.72 (± 37.62)* 19.54 (± 6.67); 22.07 (± 6.65) 28.73 (± 10.57); 31.70 (± 8.82)	

¹= no details given regarding analysis to define “% of patients with altered cognitive tests; ² = Cognitive impairment of T-scores < 36 ; ³ = Cognitive impairment was defined by a performance lower than the assessment-specific normative values in at least two tests within the same domain; ⁴=;Cognitive impaired classified as z score of < 1.5 SD below assessment-specific normative data; ⁵ = Cognitive impairment defined as T-score of < 35 , corresponding to 1.5SD from normative mean; ⁶ = Cognitive impairment defined as z-score of < 2 SD from assessment-specific normative mean; ⁷ = Scores defined according to Guilmette et al. (2020) Pc < 8 as below average and exceptionally low score, Pc 9–24 as low average score and Pc > 25 as average or above; ⁸= Subtests from the WAIS-IV; ⁹ = the percentage of the normative population who would exhibit one or more, two or more, three or more, or four or more abnormally low scores, applying a conservative threshold < 5 th percentile which is equal to < 1.67 SD from normative mean; ¹⁰ = Cumulative percentages of patients significantly above the estimated percentage for the normative population after false detection rate (FDR) correction.

Abbreviations: CWIT: Colour Word Interference Test from Delis-Kaplan Executive Function System (D-KEFS); Digit Span-2: Subtest (WMS); DSB: Digit Span Backwards; FWIT: Colour-Word Interference Test (German Version: Farbe-Wort-Interferenztest); INHIB: Inhibition Response (a variant of the go-no go task); PMR: Spanish version of FAS letter phonemic fluency task; RBANS; ROCFT: SDMT: Symbol Digit Modalities Test; Stroop: Stroop Task; TAP: Test of Attentional Performance; TMT-A: Trail Making Test Part-A; TMT-B: Trail Making Test Part-B; TOL: Tower of London; WAF: WAF battery; WCST: Wisconsin Card Sorting Test.
Significance levels * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

8.3.4 Individual Differences Related to Cognitive Function

8.3.4.1 Hospitalisation

All five studies found no significant relationship between hospitalisation and cognitive impairment (Albu et al., 2021; Birberg Thornberg et al., 2022; Braga et al., 2022; Calabria et al., 2022; García-Sánchez et al., 2022). Specifically, two studies that categorised PCS participants as requiring ICU or general ward level care revealed no greater impairments in those in ICU (Albu et al., 2021; Birberg Thornberg et al., 2022).

8.3.4.2 Clinical Variables

The clinical variables assessed differed considerably across studies. Three of four studies reported no relationship between severity of acute COVID-19 disease and cognitive impairment (Birberg Thornberg et al., 2022; Crivelli, Calandri, et al., 2022; Hellgren et al., 2021). Here, all three studies deployed the WHO Clinical Progression Scale to assess disease severity which differed from the measure used by Ferrando et al. (2022) who *did* find a negative impact of disease severity on cognitive function. The measure used here was adapted from the Centres for Disease Control and Prevention COVID-19 symptoms which is scored from 0 to 33. Those who needed supplemental oxygen, a step-down from mechanical ventilation, were associated with significantly worse memory and EF performance (Dondaine et al., 2022).

8.3.4.3 Psychiatric Factors

Two of five studies reported significant negative effects of anxiety across all domains of cognitive function (Crivelli, Calandri, et al., 2022; Delgado-Alonso et al., 2022).

Three of five studies reported significant negative effects of depression on cognitive function, specifically relating to attention and EF (Delgado-Alonso et al., 2022; Ferrando et al., 2022; Ortelli, Benso, et al., 2022). However, in one study, despite reporting a significant relationship, the variance of the cognitive tests explained by depression (BDI-II) or anxiety

(STAI) measures was low, (<15%), suggesting that cognitive deficits were not secondary to psychiatric factors (Delgado-Alonso et al., 2022). The average sample size of the studies which reported significant effects was much smaller at 61.3 compared to 373.5 for the two studies to report no significant effects (Birberg Thornberg et al., 2022; Braga et al., 2022).

Fatigue was associated with poorer cognitive function among all four studies assessing this relationship, particularly within domain of attention (Calabria et al., 2022; Delgado-Alonso et al., 2022; Ortelli, Benso, et al., 2022; Ortelli, Ferrazzoli, et al., 2022).

9.1 Discussion

9.1 Main Findings

Nineteen studies contributed to the results, with 12 reporting prevalence rates. The aims of the current review were to ascertain whether there was evidence of impairments in the cognitive domains integral to GDB among PCS individuals. These included memory, attention and EF, all of which were highlighted as impaired.

Secondly, there was varying evidence of individual and clinical differences impacting cognitive impairment. No significant relationship existed between hospitalisation and cognitive function. Just one of four studies identified a relationship between acute severity of the disease and cognitive function. During the acute stage of the disease, those requiring supplemental oxygen appeared to have worse cognitive function. Depression and to a lesser extent, anxiety, negatively influenced cognitive function. And finally, across all 4 studies, fatigue was consistently found to negatively impact cognitive function, especially in the domains of memory and attention.

9.2 Cognitive Dysfunction

Cognitive impairment was evident across all cognitive subdomains, with varying levels of impairment; the most frequently reported cognitive impairments were found in verbal learning, delayed verbal memory, sustained and selective attention, and, on EF tests, particularly influenced by processing speed. The results indicated that cognitive rehabilitation approaches targeting GDB may be suitable for PCS patients.

The current findings align with a previous systematic review which highlighted impairments across memory, attention and EF, as assessed mainly by screening measures (Daroische et al., 2021). Moreover, the cognitive impairments documented in the current review align with recent neuroimaging data which has demonstrated reduced tissue perfusion (Yus et al., 2022) and widespread cerebral hypometabolism across areas including the

prefrontal cortex, anterior cingulate, insula and caudate nucleus, which was maintained at 6-months' post-infection (Kas et al., 2021). Critically, these areas support GDBs; the anterior cingulate is implicated with initiation, attentional control and problem-solving (Kotchoubey et al., 2003); the orbitofrontal cortex is associated with motivation (Hare et al., 2010); the medial frontal cortex is associated with self-monitoring and error adaptation (Van Noordt & Segalowitz, 2012), while the caudate nucleus is similarly involved in planning the execution of movement, learning, memory, reward motivation and inhibitory control of action. Furthermore, a recent neuroimaging data meta-analysis revealed a particular reduction in the connectivity of the thalamo-cortico-cerebellar pathways which are associated with internal reward systems and self-awareness, essential for GDB (Parsons et al., 2021).

The current review highlighted impairments on tests of short-term and delayed memory which are associated in the research with fronto-parietal and temporal regions of the brain, respectively (Assem et al., 2020; Chai et al., 2018; Hershey et al., 1998; Simons & Spiers, 2003; Zokaei et al., 2019). Impairments in these cortical areas have been corroborated to a varying degree by neuroimaging data of PCS patients (Hosp et al., 2021; Shan et al., 2022). Interestingly, several studies in a recent systematic review of neuroimaging data reported *improvements* in brain abnormalities and memory impairments over time which aligns with patterns from the current review (Shan et al., 2022). For example, in the study by Cecchetti et al. (2022), compared to healthy controls, PCS patients exhibited no significantly different impairments across cognitive domains and compared to other studies within the review, these participants had the longest time since infection (10 months). This suggests that cognitive function might be restored over time. However, without longitudinal data, it is premature to draw such conclusions.

The higher levels of impairment seen on EF tests with a processing speed influence, in particular verbal fluency, aligns with a past systematic review (Daroische et al., 2021)

offering several explanations with implications for service provision. There were no obvious clinical or demographic characteristics which differentiated studies with lower and higher verbal fluency impairments. Verbal fluency tasks capture multiple aspects of executive functioning, including the ability to develop strategies to organise information, maintain rules of the task in working memory (Henry & Crawford, 2004) and inhibit irrelevant answers (Hirshorn & Thompson-Schill, 2006). It may be that a cumulative effect of impairments among these abilities account for the greater impairments, rather than impairment across one specific ability e.g., working-memory. These results may also be associated with the increased rate of fatigue in the PCS population (Ceban et al., 2022), which is known to impact processing speed (Jonasson et al., 2018). This aligns with the current review where all four studies reported a deleterious effect of fatigue on cognitive functioning. The findings highlighted that cognitive domains necessary for GDBs are impaired, indicating that cognitive rehabilitation programmes such as Goal Management Training (GMT) may be appropriate for PCS individuals.

9.3 Individual Differences

There was insufficient evidence across studies to conclude that any individual difference predictably contributed to cognitive impairment. The only consistent finding was that of fatigue which appeared to negatively influence cognitive function.

In the current review, despite higher prevalence rates of impairment reported among hospitalised samples, no association between hospitalisation and cognitive impairment was found in all five studies. This contrasts to previous research which has demonstrated a relationship between these factors (Mathews et al., 2014). However, there are other variables associated with hospitalisation which may account for the cognitive impairments evidenced in the current review. For example, research has prioritised intensive care settings where conditions such as acute respiratory distress syndrome (ARDS) and delirium are more

common and may account for cognitive change (MacLulich et al., 2009; Mikkelsen et al., 2012).

Patients requiring supplemental oxygen had associated greater cognitive impairments, specifically across memory and attentional tasks (Dondaine et al., 2022). This aligns with a recent study of COVID-19 survivors one-month post hospital discharge (Almeria et al., 2020). Hypoxia-related cognitive impairments have been documented in numerous diseases (Lanteaume et al., 2016), including acute-respiratory distress syndrome (Sasannejad et al., 2019).

Several studies within the current review examined whether a relationship existed between neuropsychiatric factors and cognitive function and as outlined above, the evidence was variable. Depression, more so than anxiety, appeared to negatively impact cognitive function, particularly affecting attention and EF. This aligns with a recent study which found that depression, not anxiety, was a significant predictor of cognitive dysfunction despite controlling for individual differences including acute illness severity (Brown et al., 2022). In the aforementioned study, severity of depression was associated with impaired attention and EF, specifically verbal fluency, aligning with the findings of the current review. Mazza et al. (2021) reported similar results. Elevated rates of neuropsychiatric symptoms are related to almost all acute or chronic illness and current findings indicate that PCS is no different (Scott & Schoenberg, 2010; Vanderlind et al., 2021).

Four studies documented the detrimental impact of fatigue on cognitive function, particularly sustained attention. This is in contrast to recent research which did not find any relationship between these variables in a PCS sample, suggesting that fatigue and cognitive dysfunction are two discrete consequences of COVID-19 (Hartung et al., 2022). The current results align with previous research among acquired brain injury populations, where associations between fatigue and sustained attention are observed (Dillon et al., 2022),

relating to the concept that fatigue can temporarily reduce attentional capacity (Zimmermann & Leclercq, 2004).

9.4 Implications for Service Development and Rehabilitation

Goal Management Training (GMT), a standardised cognitive remediation protocol targeting executive functions necessary for GDBs, has recently proven beneficial across nineteen patient populations with cognitive impairments (Stamenova & Levine, 2019), including psychiatric populations with depression and PTSD who face similar executive functioning difficulties (Hagen et al., 2020). A recent systematic review highlighted that GMT has additional beneficial outcomes to long-term memory, indicating that GMT could be an effective rehabilitation intervention for PCS patients (Stamenova & Levine, 2019). GMT may simultaneously target ongoing psychological difficulties in PCS patients (Hagen et al., 2020; Millman et al., 2022). Indeed, a randomised controlled trial analysing the efficacy of GMT in PCS is underway (Hagen et al., 2022). The current findings indicate that standardised rehabilitation strategies targeting GDBs will be important in streamlining services and supporting patients to manage the ongoing cognitive sequelae with the aim of increasing functioning and reducing disability.

9.5 Strengths

The reviewers searched a variety of databases, including the grey literature, to ensure the adequate capture of new studies given the quickly evolving research surrounding COVID-19. The review criteria demanded that studies made concerted efforts that cognitive impairments did not precede COVID-19 infection to limit interference with outcome data. Furthermore, by excluding studies which solely used screening tools to assess cognitive function, the outcomes are likely more sensitive and therefore a more accurate representative of cognitive dysfunction among this emerging population.

9.6 Limitations

There was substantial variance across the studies, making it difficult to draw reliable conclusions, including the varying criteria to define impaired test scores, different control groups used and differing definitions of acute COVID-19 severity. For instance, severity was variously defined via the WHO Clinical Progression Scale (Ortelli, Ferrazzoli, et al., 2022); an adapted instrument from the Centres for Disease Control and Prevention COVID-19 Symptoms (CDC; (Ferrando et al., 2022) and a modified scale developed by the Robert Koch-Institute (Dressing et al., 2022). Moreover, no studies indicated which SARS-Cov-19 variant participants were experiencing, (Delta, Beta, Gamma etc.), which may differentially impact cognitive function.

There was an overrepresentation of studies with hospitalised individuals, reflecting a sampling bias. Additionally, there were several studies where the range of time-from-infection was less than 12 weeks, yet the mean was 12 weeks or more, resulting in potentially skewed cognitive outcomes. It would be recommended that future studies set a definition of PCS patient group according to the NICE-SIGN-RCGP (2021) definition to ensure comparability across studies. Lastly, COVID-19 research is incredibly fast paced and from the time of conception to write-up, several other systematic reviews reporting on cognitive impairments associated with COVID-19 have been published, although without a specific focus on PCS patients (Biagianti et al., 2022; Velichkovsky et al., 2023). The researcher wishes to acknowledge this, although clearly had no prior means of anticipating the publication of said reviews. Further, the writer has made concerted efforts to propose a unique angle examining impairments specifically relating to GDB which may relate to the current reduced workforce and secondly, examine studies which analysed PCS affected individuals, not individuals previously infected with COVID-19 in the broader definition. These aforementioned distinctions are important to highlight in the context of this strategic review.

9.7 Future Research

Currently, much of the research design limits an understanding of the trajectory of cognitive impairment among PCS patients across vocational and occupational environments, indicating further qualitative *and* quantitative longitudinal research with larger sample sizes is needed. It will be important to stratify participants by disease severity in ongoing research to understand the differing impact, using a common outcome measure of disease severity (Marshall et al., 2020). It may be that those who required ICU level of care better reflect a population with post-intensive care syndrome (PICS) (Jackson et al., 2014). Indeed, a recent study remarked that 75% of a PCS sample from ICU met PICS criteria and their needs may differ from other subgroups of PCS patients (Nanwani-Nanwani et al., 2022). Future research ought also to increase the representation of those who did not require hospitalisation for their symptoms.

Additionally, individuals with pre-existing as well as no prior cognitive impairments require inclusion in future research, to determine the impact of SARS-Cov2-19 on current cognitive functioning. Existing research data of pre-pandemic outcomes may be deployed to evaluate intra-individual changes in those who were infected and later developed PCS. Research in this area for future consideration ought also to expand cross-culturally, paying particular attention to different sociodemographic and ethnic backgrounds, given that COVID-19 has disproportionately affected Black, Asian and Minority Ethnic communities (Nolen et al., 2022). As above, higher quality studies are needed to enable researchers and clinicians to draw accurate conclusions.

9.8 Conclusion

This review indicates that cognitive impairments are evident across domains of memory, attention and executive function in PCS participants and that certain psychological factors, notably fatigue, have a negative influence on cognitive functioning. Time from infection in studies included in the current review ranged from 3.4 to 10 months, so future

longitudinal research is required to establish whether impairments persist or alleviate over time. For the significant number of PCS patients currently out of work, standardised interventions targeting GDBs may prove effective in alleviating disability and increasing well-being in the short-term.

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11.1 Chapter One Appendixes

11.1 Modified Newcastle-Ottawa Scales

Cross-sectional Studies

i. Selection	
<i>1. Representativeness of the sample</i>	<ul style="list-style-type: none"> a. Truly representative of target population (e.g., nation-wide database)* b. Somewhat representative of target population (e.g., city, hospital/hospital system, social media survey)* c. Selected groups of participants (i.e., by subgroup: sex, race, occupation, insurance coverage, disease severity, ICU treatment status, pre-existing condition). Restricting inclusion criteria to adults does not count as a subgroup. d. No description of the derivation of the included subjects
<i>2. Sample size</i>	<ul style="list-style-type: none"> a. Justified and satisfactory (including pre-determined sample size calculation)* b. Not justified (not pre-determined through calculation) c. No information provided
<i>3. Non-respondents</i>	<ul style="list-style-type: none"> a. Comparability between respondents and non-respondents is established, and the response rate is satisfactory (>60%) or proportion of target sample recruited attains pre-specified target* b. Unsatisfactory recruitment rate, no summary data on non-respondents, or the comparability between respondents and non-respondents is unsatisfactory c. No description of the response rate or the characteristics of the responders and non-responders
<i>4. Ascertainment of the exposure [COVID-19]</i>	<ul style="list-style-type: none"> a. Validated measurement tool (laboratory testing), or secure medical/hospital records indicative of test positivity** b. Diagnosis based upon clinical judgment, or record-linkage (e.g., ICD)* c. Parental/personal recall only (self-report of test positivity)
ii. Comparability	
<i>1. Comparability of subjects in different outcome groups on the basis of design or analysis</i>	<ul style="list-style-type: none"> a. Data/ results controlled/adjusted for both age and sex, or separate proportions/analyses reported for each age group and sex* Star given if comparison to normative data (if adjusted for age and sex)* b. Data/results controlled/adjusted for comorbidities, or separate proportions/analyses reported for each comorbidity identified*
iii. Outcome	
<i>1. Assessment of the outcome [cognitive function]</i>	<ul style="list-style-type: none"> a. Confirmation of outcome i.e., validated objective assessment tool (e.g., established cognitive testing e.g., Digit Span, Trail Making Test) for at least 1 domain of interest* (<i>inclusion criteria</i>) b. Structured/systematic interview or questionnaire conducted by trained healthcare or research professional c. Unstructured self-report (i.e., open question regarding symptoms) and/or not conducted by trained healthcare or research professional (i.e., self-administered) or not stated d. No description
<i>2. Statistical methodology</i>	<ul style="list-style-type: none"> a. Statistical test used to analyse the data clearly described and appropriate* b. Statistical test not appropriate, not described or incomplete

Prospective Cohort Studies

i. Selection	
<i>1. Representativeness of the exposed cohort [tested/clinically diagnosed COVID-19 positive]</i>	<ul style="list-style-type: none"> a. Truly representative of target population (e.g., nationwide database)* b. Somewhat representative of target population (e.g., city, hospital/hospital system, social media survey)* c. Selected groups of participants (i.e., by subgroup: sex, race, occupation, insurance coverage, disease severity, ICU treatment status, pre-existing condition). Restricting inclusion criteria to adults does not count as a subgroup. d. No description of the derivation of the cohort
<i>2. Selection of the non-exposed cohort [tested COVID-19 negative/never tested COVID-19 positive or suspected to have had COVID-19]</i>	<ul style="list-style-type: none"> a. Drawn from the same community/database/hospital as the exposed cohort* b. Drawn from a different source c. No description of the derivation of the non-exposed cohort d. No non-exposed cohort included
<i>3. Ascertainment of exposure [COVID-19]</i>	<ul style="list-style-type: none"> a. Validated measurement tool (laboratory testing), or secure medical/hospital records indicative of test positivity* b. Diagnosis based upon clinical judgment, or record-linkage (e.g., ICD)* c. Parental/personal recall only (self-report of test positivity)
<i>4. Evaluation outcome of interest (cognitive dysfunction) present prior to COVID-19 infection</i>	<ul style="list-style-type: none"> a. Yes* [reporting of this was part of inclusion criteria] b. No
ii. Comparability	
<i>1. Comparability of cohorts on the basis of the design or analysis</i>	<ul style="list-style-type: none"> a. Data/ results controlled/adjusted for both age and sex, or separate proportions/analyses reported for each age group and sex* Star given if comparison to normative data (if adjusted for age and sex)* b. Controls/adjusts and/or matches and/or regression analysis for co-morbidities identified* c. Inadequate degree of control
iii. Outcome	
<i>1. Assessment of outcome [cognitive function]</i>	<ul style="list-style-type: none"> a. Confirmation of outcome i.e., validated objective assessment tool (e.g., established cognitive testing e.g., Digit Span, Trail Making Test) for at least 1 domain of interest* [inclusion criteria] b. Structured/systematic interview or questionnaire conducted by trained healthcare or research professional c. Unstructured self-report (i.e., open question regarding symptoms) and/or not conducted by trained healthcare or research professional (i.e., self-administered) or not stated d. No description
<i>2. Was follow-up long enough for outcomes to occur?</i>	<ul style="list-style-type: none"> a. Yes, 12+ weeks from diagnosis of COVID-19 (inclusion criteria)* b. Not stated c. No (<12 weeks; exclusion criteria)
<i>3. Adequacy of follow up of cohorts</i>	<ul style="list-style-type: none"> a. Complete follow up; all subjects accounted for* b. Subjects lost to follow up unlikely to introduce bias: ≤20% of initial sample size lost, <u>or</u> description provided of those lost* c. Lost >20 % of initial sample size during follow up, <u>and</u> no description of those lost d. No statement

11.2 Appendix B: Submission Guidelines for Brain, Behavior, and Immunity



BRAIN, BEHAVIOR, AND IMMUNITY

AUTHOR INFORMATION PACK

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ISSN: 0889-1591

DESCRIPTION

Brain, Behavior, and Immunity, founded in 1987, is the official journal of the [Psychoneuroimmunology Research Society](#) (PNIRS). This innovative journal publishes peer-reviewed basic, experimental, and clinical studies dealing with **behavioral, neural, endocrine, and immune system** interactions in humans and animals. It is an international, interdisciplinary journal devoted to original research in neuroscience, immunology, integrative physiology, behavioral biology, psychiatry, psychology, and clinical medicine and is inclusive of research at the molecular, cellular, social, and whole organism level. The journal features online [submission](#) and review. Manuscripts are typically peer-reviewed and returned to authors within 30 days of submission, leading to timely publication of experimental results. There are no submission fees or page charges for *Brain, Behavior, and Immunity*, which is published eight times a year. Detailed instructions for authors can be found at <http://www.elsevier.com/journals/brain-behavior-and-immunity/0889-1591/guide-for-authors>.

Research areas include: Physiological mechanisms that convey messages between the immune and nervous systems and regulate their functions Stress and immunity, including the role of stress-related hormones and neurotransmitters on the immune system.Actions of cytokines, growth factors and PAMP activation on neuronal and glial cells that regulate behavior, learning, memory and neurogenesisRole of hormones, growth factors and cytokines in the immune and central or peripheral nervous systemsInteractions between the immune system and brain that are involved in development of neurological, psychiatric, and mental health disordersRole of immunological processes in neurodegenerative disordersThe effects of psychotropic medications on immunological mechanisms and their potential relevance to therapeutic interventionsNeuroimaging studies examining how immunological mechanisms affect brain structure and functionClinical trials and experimental studies testing the effects on both immune stimulation and immune suppression on brain and behaviorThe role of microglia in pain, psychological processes and in psychiatric disordersImmunological mechanisms involved in traumatic brain injury and its resolutionImmunologic disorders, infection and behaviorRole of the immune system in development and maintenance of inflammatory and chronic painImmune mechanisms that regulate the blood-brain-interface (BBI)Immune factors that affect health psychologySleep, exercise, immunity and healthImmune system interactions that affect behavior following use of psychotropic drugs, alcohol and other drugs of abuseHealthy aging of the immune system and brainRole of inflammation and stress during perinatal developmentCancer and its treatment, stem cells and their effects on brain behavior and immunity Reciprocal communication between the microbiome, immune and nervous systemsRegulation of nerve injury and repair by the immune systemPsychosocial, behavioral, and neuroendocrine influences on immunity and on the development and progression of immunologically-mediated diseasesNutrition, inflammation, obesity and behaviorGenomics of behavior and immunity

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AUDIENCE

Neuroscientists, Immunologists, Endocrinologists, Physiologists, Psychiatrists, Rheumatologists, Clinicians

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Chapter Two: Empirical Research Paper

Exploration of the Outcomes and Experiences of Previously Hospitalised Patients with Post Covid-19 Syndrome: A Mixed Methods Approach

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Orcid ID: 0009-0009-3002-6635

Word Count: 11, 213

Keywords:

Post Covid-19 Syndrome; Cognitive Impairment; Subjective Cognitive Complaints; Neuropsychological Assessment; Covid-19; PCS

Short Running Title: Post Covid-19 Syndrome Profile (Max 40 characters)

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Prepared in the style for submission to *Journal of Neuropsychology*

12.1 Empirical Paper Abstract

The aim of the current study was to examine previously hospitalised patients with Post Covid-19 Syndrome (PCS) presenting with cognitive complaints to increase the understanding of the neuropsychological profile of patients. The study sought to understand their subjectively reported difficulties, objective cognitive impairments and their relative relationship. This observational, cross-sectional study consisted of 21 PCS patients (47.6% female), on average two years' post-infection. Self-reported experiences were explored via Thematic Analysis; raw scores from objective cognitive assessments were converted into T-scores and those with impaired (T-score <35) scores were identified; one-sample t-tests were conducted comparing the mean T-score of each cognitive test with normative data; Spearman's correlations were conducted to assess the relationship between subjective and objective assessments. Thematic analysis identified four themes concerning the types of difficulties experienced; 'functional consequences', 'cognitive changes', 'new-onset mental-health difficulties' and 'frequency of impact'. No significant differences were identified between the study's overall sample mean and the normative mean across cognitive domains assessed. However, a pattern of impaired individual test scores was observed in which PCS patients presented with primary attentional impairments with an executive component. Several significant relationships were observed between subjective complaints and objective cognitive assessments. Results reinforced the importance of an integrated approach to neuropsychological assessment and formulation featuring both subjective and objective assessment criteria. Future longitudinal research with larger sample sizes and matched controls would determine both the long-term cognitive impacts and extent to which psychological factors may influence cognitive functioning in the PCS population.

13.1 Introduction

Coronavirus disease 2019 (Covid-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is associated with over 637 million infections and 6.62 million deaths globally (WHO, 2023). Of those infected with Covid-19, not all fully recover, experiencing a range of continuing symptoms, including physical, neurological and cognitive difficulties months following initial infection (Chen et al., 2022). The constellation of such ongoing symptoms, or Post-Covid-19 Syndrome (PCS), has now been defined globally and nationally by the World Health Organisation, National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and Royal College of General Practitioners as “symptoms persisting for more than 12 weeks from infection and not explained by an alternative diagnosis” (NICE-SIGN-RCGP, 2021).

Following pressures to manage the acute phase of this illness, healthcare services now face an unprecedented need to respond to facilitate symptom management and potential recovery for people experiencing ongoing consequences of infection by the novel virus COVID-19 PCS (Mahase, 2021). To meet this requirement, the development of effective services will demand a comprehensive understanding of patients’ clinical needs and appropriate treatment options. The purpose of the current research is to develop an enriched understanding of the neuropsychological profile of people experiencing PCS and to establish whether subjective self-reports are consistent with objective cognitive assessments. This will inform treatment approaches and contribute to the growing body of literature on long-term neuropsychological outcomes for people with post Covid syndrome.

Service Developments for Patients with PCS

In 2020, facing this new and significant PCS patient population with complex and multifactorial needs, the Scottish Government invested £4.5 million over three years to

establish a network of clinicians to support the unique mental health needs of previously hospitalised Covid-19 patients (Scottish-Government, 2021). Each health board had autonomy in the development and operation of these networks, known as the Mental Health after Covid-19 Hospitalisation (MACH) services. Patients who were not hospitalised with COVID-19 are not supported via this service, with separate funding streams being established to meet their ongoing needs. The Scottish Government recommended specialised services with multi-disciplinary, integrated approaches to rehabilitation, encompassing treatment of cognitive, emotional, psychosocial and behavioural sequelae (Cossette, 2020; Scottish-Government, 2021). Research that supports practitioners' understanding of the particular needs and characteristics of the PCS population will be essential in providing effective patient care, informing future service development, delivery and refinement.

The literature indicated a risk for developing cognitive impairment among hospitalised samples. For example, those requiring ICU care and mechanical ventilation often present in severe respiratory failure and/or acute respiratory distress syndrome (ARDS) characterised by severe hypoxemia, risking the development of cognitive impairments (Sasanejad et al., 2019). A recent study identified cognitive impairments in 45% of mechanically ventilated PCS patients, although this was assessed via a cognitive screening tool which has low sensitivity to mild or moderate cognitive impairment (Maley et al., 2022). Research has reported direct and indirect effects on the central nervous system (CNS); these include neuroinflammation, encephalopathies (Helms et al., 2020; Nersesjan et al., 2021; Paterson et al., 2020), stroke (Beyrouiti et al., 2020), elevated cerebrospinal fluid antibodies and experiences of low oxygen levels (Franke et al., 2021; Varatharaj et al., 2020), putting individuals at risk for developing cognitive impairments. Higher rates of persistent symptoms, specifically cognitive symptoms in hospitalised patients, may also be impacted by the direct effects of hospitalisation (Dorman-Ilan et al., 2020; Hosey & Needham, 2020;

Matalon et al., 2021; Nakanishi et al., 2021; Ritchie et al., 2020). Accordingly, understanding PCS patients' needs from a neuropsychological perspective will be valuable given the discipline's specialism in 'normal and abnormal functioning of the central nervous system as related to human behaviour' (Beaumont, 2008).

Subjective Experiences of Cognitive Difficulties

To understand the needs of PCS patients and inform the development of person-centred, accessible, easily navigable and comprehensive healthcare pathways, it is necessary to develop an appreciation of the subjective experiences of PCS patients. Identifying patterns of self-reported symptoms via qualitative research is vital to developing an in-depth understanding of patients' needs, particularly for complex and insufficiently understood conditions like PCS (Crowe et al., 2015; Fossey et al., 2002), and is supported via Government initiatives and guidelines (Scottish-Government & COSLA, 2021).

Two recent qualitative studies of cognitive difficulties among those with PCS highlighted marked negative impact across all aspects of their relationships and personal and professional identities (Callan et al., 2022; Humphreys et al., 2021). The subjective experiences of participants in this study were closely linked to aspects of cognitive functioning, especially those of executive function, including planning, decision-making, flexibility and working memory, in addition to selective and sustained attention. The ongoing subjective cognitive complaints (SCCs) reported are consistent with digital surveys (Davis et al., 2021; Ziauddeen et al., 2022), and cohort studies (Taquet et al., 2021). Distinguishing between cognitive impairments per se and the subjective experiences of those dealing with these impacts, Callan et al. (2022) highlighted that self-advocacy and negotiation of healthcare services was challenging for individuals with PCS, faced with additional memory and word-finding difficulties. The authors of this latter study noted the challenges these patients were regularly experiencing were deemed to be minimised, disregarded or attributed

to mental health difficulties, leaving participants feeling invalidated and unsupported. This finding is supported by Ladds et al. (2020), although their sample was not entirely representative of the current PCS definition. As such, to support the development of current and future services, and provide patients with improved management of PCS symptoms, clinicians and researchers must examine the lived experiences of PCS patients in a consistent and purposeful manner.

Subjective and Objective Associations

Understanding the association between subjective complaints and objective cognitive assessments for PCS patients will be important in supporting clinicians' understanding of the symptomology of PCS, to inform approach to assessment, diagnosis and treatment.

In neuropsychological practice, subjective information in the form of patient, or relative/ carer reports are used along with objective information, usually in the form of cognitive assessment data. The challenge for the neuropsychologist is to integrate assessment information into a formulation to enable patients and families to form a clear clinical picture (Scott, 2010). To do so, the clinician must understand the relationship between subjective and objective information gathered in clinical settings. This relationship has been studied in other patient groups which offers valuable insight. Subjective cognitive complaints such as forgetfulness and slowed task completion have previously been associated with objectively measured cognitive function in patients with hypertension (Uiterwijk et al., 2014), mild cognitive impairment (Miranda et al., 2008), early Alzheimer's disease (Lam et al., 2005) and bipolar disorders (Arts et al., 2011). Conversely, several studies have reported no association between SCCs and objective cognitive outcomes among patient groups, including those with dementia and schizophrenia (Galeone et al., 2011; Tomida et al., 2010). When subjective and objective outcomes are inconsistent, this implies a higher reliance by clinicians on objective assessments and behavioural observations.

In a study among participants with affective disorders, where cognitive outcomes were not related to SCCs, the subjective cognitive difficulty was explained by depression rather than by objective cognitive impairments (Svendsen et al., 2012). In recent PCS literature, Voruz, Cionca, et al. (2022) highlighted that those with the most psychological complaints reported the greatest SCCs, while exhibiting minimal objective cognitive deficits, aligning with earlier data (Almeria et al., 2020). It may be that patients' psychological or non-specific symptoms such as fatigue, are more closely related to their SCCs rather than any specific cognitive deficits. Alternatively, cognitive complaints are perhaps too subtle to be identified on formal assessment yet still causing an impact on patients' daily lives. Understanding this relationship further in PCS will be important to support clinical assessment; if subjective and objective reports are inconsistent, clinical formulation may need to identify other contributory factors to explain the perceived cognitive difficulties.

Cognitive Characteristics

Additionally, developing an understanding of the relationship between subjective and objective cognitive difficulties requires a detailed understanding of the objective cognitive characteristics among patients. To date, there is significant variation in the reported prevalence of cognitive impairment among those with PCS, with cognitive symptoms not yet consistently defined or measured.

A review by Honarmand et al. (2020) reported prevalence rates ranging from 35% to 81%, while Del Brutto et al. (2021) reported a lower rate of 21%. Honarmand et al. (2020) highlighted prevalence rates being greatly influenced by the assessment tools administered, ranging from brief screening tools such as the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) to more comprehensive objective cognitive assessment, as would be used in clinical practice by neuropsychologists. Indeed, systematic reviews have reported deficits in executive function, attention, and memory, with most being assessed via screening

tools (Crivelli, Palmer, et al., 2022; Tavares-Júnior et al., 2022). These screening tools, primarily used for detecting dementia, may be limited in their sensitivity to identify cognitive deterioration in younger patients (McIntyre et al., 2019). In an analysis of both MoCA and neuropsychological evaluation among 60 PCS participants, Lynch et al. (2022) found that the MoCA was insensitive in accurately detecting mild and greater degrees of cognitive deficit when compared to neuropsychological assessments. Even if PCS patients score within the “normal” range, yet self-identify cognitive difficulties, a formal neuropsychological assessment was advised by Lynch et al. (2022).

A further challenge is that studies administering comprehensive neuropsychological assessments have reported impairments across numerous cognitive domains; thus relevant cognitive domains implicated in COVID-19 are not clearly defined, requiring additional research. Lauria et al. (2022) reported impairments across processing speed, working memory and executive functions. However, these results were specifically in a sample of adults, aged 65 and older, thereby not representative of the wider population. Wild et al. (2022) reported that compared to healthy controls, PCS participants performed significantly worse on tests of reasoning, verbal learning and processing speed, while short-term memory was intact, indicating domain-specific impairments. Recently, Voruz, Cionca, et al. (2022) reported impairments in domains of cognitive functioning assessed among three groups of PCS participants with varying acute illness severity. Impaired domains included perception, ideomotor praxis, language, executive functions, attention, memory and logical reasoning. Six-nine months’ post-infection, differential impairments were evident across the groups. Compared to the non-hospitalised group, those requiring ICU care exhibited greater impairments on episodic long-term memory and greater anosognosia for memory dysfunction. Indeed, as evidenced across several studies, cognitive impairment may be

impacted across multiple domains, which patently requires further investigation and clarification.

A limitation of studies investigating the cognitive outcomes of COVID-19 is the variation in methodology, notably the variation in the parameters for inclusion criteria, in particular, the defined time period since having COVID-19, further inhibiting the development of a clear picture of the cognitive sequelae among PCS patients. Most studies have defined their PCS patient group as those with a mean ‘time since infection’ of 3 months. This definition potentially permits participants at all stages of SARS-CoV-2 infection to be included. Other studies reported time since infection ranging from 3 weeks (Bungenberg et al., 2022) to 12 months (de Paula et al., 2022).

The variable rates of impairment and cognitive domains implicated prevent a coherent understanding of the patterns of cognitive sequelae of PCS patients, which impedes clinicians’ ability to adequately assess and identify cognitive changes attributable to COVID. This supports the need for the current research project as a valuable and necessary contribution.

Summary and Study Aims

As summarised above, studies offer preliminary evidence showing the putative role of COVID-19 infection in cascading illness extension in domains of cognitive functioning. Patients with cognitive sequelae may require rehabilitation, resulting in increased demand on existing services or the need for health services to create additional services to meet this demand. The literature is currently lacking a detailed understanding of PCS patients’ neuropsychological needs, which can be addressed via qualitative methodology, to understand potential patterns of difficulties experienced by individuals suffering from PCS in the chronic stage of recovery. As described above, the integration of subjective and objective information is a critical aspect of neuropsychological assessment, formulation and treatment

planning. It will be valuable for clinicians to be enabled to distinguish the relationships between subjective complaints and objective assessments when working with PCS patients, in order to offer the most appropriate care for this emerging patient group. To better understand these dynamics, a broader clinical picture of the cognitive domains implicated, and the extent of associated impairments will be necessary.

The current research project seeks to develop our understanding of the neuropsychological profile of individuals with PCS to inform clinical practice and more broadly, to support the development of appropriate services and recommendations for patient care. This research focuses on PCS patients who were previously hospitalised with Covid-19 during the pandemic, who opted-into the MACH service in NHS Grampian with complaints of ongoing symptoms. The project is driven by three empirical research questions:

- 1) What difficulties are previously hospitalised PCS patients with ongoing cognitive complaints reporting?
- 2) Do previously hospitalised PCS patients with ongoing cognitive complaints have objective cognitive impairments?
- 3) Are PCS patients' subjective cognitive complaints consistent with their objective cognitive assessments?

14.1 Methods

14.1 Design

The current study is a single-group, cross-sectional observational design. The data collected as part of the current study draws upon data collected from a newly funded Mental Health after Covid-19 Hospitalisation (MACH) Service within NHS Grampian. The service is led by a Multi-Disciplinary Team (MDT) with input from Neuropsychology Department.

14.2 Recruitment and Procedures

Figure 1 displays the recruitment process of the project. Participants were recruited through the MACH Service between May 2022 and February 2023. At the point where individuals were invited to participate in the current research project, they had already attended a 30-minute screening appointment with either a psychologist or psychiatrist from the MACH service via Attend Anywhere (NearMe), the NHS secure telemedicine service and had completed a series of psychometric measures which are detailed below. By nature of opting into this service, the participants represent a self-selecting sample of patients reporting ongoing subjective complaints.

Following a screening appointment, patients who indicated having cognitive changes via the Cognitive Change Index (CCI) and/or to their treating clinician, were referred to the Neuropsychology Department to undertake a comprehensive neuropsychological assessment. Individuals who declined to participate in the research project received neuropsychological assessment as part of routine clinical practice regardless (Figure 1). Neuropsychological assessments incorporated tests for multiple cognitive domains including short- and long-term verbal and visual memory, selective and sustained attention, processing speed and executive functions. Neuropsychological assessments were conducted by experienced clinicians and lasted approximately 1.5 hours. If participants indicated they were fatigued, a second appointment was made to continue the assessments within 10 days of the initial appointment.

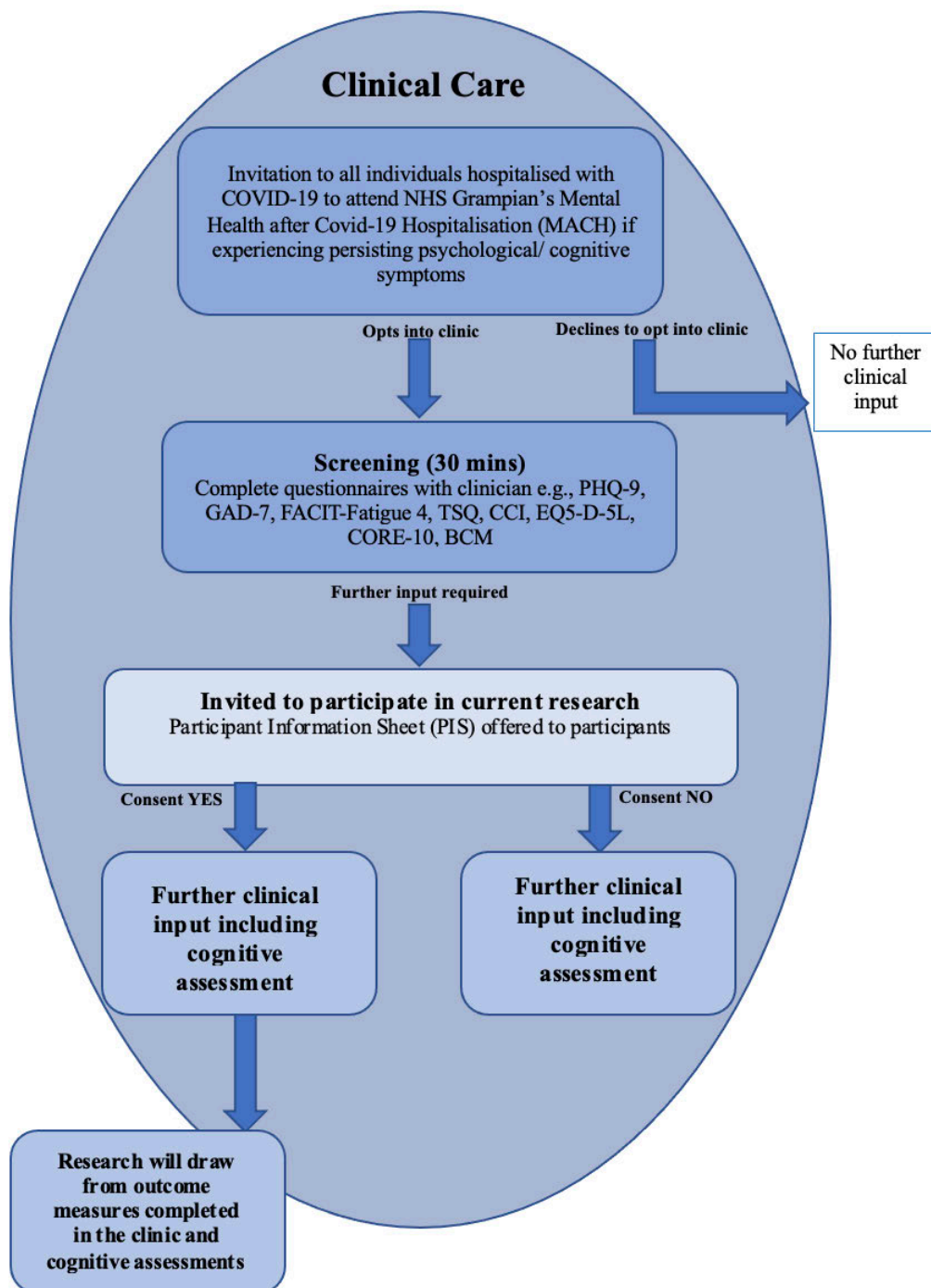


Figure 1: *Flow of Data Collection*

14.3 Participants

The single group of participants consisted of individuals aged 18 and over who were previously hospitalised with Covid-19 within NHS Grampian from January 2020 to present day. Participants were identified as being eligible for the current research project by their

initial treating clinician during the initial screening appointment. The treating clinician was able to identify those who were infected with Covid-19, twelve or more weeks previously, and that their symptoms were not explained by any other diagnosis to meet the criteria for ‘Post-Acute Covid-19 Syndrome’ as defined by NICE-SIGN-RCGP (2021). If individuals indicated that they were experiencing *persisting* cognitive difficulties via the CCI and/ or verbally to the treating clinician, they were deemed eligible for the current research.

Exclusion criteria encompassed individuals with a Learning Disability or Intellectual Disability, as classified by ICD-10; individuals with clinically noted cognitive change, diagnosis of dementia, current psychiatric and/or severe sensory, visual or hearing impairment presentation thought to interfere with cognitive testing; individuals with an active dependency on alcohol or recreational drugs; individuals not able to engage with questionnaires or cognitive assessment due to a limited level of English ability such as English not being their first language and, lastly, individuals lacking capacity, as assessed by the treating clinician. Figure 2 displays the recruitment of participants for the study. One participant indicated that they had experienced a ‘previous head injury’ via a demographic questionnaire. However, the assessing clinician reported this as a knock to the head with no inpatient admission nor clinically noted cognitive change in their medical notes and so they were included in the current analysis.

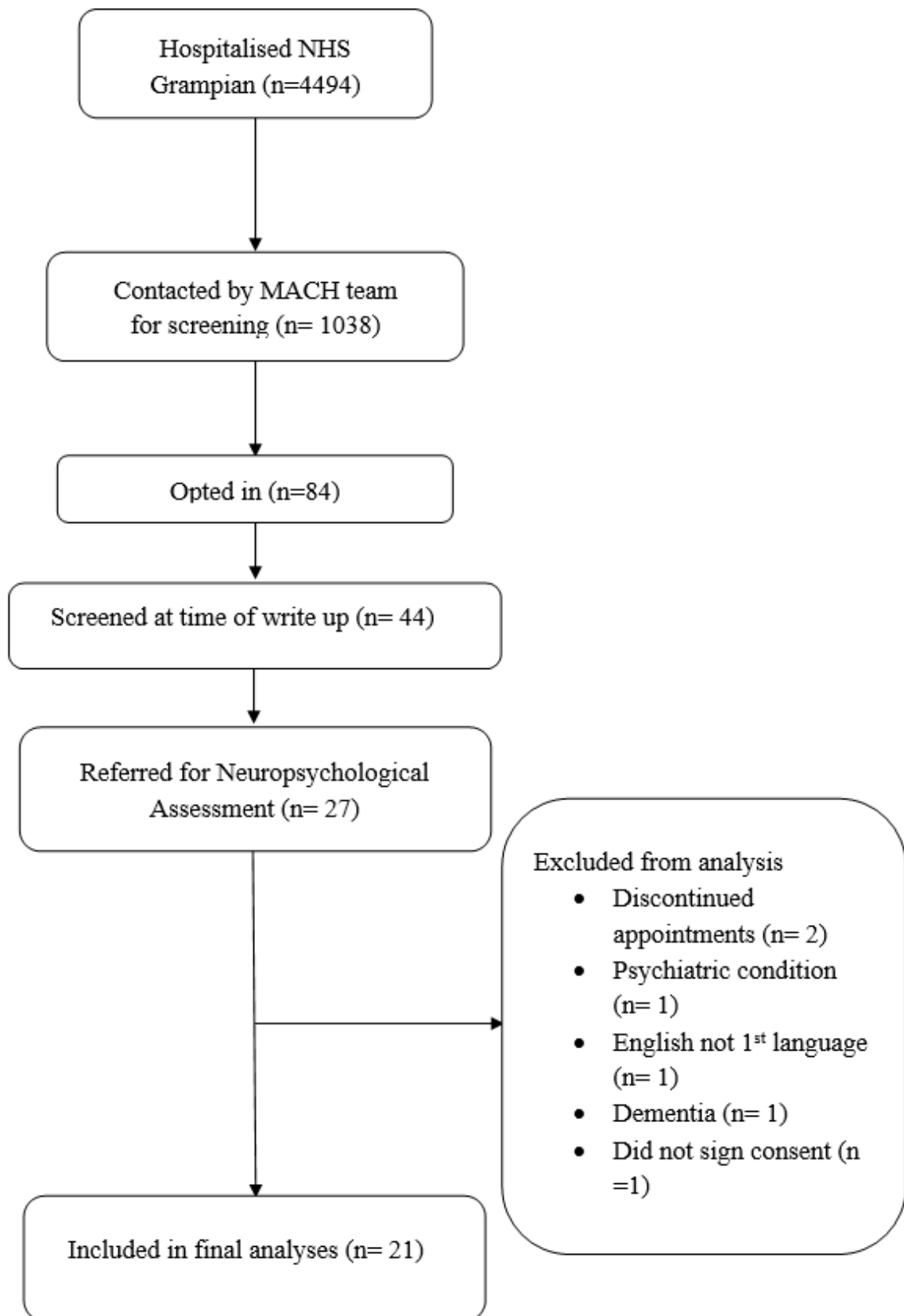


Figure 2: *Participant Flow Diagram*

Almost half (47.6%) of participants were female, identified as White (90.5%) or White-Scottish (9.5%) and were mostly (81%) of working age i.e., younger than 70 years of age. A proportion of participants were ventilated (28.5%) and the mean time elapsed since infection to assessment was two years and two weeks. Table 1 summarises the characteristics of the participants.

Table 1

Participant Characteristics

Characteristic	N (%)	M (SD)/ Median (IQR)
Age Group		
46-50	1 (4.8)	
51-60	7 (33.3)	
61-70	9 (42.9)	
71-75	3 (14.3)	
Ethnic Group		
White	19 (90.5)	
White Scottish	2 (9.5)	
Sex (% Female)	10 (47.6)	
Length of Hospitalisation (days)	-	20.6 (3-95)
Ventilated (% Yes)	6 (28.5)	
Time elapsed between date of admission/ infection to assessment (days)	-	746.4 (571-1035)
GAD-7	21 (100)	13.0 (0-21)
PHQ-9	21 (100)	24.4 (7.9)
FACIT-4	20 (95.2)	22.6 (11.3)

14.4 Ethical Approval

The study was granted approval by the University of Edinburgh Health in Social Science Research Ethics Team (HiSS Reference CLPS107), and sponsored by University of Edinburgh College of Arts, Humanities and Social Sciences (CAHSS) Research Governance Team. Secondly, ethical approval was granted by NHS North East – Newcastle & North Tyneside Research Ethics Committee (REC Reference 21/NE/0175; Approved 21st October 2021 and on 31st May 2022 following a substantial amendment; See Appendix A). The research was subsequently registered with the NHSG Research and Development Department receiving authorisation to commence locally (R&D Reference 2021MH003E; Approved 9th November 2021 and 26th June 2022 following a substantial amendment; See Appendix B).

14.5 Measures

14.5.1 Demographic Information

This included age, sex, ethnicity, gender, number of days spent in hospital and the absence or presence of ventilation.

14.5.2 Subjective Complaints of PCS

The ‘Psychological and Cognitive Changes Since having Covid-19’ (BCM) is a bespoke measure designed by a Consultant Clinical Neuropsychologist in NHSG which captured individuals’ perceived difficulties and changes to their psychological and cognitive function since being infected with Covid-19. Participants were asked to rate on a 4-point Likert scale whether they had experienced any changes in mood, anxiety, attention, planning/organising ability and memory. Responses included “no change”, “minor change”, “moderate change” and “significant change”. Participants were then asked, “Has this affected the following: daily activities, work or study and relationships”. Again, participants rated answers on a 4-point Likert scale where responses included “never”, “rarely”, “sometimes”

and “all of the time”. After participants rated their responses, they were invited to describe “any changes you have experienced in these areas since having Covid-19” in a free text box below. Participants had the option to write as little or as much as they wished in this box to describe their experiences. Internal consistency for the current sample was high ($\alpha = .82$). The measure is displayed in Appendix C.

14.5.3 Objective Outcome Measures

Cognitive Change Index (CCI) (Rattanabannakit et al., 2016).

The CCI is a 20-item, self-report tool measuring perceived cognitive decline across domains of memory, executive function and language. Higher scores indicate more difficulties. Other measures including the Cognitive Failures Questionnaire and the Everyday Memory Questionnaire were considered, although the CCI was chosen following consultation with the Consultant Clinical Neuropsychologist. The language is accessible, facilitating ease of completion. The CCI has shown high internal consistency $\alpha=0.96$ (Rattanabannakit et al., 2016).

Patient Health Questionnaire-9 (Kroenke et al., 2001).

The PHQ-9 is a self-report measure assessing depression severity, which parallels the 9 symptoms used to diagnose Major Depressive Disorder according to the DSM-IV criteria, with higher scores indicating more severe symptoms. The 9-item tool with 4 options measuring levels over the previous two-weeks, ranging from “not at all” to “nearly every day”. Scores range from 0-27 with cut-off scores of 4, 10, 15 and 20 representing clinical criteria of mild, moderate, moderately-severe and severe depression respectively. It is recommended by (NICE, 2012) and used in a variety of populations both clinically and in research. It has good internal consistency ($\alpha = 0.86-0.89$) (Kroenke et al., 2001).

Generalised Anxiety Disorder-7 (Spitzer et al., 2006).

This standardised measure (GAD-7) was originally developed to monitor Generalised Anxiety Disorder (NICE, 2012). The 7-item tool with 4 options measuring levels of anxiety over the previous two-weeks, ranging from “not at all” to “nearly every day”. Scores range from 0-21 with cut-off scores of 5, 10 and 15 representing clinical criteria of mild, moderate and severe anxiety, respectively. It is routinely utilised in primary care and mental health services to monitor reported symptoms with good internal consistency; higher scores indicate more severe symptoms.

Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F; (Hewlett et al., 2011)).

Originally developed for assessing fatigue and tiredness and its effect on daily functioning in cancer patients, this 13-item tool has been validated for use among several other chronic illness populations. There are 5 Likert-type responses, ranging from “not at all” to “very much” and scores range from 0-52 with higher scores indicating less fatigue. It has demonstrated good reliability ($\alpha = 0.90-0.94$) and validity across populations and in long-term conditions such as MS, cancer and neurologic disorders (Butt et al., 2013; Hagell et al., 2006; Hewlett et al., 2011).

14.5.4 Cognitive Assessments

14.5.4.1 Memory

California Verbal Learning Test, Second Edition. (Delis et al., 2000).

This measures both immediate and delayed verbal memory abilities with cueing dimensions. Participants engage in ‘free’ and cued recall of a series of unrelated items (List A). Thereafter, there is a 20 minute ‘long delay’ which measures recall of List A under the

same two conditions of ‘free’ and ‘cued’. Internal consistency is good ($\alpha = 0.78-0.94$) and normed against a more accurate representative of demographic characteristics (*Delis et al., 2000*). The test demonstrates good criterion validity among numerous neurological conditions (*Baldo et al., 2002*). Raw scores are converted to age and sex adjusted z-scores.

The Logical Memory subtest of the Wechsler Memory Scale, 4th Edition (WMS-IV; (Wechsler, 2009))

This test measures verbal memory and learning. Individuals are told two short stories and they are required to recall as much as possible immediately, and after a 20–30-minute delay. For adults aged 65 and above, Story A is repeated. Following the delayed subtest, a recognition test is administered which requires participants to respond “yes/no” to several questions about the stories. The test is sensitive to detect subtle memory changes as an ecologically valid measure paralleling the demands placed on memory during everyday life (*Lezak, 2012*). Raw scores are converted to age adjusted scaled scores.

Rey-Osterrieth Complex Figure Test (ROCF) (Osterrieth, 1944); Rey (1941)

This primarily measures visual memory and visual-spatial constructional ability. Participants are shown a complex figure and asked to copy it, after which, the original image is removed. Participants complete an immediate recall followed by a delayed recall of 20-30 minutes. Internal reliability coefficients for copy condition is greater than $\alpha = 0.60$, and greater than $\alpha = 0.80$ for both immediate and delayed recall conditions (*Strauss et al., 2006*). Raw scores are converted to age adjusted T-scores.

Digits Forwards & Backwards Span from the Wechsler Memory Scale, 4th Edition (WMS-IV; (Wechsler, 2009))

These tests measure attention/short-term retention capacity (DSF) and working memory (DSB) (Lezak, 2012). During both tests, the examiner reads aloud a series of random numbers of increasing sequence length at a rate of one number per second. DSF requires the participant to repeat each sequence exactly while DSB demands the sequence repeated in the reversed order. Scores of 7 and 4-5 are deemed *within normal limits* on DSF and DSB, respectively. On DSB, a score of 3 is deemed as borderline to impaired, depending on the participant's educational background while 2 is impaired regardless (Lezak, 2012).

14.5.4.2 Attention

Elevator Counting & Elevator Counting with Distraction subtests of the Test of Everyday Attention (TEA) (I. H. Robertson, Ward, T., Ridgeway, V., & Nimmo-Smith, I. , 1996; Robertson, 1994).

These two subtests are widely used clinically and are ecologically valid measures of sustained and selective attention (I. H. Robertson, Ward, T., Ridgeway, V., & Nimmo-Smith, I. , 1996). During elevator counting, individuals establish which imagined floor they are on by counting a series of 7 strings of tones. One point is awarded for correctly identifying each string of tones. The normal score is the maximum 7, while a score of 5 or less is considered *definitely abnormal*. Elevator with Distraction requires individuals to count the same pitched tones from the previous test while ignoring higher pitched distractor tones. This mimics the auditory distractions individuals hear in daily life. Here, 10 strings of tones are played for a maximum score of 10 points which are then converted to age-adjusted scaled scores.

14.5.4.3 Executive Function Verbal Fluency (Phonemic and Semantic)

Verbal fluency measures an individual's ability to produce fluent speech as well as 'executive' aspects of verbal behaviour including cognitive flexibility and organisation of information (Lezak, 2012). Assessment of this includes phonemic (FAS) and semantic (animals) fluency. Individuals are given 1-minute to generate as many words that begin with the given letter (FAS) or category (animals). Fluency tests have demonstrated sensitivity to acute deficits following mild-traumatic brain injury (mTBI) (Belanger et al., 2005). Raw scores are converted to age and education adjusted T-scores.

Zoo Map Subtest of the Behavioural Assessment of Dysexecutive Syndrome (Wilson et al., 1998).

The Zoo Map subtest will measure planning and organisational abilities. Participants have two attempts to plan a route through a zoo while adhering to sets of rules with varying amount of instructions. For both attempts, a total sequence score (number of correctly visited places in the correct order), planning time and total time is recorded. Penalties are imposed for rule breaks and lack of speed. An overall profile score is calculated taking into account performance on both attempts. The test demonstrates adequate discriminant and ecological validity (Norris & Tate, 2000; Wilson et al., 1996). Raw scores are not able to be standardised against normative data as this test forms part of a larger battery (BADS); only overall performance on each subtest allows performance to be compared to normative data.

Color Trails Test-2 (D'Elia, 1996).

In Part 2, participants connect digits within circles with alternate colour and completion times are recorded for each trial. Part 2 captures executive aspects of complex information processing, mental flexibility and working memory (Lezak, 2012). Adult version

is for ages 18-89. Normative data is based on a sample of 1528 healthy volunteers across various ethnicities (D'Elia, 1996). Total time taken to complete the task (raw scores) are converted to age and education adjusted T-scores.

14.5.4.4 Processing Speed Color Trails Test-1 (D'Elia, 1996).

Part 1 of the test will assess processing speed as well as non-verbal aspect of sustained and divided attention. Participants are asked to connect digits within circles in ascending numerical order, beginning with 1 to 25. Total time taken to complete the task (raw scores) are converted to age and education adjusted T-scores.

14.6 Data Analyses

14.6.1 Research Question 1: What difficulties are previously hospitalised PCS patients with ongoing cognitive complaints reporting?

In order to address this research questions, questionnaire data from the *Psychological and Cognitive Changes Since having Covid-19 measure (BCM)* was analysed via inductive thematic analysis (Braun & Clarke, 2006; Braun et al., 2012). Firstly, completed outcome measures were transcribed by a clinician in the MACH clinic and transferred to the researcher. The researcher then completed readings and re-readings of the individual transcriptions in Microsoft Word to facilitate familiarity of the data. The researcher then generated initial codes from the individual responses. Initial codes were colour referenced and ascribed provisional theme definitions. The themes were re-read to guarantee that all information was meaningfully coded and had been incorporated into appropriate themes. A sense-checking process was implemented under supervision; the principal change was that the initial theme of 'Adjustment Difficulties' was re-named 'Functional Consequences' in

line with the data and research objectives. The final themes and subthemes were then contextualised and written in line with the current literature.

14.6.2 Research Question 2: Do previously hospitalised PCS patients with ongoing cognitive complaints patients have objective cognitive impairments?

Hypothesis 1: Previously hospitalised PCS patients with ongoing cognitive complaints will have impaired test scores across cognitive domains.

Neuropsychological data was analysed using IBM SPSS V29 (Corp., 2022), or equivalent.

To address **Hypothesis 1**, individual raw scores for each cognitive assessment were converted into T-scores, z-scores and/or scaled scores according to age, sex and education adjusted normative data (where available). To facilitate comparison across tests, z-scores and scaled scores were then transformed to T-scores in SPSSv29. Descriptive analyses were applied to cognitive outcomes which were displayed as mean +/- standard deviation, or median and interquartile range (IQR) for data not normally distributed as assessed by Shapiro-Wilk test.

To identify whether impairments across cognitive domains existed, a definition of ‘impairment’ was needed. ‘Impaired’ test scores were defined as equal to, or less than a T-score of <35 or 1.5 standard deviations (SD) below the normative sample mean. This cut-off criteria is often used in neuropsychological research (Binder et al., 2009). The number of participants with impaired scores and the percentage was reported for each cognitive test.

Hypothesis 2: Previously hospitalised PCS patients with ongoing cognitive complaints will have more cognitive impairments than the normative population.

To determine whether there were significant differences in cognitive test scores among PCS participants and normative data, a series of one-sample t-tests comparing the

mean T-score of each cognitive test among the PCS group with the (where available) normative data were carried out. The normative population mean is 50 (10SD) for T-scores. The cut-off value for determining statistical significance, was set at 0.05. Effect sizes for these comparisons were reported to determine the size of difference. Effect sizes were classified as small (0.20-0.49), medium (0.50-0.79) and large (0.80-1.00) (Cohen, 1988). Two variables of cognitive tests 'CTT-1' and 'TEA-ECD' violated assumptions of normality as assessed by Shapiro-Wilk test ($p > .05$). Outliers in the data were visually inspected via boxplots and there was one extremely low score on CTT-1 which was removed from this test. Subsequently, variable 'CTT-1' was normally distributed. Transforming the variable 'TEA-ECD' using the logarithmic transformation for strongly, positively skewed data in SPSS v29 failed to restore normality. As such, a one sample t-test was carried out regardless as this test is fairly robust to violations of normality (Field, 2017).

14.6.3 Research Question 3: Are PCS patient's subjective cognitive complaints consistent with objective cognitive assessments?

Hypothesis 3: Previously hospitalised PCS patients with more memory complaints will demonstrate greater deficits on memory tests, consistent with their reports.

Hypothesis 4: Previously hospitalised PCS patients with more attentional complaints will demonstrate greater deficits on attentional tests, consistent with their reports.

Hypothesis 5: Previously hospitalised PCS patients with more planning/ organising complaints will demonstrate greater deficits on executive function tests, consistent with their reports.

Concerning all hypotheses above, a reliability analysis was carried out on the *Psychological and Cognitive Changes Since having Covid-19* (BCM) measure. A Cronbach's

alpha (α) over .7 was considered a high internal consistency (DeVellis & Thorpe, 2021; Kline, 2015). The six items assessing perceived changes demonstrated a high level of internal consistency ($\alpha = .82$). The variables of ‘memory’, ‘attention’ and ‘planning/organising’ from the BCM measure were ordinal and violated assumptions of normality using the Shapiro-Wilk test ($p > .05$). As such, a series of non-parametric tests using Spearman’s correlation (Field, 2017) were conducted according to the above hypotheses (one-tailed). A more conservative cut-off value for determining statistical significance, was set at 0.01 to adjust for multiple comparisons.

From a clinical perspective, patients can lack understanding of the conceptual basis of various cognitive domains; in real terms, cognitive domains are interconnected and being asked to accurately report complaints in specific domains may yield inaccurate results (Schoo et al., 2013). For example, subjective complaints of forgetfulness may actually represent attentional lapses rather than objective memory deficits (Lezak, 2012). As such, relationships other than those specific to the above hypotheses were explored.

15.1 Results

15.1 Research Question 1: What difficulties are previously hospitalised PCS patients with ongoing cognitive complaints reporting?

Twenty-one responses were analysed thematically (Braun & Clarke, 2006; Braun et al., 2012). Four main themes and eleven subthemes were identified. The frequency of these themes are reported in Table 2.

15.1.1 Functional Consequences

15.1.1.1 Subtheme: Changes in Functional Abilities

Eleven participants noticed more difficulties functioning compared to their pre-covid-19 selves across multiple environments including changes in their social abilities, identity and ability to work. The majority of the current sample were of working age and many changes to functional abilities were specifically described in relation to this environment. Difficulties functioning were noticed across all levels of task complexity such as getting in and out of the bath to analysing complex information in occupational settings:

“I find it hard to concentrate and focus on tasks, whereas before I would dive in with a clear plan and understanding and be able to quickly see it through to completion”

(P#8)

Functional difficulties were identified driving and at home:

“I haven't driven since Jan 21. I get frustrated not being able to do things e.g., home repairs” (P#9)

Five participants did not distinguish between physical or mental fatigue but noticed that a general feeling of fatigue had a big impact on their functional ability:

“Tiredness and fatigue problematic at times.” (P#9)

15.1.1.2 Subtheme: Emotional Consequences related to Changes in Functional Abilities

Thirteen participants reported emotional challenges related to the changes in their functional abilities. This includes descriptions of frustration, upset, low mood and worry. Two participants reported a loss of confidence, while two described a loss in their identity. Two participants also described social isolation, particularly with colleagues and family members. One participant mentioned that they had to rely more on family members which may contribute to the emotional difficulties associated with a loss of independence.

“I feel really unconfident at work because I now struggle so much with the things I used to be good at...” (P#8)

“I get easily frustrated and annoyed at myself.” (P#21)

“Feeling distanced from my wife” (P#12)

Three participants indicated a lower mood state associated with functional changes:

“[I] developed depression because I can't do what I used to.” (P#20)

15.1.2 Cognitive Changes

15.1.2.1 Subtheme: Memory

Memory difficulties were reported by five participants and included general feelings of forgetfulness, having a poor memory as well as specific problems identified with short-term memory and word recall:

“My memory is awful” (P#6)

15.1.2.2 Subtheme: Attention

Nine participants reported difficulties with attention. Specifically, six participants found it difficult to concentrate on tasks for long periods of time which relates to the concept of sustained attention. Three participants described distractibility and described variations of mind wandering which corresponds to selective attentional abilities (Lezak, 2012):

“[there is] a sense of constant distraction, much more easily distracted” (P#5)

“[I] lose [my] train of thought” (P#11)

“I also find it hard to concentrate as in when reading the paper, I can't seem to finish a story or when watching tv my mind wanders.” (P#14)

15.1.2.3 Subtheme: Executive Function

Six participants described difficulties with abilities included in executive functioning processes such as prioritising, planning, coordinating and completing complex tasks and analysing information. Family members would often take over chores around the house:

“[I] find it difficult to co-ordinate/plan - would get someone else to do it for me.”

(P#20)

15.1.3 New Onset Psychological Difficulties

In addition to the emotional consequences experienced by participants, they described *new-onset* psychological difficulties which were not a direct consequence of their reduced functioning per se, but a consequence of their experiences being infected with Covid-19 and their lives during the pandemic.

15.1.3.1 Subtheme: Anxiety

Seven participants described anxiety generally as well as specifically related to health anxiety and concerns about being around people and crowds again. The descriptions of being easily triggered correspond to the concept of hypervigilance which is embedded health, and social anxiety models (Clark et al., 2005; Richards et al., 2014; Salkovskis & Warwick, 2001):

“Even now I can get anxiety out of nowhere. This is mainly related to health.” (P#8)

“[I've] never been anxious before but now the least thing can make me anxious.”

(P#20)

15.1.3.2 Subtheme: Symptoms of PTSD

Three participants described intrusive memories of being in hospital which resonate with the description of flashbacks as a re-experiencing of the traumatic memory (Brewin, 2015):

“[I have] flashbacks triggered by thoughts, sounds or images can cause emotional response and adrenaline flush.” (P#4)

“Also having flashbacks to ICU.” (P#16)

15.1.3.3 Subtheme: Emotional Dysregulation

Four participants described increases in day-to-day emotional reactivity as well as inhibiting emotional responses. Participants found themselves to be increasingly short-tempered, irritable and less tolerant.

“[My] emotional control [is] affected.” (P#4)

“[I] can be very short tempered and abrupt” (P#11)

15.1.4 Impact

15.1.4.1 Subtheme: Widespread

Seven participants indicated that the impact of living with PCS was noticed across multiple aspects of their lives including in occupational, vocational and social environments.

“affects all aspects of daily life” (P#2)

15.1.4.2 Subtheme: Frequency

Eight participants commented that they experienced these changes very frequently, some every day. Three participants noticed that symptoms fluctuated day-to-day.

“it's [symptoms] like a wave - wiper blade” (P#11)

Table 2

Frequency of themes and sub-themes identified concerning the ongoing difficulties reported by participants.

Themes and sub-themes	Frequency of references to the sub-themes
Functional Consequences	
Changes in Functional Abilities	11
Emotional Consequences related to Changes in Functional Abilities	13
Cognitive Changes	
Memory	5
Attention	9
Executive Function	6
New Mental Health Difficulties	
Anxiety	7
Post-traumatic Stress symptoms	3
Emotional dysregulation	4
Impact	
Widespread	7
Frequency	8

15.2 Research Question 2: Do previously hospitalised PCS patients with ongoing cognitive complaints patients have objective cognitive impairments?

Hypothesis 1: Previously hospitalised PCS patients with ongoing cognitive complaints will have impaired test scores across cognitive domains.

There was some evidence to support this hypothesis as impairments (T-score <35) were observed across some, but not all cognitive domains (Table 3). Impairments were most frequently observed on tests of planning/ organising (Zoo Map Profile) where 63.2% of the sample demonstrated impairments; 36.8% of the sample demonstrated impairments on tests of delayed visual memory (ROCFT-Delayed) and 28.6% on sustained attention (TEA-EC). On tests of selective attention (TEA-ECD) 23.8% of the sample demonstrated impairments and 25% on immediate visual memory (ROCFT-Immediate). Impairments across immediate (CVLT-II SDCR) and delayed (CVLT-II LDCR) cued recall were also observed among 19.0% and 20% of the sample, respectively.

Hypothesis 2: Previously hospitalised PCS patients with ongoing cognitive complaints will have more cognitive impairments than the normative population.

The findings were inconsistent with this hypothesis as mean T-scores in the current sample were not statistically different from the means of normative data across any cognitive assessment ($p > .05$). All effect sizes comparing obtained mean T-scores to normative means were either negligible (Cohen's $d < 0.20$) or small (Cohen's $d 0.20-0.49$) as can be seen in Table 4.

Table 3

Means, standard deviations, effect sizes of neuropsychological measures and their relationships with subjective cognitive complaints.

Cognitive Domain	Cognitive Assessment	n	Impaired† scores n (% of sample)	T-Score Mean (SD)‡	Cohen's D [95% CI]	Memory (BCM) Rho (<i>p</i>)	Attention (BCM) Rho (<i>p</i>)	Planning/ Organising (BCM) Rho (<i>p</i>)
Memory – Verbal								
Learning	CVLT-II T1-	21	3 (14.3)	48.4 (12.9)	0.12	-0.29	-0.46	-0.45
	T5				[-0.55, 0.31]	(.105)	(.021)	(.019)
	DSF	21	4 (19.0)	6.0 (5-9)	-	-0.15	-0.30	-0.40
				raw		(.255)	(.102)	(.036)
Memory-Immediate								
Recall								

Cognitive Domain	Cognitive Assessment	n	Impaired† scores n (% of sample)	T-Score Mean (SD)‡	Cohen's D [95% CI]	Memory (BCM) Rho (<i>p</i>)	Attention (BCM) Rho (<i>p</i>)	Planning/ Organising (BCM) Rho (<i>p</i>)
	CVLT-II	21	3 (14.3)	48.3 (11.1)	0.15	-0.48	-0.51	-0.42
	SDFR				[-0.58, 0.28]	(.013)	(.011)	(.030)
	Logical Memory I	21	2 (9.5)	50.0 (10.0)	0.00	-0.22	-0.09	0.10
					[-0.43, 0.43]	(.171)	(.348)	(.333)
	ROCFT- Immediate	20	5 (25)	46.9 (17.5)	0.18	-0.39	-0.29	-0.32
					[-0.62, 0.26]	(.046)	(.117)	(.087)
Memory-Delayed Recall	CVLT-II	21	2 (9.5)	50.0 (9.2)	0.00	-0.51*	-0.56*	-0.57*
	LDFR				[-0.43, 0.43]	(.010)	(.005)	(.003)

Cognitive Domain	Cognitive Assessment	n	Impaired† scores n (% of sample)	T-Score Mean (SD)‡	Cohen's D [95% CI]	Memory (BCM) Rho (<i>p</i>)	Attention (BCM) Rho (<i>p</i>)	Planning/ Organising (BCM) Rho (<i>p</i>)
	Logical	21	1 (4.8)	50.0 (10.0)	0.00 [-0.43, 0.43]	-0.29 (.099)	-0.18 (.228)	-0.07 (.377)
	Memory II							
	ROCFT-Delayed	19	7 (36.8)	45.6 (18.2)	0.24 [-0.70, 0.22]	-0.43 (.032)	-0.35 (.077)	-0.39 (.049)
Memory-Cued Recall	CVLT-II	21	4 (19.0)	48.6 (12.9)	0.11 [-0.54, 0.32]	-0.48 (.013)	-0.54* (.007)	-0.56* (.004)
	SDCR							
	CVLT-II	15	3 (20)	48.0 (11.0)	0.18 [-0.69, 0.33]	-0.61* (.008)	-0.85** (<.001)	-0.73** (<.001)
	LDCR							

Cognitive Domain	Cognitive Assessment	n	Impaired† scores n (% of sample)	T-Score Mean (SD)‡	Cohen's D [95% CI]	Memory (BCM) Rho (<i>p</i>)	Attention (BCM) Rho (<i>p</i>)	Planning/ Organising (BCM) Rho (<i>p</i>)
Attention								
	TEA EC (n doubtful/ abnormal)	21	6 (28.6)	6.6 (0.9) raw	-	-0.34 (.069)	0.41 (.037)	0.29 (.105)
	TEA ECD	21	5 (23.8)	48.4 (39.9- 73.9)	0.00 [-0.43, 0.43]	-0.34 (.069)	-0.39 (.044)	-0.27 (.122)
Executive Function								
	Phonemic Fluency	21	3 (14.3)	46.4 (9.5)	0.38 [-0.82, 0.07]	-0.11 (.319)	-0.49 (.014)	-0.30 (.091)

Cognitive Domain	Cognitive Assessment	n	Impaired† scores n (% of sample)	T-Score Mean (SD)‡	Cohen's D [95% CI]	Memory (BCM) Rho (<i>p</i>)	Attention (BCM) Rho (<i>p</i>)	Planning/ Organising (BCM) Rho (<i>p</i>)
	Semantic Fluency	21	5 (23.8)	45.9 (13.6)	0.30 [-0.74, 0.14]	-0.20 (.197)	-0.25 (.143)	-0.31 (.083)
	Zoo Map A Plan Time	19	-	60.9 (60.6)	-	-0.12 (.316)	0.10 (.347)	0.15 (.274)
	Zoo Map A Sequence Score	20	-	4.6 (3.0)	-	-0.21 (.189)	-0.22 (.179)	-0.26 (.137)
	Zoo Map Profile§	20	12 (63.2)	2.3 (1.2)	-	-0.27 (.123)	-0.21 (.190)	-0.02 (.466)
	CTT-2	21	2 (9.5)	51.9 (9.8)	0.19 [-0.24, 0.62]	-0.66** (<.001)	-0.55* (.006)	-0.54* (.005)

Cognitive Domain	Cognitive Assessment	n	Impaired† scores n (% of sample)	T-Score Mean (SD)‡	Cohen's D [95% CI]	Memory (BCM) Rho (p)	Attention (BCM) Rho (p)	Planning/ Organising (BCM) Rho (p)
	DSB (n 'Borderline')	21	3 (14.3)	4.0 (3-7) raw	-	-0.49 (.012)	0.31 (.091)	0.37 (0.48)
Processing Speed	CTT-1	21	1 (4.8)	52.7 (7.53)	0.36 [-0.10, 0.81]	-0.51* (.009)	-0.53* (.008)	-0.58* (.003)

Note. CVLT-II T1-T5: California Verbal Learning Test 2nd Ed. Trials 1-5, CVLT-II SDFR: California Verbal Learning Test 2nd Ed. short-delay free recall, CVLT-II LDFR: California Verbal Learning Test 2nd Ed. short-delay free recall long-delay free recall, CVLT-II SDCR: California Verbal Learning Test 2nd Ed. short-delay free recall short-delay cued recall, CVLT-II LDCR: California Verbal Learning Test 2nd Ed. short-delay free recall long-delay cued recall, TEA EC: Test of Everyday Attention-Elevator Counting, TEA ECD: Test of Everyday Attention-Elevator Counting with Distraction, raw: raw score

† Impairment measured as T-score ≤ 35 ; $\leq 1.5SD$, ‡M (SD) or median (IQR) for data not normally distributed, § 'Impaired' Zoo Map Profile scores were defined as scores < 2.44 the M of healthy population from (Wilson et al., 1998).

‘-’= t-test not performed as normative data not available to convert raw scores to norm adjusted scores

BOLD significant at * $p < .01$, ** $p < .001$.

15.3 Research Question 3: Are PCS patient's subjective cognitive complaints consistent with objective cognitive assessments?

Hypothesis 3: Previously hospitalised PCS patients with more memory complaints will demonstrate greater deficits on memory tests, consistent with their reports.

This hypothesis was partially supported in light of several significant relationships observed (Table 3) between subjective memory complaints via BCM 'Memory' variable and objective cognitive tests of delayed verbal and delayed cued memory (CVLT-II LDFR ($p=.010$); CVLT-II LDCR ($p=.008$)).

Hypothesis 4: Previously hospitalised PCS patients with more attentional complaints will demonstrate greater deficits on attentional tests, consistent with their reports.

This hypothesis was not supported as no significant relationships were observed (Table 3) between subjective attentional complaints via BCM 'Attention' variable and objective cognitive tests of sustained and selective attention (TEA ED ($p=.037$); TEA-ECD ($p=.044$)).

Hypothesis 5: Previously hospitalised PCS patients with more planning/ organising complaints will demonstrate greater deficits on executive function tests, consistent with their reports.

This hypothesis was partially supported in light of one significant relationship observed (Table 3) between subjective planning/ organising complaints via BCM 'Planning/ Organising' variable and objective cognitive tests of executive functioning (CTT 2 ($p=.005$)).

16.1 Discussion

The current study sought to examine patients who were presenting with cognitive complaints to increase the literature's understanding of the neuropsychological profile of patients through their self-reported experiences, their objective cognitive assessments and the relationship between these two studied areas. In the present study, subjective reports of the consequences of Covid-19 infection included functional consequences, cognitive changes and new-onset mental-health difficulties, with these challenges affecting participants across all areas of their lives, on a daily basis. No significant differences existed between the overall sample mean and the normative mean across any cognitive domain assessed. However, a pattern of impaired individual test scores was observed across the tests, indicating that PCS patients in the current study presented with primary attentional impairments with an executive component. Significant negative relationships were observed between subjective complaints of memory and objective memory assessments, and between subjective complaints of planning/ organising with specific areas of objective executive function assessments. Together with the individual-level impairments and additional relationships observed, participants' subjective cognitive complaints might better reflect executive attentional impairments, impacting memory processes. In summary, the neuropsychological needs of PCS patients in the current study identified a range of cognitive, emotional, psychosocial, and behavioural difficulties. The findings are presented according to the research questions as laid out in the introduction section.

16.1 Research Question 1: What difficulties are previously hospitalised PCS patients with ongoing cognitive complaints reporting?

Difficulties impacting PCS patients' daily lives were identified via thematic analysis including functional consequences of PCS, cognitive changes, new onset mental-health

difficulties and the relative frequency of these issues. The findings indicated that some PCS patients continue to experience a range of complex difficulties two years' post-infection.

The present findings extend the results of the scarce number of qualitative studies analysing the lived experiences of cognitive difficulties among PCS individuals by offering information that some PCS patients continue to experience cognitive difficulties two years' post infection (Callan et al., 2022; Ladds et al., 2020). The qualitative analysis demonstrated that cognitive processes related to executive function including planning, organising and analysing complex information were reported by PCS patients, in addition to the commonly reported memory and concentration difficulties reported in the literature (Goërtz et al., 2020; Ziauddeen et al., 2022). Difficulties with memory reported by the current sample align with memory complaints among other self-selecting PCS patients (Kozik et al., 2022) and among 66.2% of PCS patients self-reporting brain fog (Jennings et al., 2022). Distinct from the current study, less than half of patients in the latter study were previously hospitalised, indicating that a proportion of the PCS population, including the non-hospitalised population are also experiencing memory complaints. Also common in the literature are self-reported difficulties of concentration, which have been found to persist up to 12-months (Seeßle et al., 2022). The self-reported difficulties in the current sample in concentrating on tasks for long periods of time and an increase in distractibility and mind-wandering relate to concepts of sustained and selective attention in the literature respectively, which are required for other cognitive processes such as learning and memory, in order to function adequately (Fortenbaugh et al., 2017; Lezak, 2012).

Changes in functional abilities relating to varying levels of task complexity were identified. This extends findings of self-reported challenges with activities of daily living and specific difficulties with domestic chores, driving and work in other PCS samples (Ladds et al., 2020; Vanichkachorn et al., 2021). However, time from infection to assessment in the

aforementioned studies were 3-weeks and 3-months, respectively. Participants in the current study experienced changes in their functional abilities, on average two years' post-infection, indicating long-term impact and emphasising the need for proactive interventions to be offered by services.

Reports of emotional consequences related to changes in patients' functional abilities correspond to subjective reports in neurological conditions such as acquired brain injury (Anson & Ponsford, 2006; Fleming et al., 2012), where individuals' emotional, physical and cognitive changes contribute to reduced functional capacity and limited social engagement (WHO, 2006). Indeed, two years' post-infection, the additive impact of ongoing symptoms resulting in reduced functional capacity across a variety of environments, together with illness uncertainty, has been found to markedly affect individuals' psychological state and quality of life (Caruso et al., 2014; Mishel, 1988). It is also important to consider that the current sample were hospitalised and self-seeking support from a mental health service, meaning that they are a potentially skewed population for quality of life measurement (Sareen et al., 2005; Slade et al., 2005).

Due to the self-presenting nature of participants to a mental health service, there was an expectation that psychological difficulties would be observed. Indeed, high levels of anxiety, depression and psychological distress present in the current sample were identified relative to rates from previous prevalence studies on PCS (Colizzi et al., 2022; Fernández-de-Las-Peñas et al., 2021; Titze-de-Almeida et al., 2022; Vanderlind et al., 2021). The qualitative analysis supported previous insight that participants experienced psychological difficulties in addition to the emotional consequences of experiencing a reduced functional capacity and in relation to the present study, these difficulties were ongoing two years' post-infection. Psychological difficulties experienced by the current sample may be due to both direct biological mechanisms (Generoso et al., 2021) and/ or indirect effects including social

isolation, illness and economic uncertainty, a constant threat of infection and even enduring fatigue (Conway III et al., 2020; Freeston et al., 2020; Knox et al., 2022).

Thematic analysis also highlighted that the sample experienced fluctuations in their symptoms day-to-day, which aligns with recent qualitative results (Callan et al., 2022), quantitative findings (Ortelli, Benso, et al., 2022) and the WHO-governed Delphi consensus definition of PCS (Soriano et al., 2022). The fluctuating and associated uncertain nature of symptoms may reinforce participants' negative psychological consequences (Crook et al., 2021; Mishel, 1988). Illness uncertainty plays a role in adverse mental health outcomes in clinical health populations where illness course and duration is often uncertain and unpredictable, including asthma (Hommel et al., 2003) and breast-cancer survivors (Mishel et al., 2005).

This qualitative analysis enriched the knowledge base of the neuropsychological profile of patients who were presenting with cognitive complaints by identifying the types of difficulties experienced, featuring cognitive, functional, and psychological dimensions two years' post-infection.

16.2 Research Question 2: Do previously hospitalised PCS patients with ongoing cognitive complaints have objective cognitive impairments?

All participants in the current sample would be classed as experiencing moderate-severe forms of the acute disease i.e., requiring hospitalisation with varying levels of oxygen requirements, according to the WHO Clinical Progression Scale (Marshall et al., 2020), which may impact cognitive processes (Sasannejad et al., 2019). Furthermore, given the prevalence of cognitive impairment among critical illness survivors (Hayhurst et al., 2020; Hopkins & Jackson, 2006) and PCS patients, requiring both mechanical ventilation (Costas-Carrera et al., 2022; Maley et al., 2022) and supplemental oxygen (Dondaine et al., 2022), the current study expected to observe similar patterns. However, there were no significant differences between the overall sample mean and the normative mean across any cognitive

domain assessed. The current sample size was small, which likely contributed to a lack of effect observed. Further, the tests selected may not have been sufficiently sensitive to detect subtle cognitive impairments among the sample.

Despite the lack of an overall difference, impaired individual test scores as defined by T-score of <35 or 1.5SD below the normative sample mean were observed; the pattern observed across the tests indicate that PCS participants in the current study presented with primary attentional impairments with an executive component. The frequency of participants with impairments on tests of sustained and selective attention were 28.6% and 23.8%, respectively. On a task requiring the integration of complex information to facilitate planning and organisation, 63.2% of patients demonstrated impairments. Further, relatively greater impairments across cued memory recall compared to free memory recall tasks were also observed. This may be explained in the context of the attentional impairments; information must be attended to, in order to then be encoded in memory and subsequently retrieved from memory. Thus, attention is required in the initial stages of memory. However, information not initially attended to is therefore not encoded nor able to be retrieved. That is, no amount of cueing will facilitate retrieval of information which has failed to be encoded in the first place (Lezak, 2012). Impaired scores observed on visual memory tests in the current study (ROCFT-Immediate & Delayed) are higher at 36.8% than findings from recent research. Two previous studies using the same assessment tool reported impairments among 16% of hospitalised participants (Delgado-Alonso et al., 2022) and 16.9% of hospitalised and non-hospitalised participants (Calabria et al., 2022), respectively. These studies both recruited more participants than the current sample which might explain the difference. This could also be explained by the self-selecting nature of the current population where participants presented with cognitive concerns. It suggests that not only verbal, but visual memory is impacted in the present population. It is not clear whether this might be due to visually

attending to information or the storage or retrieval of information however, given the consistency with verbal memory difficulties, it is possible that attentional systems are influencing coding of information.

The sample also displayed high levels of psychological symptoms which have been shown to impact cognitive functioning among other PCS populations (Brown et al., 2022; Mazza et al., 2021) and may have contributed to the current findings. Tests of memory, attention and executive functioning are all highly susceptible to concurrent variables such as anxiety, fatigue, pain, medications and impaired attentional processes (Lezak, 2012). Psychological processes can impact on test performance and cognitive ability, however, the two may also present co-morbidly. A leading hypothesis proposed in the literature is that neuroinflammation following cytokine storms associated with the acute infection, may result in cognitive impairments, and, may underly the comorbid mood disorders observed in PCS patients (e Silva et al., 2022; Vanderheiden & Klein, 2022). A number of participants in the current study showed impairments in cognition, particularly in attention and EF processes, suggesting long-term impact of cognitive difficulties in patients with COVID-19. However, the sample was not of sufficient size to demonstrate a significant effect across all participants. Thus, more research with larger sample sizes is required to explore the long-term impact on cognition of COVID-19 and the variance of this in relation to psychological factors.

16.3 Research Question 3: Are PCS patients' subjective cognitive complaints consistent with objective cognitive assessments?

Comparison between subjective complaints and objective cognitive assessment showed some significant relationships. These were between SCCs of memory with memory tasks and complex information processing; SCCs of attention with memory tasks and complex information processing and lastly, SCCs of planning/ organising with memory tasks and complex information processing.

Subjective complaints of memory were negatively associated with objective tests of delayed free recall (CVLT-II LDFR) and cued recall (CVLT-II SDCR & CVLT-II LDCR) which suggests that *those who did have objective memory impairments were able to accurately identify memory issues*. This aligns with a recent study of PCS patients where a relationship was found between SCC of memory and objective delayed memory performance using the Oxford Cognitive Screen-Plus (Kozik et al., 2022). However, the conclusion that *those who did have objective memory impairments were able to accurately identify memory issues* may be too simplistic an explanation given the few objective impairments on memory tests, and with the relationship being specifically with free recall and cued recall.

Accordingly, it may be that the memory difficulties are due to storage rather than retrieval, as cueing did not help with recall and so it is likely that information was not there to be retrieved in the first place (Delis et al., 2000; Lezak, 2012). Thus, any problems with memory are likely due to information not being stored efficiently, or at all. Attentional processes influence the storage of information where a lack of attention to information means that it is not available for storage (Atkinson & Shiffrin, 1968; Brown & Craik, 2000; Markowitsch, 2000). In addition, negative relationships were found between SCCs of both attention and separately, planning/ organising, with objective tests of delayed free recall (CVLT-II LDFR) and cued recall (CVLT-II SDCR & CVLT-II LDCR). It is possible that SCCs of memory are indicative of attentional processing impairments rather than primary memory difficulties.

Further evidence for this is in the recurring negative relationships observed across all areas of complaints (memory, attention and planning/organising) with tests assessing sustained attention, processing speed (CTT-1) and divided attention (CTT-2) (D'Elia, 1996). The subjective experience of memory difficulties may be more complex than a direct relationship with memory impairment and instead, is related to impaired ability to attend to and/ or processing speed difficulties related to more complex information which impacts on

memory functioning. In relation to the notable model of working memory by Baddeley and Hitch (1974), difficulties with attention and processing speed may impede the opportunity for information to be maintained and manipulated in working memory, preventing long-term storage (Baddeley, 2012; Baddeley & Hitch, 1974). This is consistent with the pattern of low tests scores observed on objective assessments at the individual level.

Consistent with their reports, the negative relationship between SCCs of planning/organising and tests CTT-1 & CTT-2, indicate that individuals are aware and can accurately identify objective difficulties processing information and switching between tasks (mental flexibility) i.e., cognitive skills required for planning and organising in everyday life (Lezak, 2012). The negative relationships between SCC of attention with CTT-1 & CTT-2 suggest that complaints of attention better reflect difficulties processing information and/or with divided attention that patients interpret as an attentional problem. This may explain the unexpected finding that complaints of attention were not associated with poorer test scores on objective tests of attention (TEA). Alternatively, attentional assessments may not have been sensitive enough to detect attentional deficits in this PCS sample.

Of note, there were several relationships not established between subjective complaints and objective tests; subjective information used in correlational analyses was gathered via questionnaires, not during clinical interview, reducing the opportunity to prompt or probe for detailed accounts of difficulties to relate to objective assessment, potentially impacting these findings. Further, the study could not exclude the possibility that other factors accounted for subjective cognitive complaints. For example, anxiety, depression, fatigue and personality variables have explained overall SCCs in other populations including stroke (van Rijsbergen et al., 2019) and older adults (Carrasco et al., 2017; Pearman & Storandt, 2004). This will require further research with larger sample sizes to determine predictive factors.

The study can conclude that participants were aware and able to identify difficulties with complex information processing used in everyday life, reflected in the negative relationship between SCCs of planning/ organising and CTT-1 & CTT-2. For those who *did have objective memory impairments, they were able to accurately identify memory issues*. However, given the few objective impairments across tests of memory, this interpretation is imprecise. More likely is the conclusion that SCCs are indicative of attentional processing difficulties which are impacting memory processes, as this aligns with the pattern of low scores in attention across objective assessments in the present population.

16.4 Strengths & Limitations

While the study did not incorporate a matched control group, age, sex and educational adjusted normative data was used as available, enabling the study to adequately report on the presence or absence of cognitive impairments, strengthening the validity of the findings. Further, the neuropsychological assessment process is a combination of patient account, observation, and normative test data. Many research studies in the current literature consider the test data in isolation, which risks reaching conclusions which are over reliant on tests, posing challenges to clinical validity. The combined analysis of subjective and objective information in the current study is more representative of that which would be gathered in clinical practice, lending to the validity and reliability of the results.

In terms of limitations, the sample is not entirely representative of PCS patients as all were hospitalised. The sample size was smaller than the originally desired number, limiting the power to detect significant quantitative results and conduct predictive analyses. However, as the study's methodology was mixed methods, the sample size was appropriate for the qualitative aspect. The researcher made every attempt to increase the sample size but there were several inhibiting factors, including a small team organising the MACH clinic with limited capacity to conduct assessments, staff absences, and travel disruption due to adverse

winter weather. The observational design of the study, without a control group, prevented any conclusions being made on the causality of cognitive impairment resulting from Covid-19.

The exclusion-inclusion criteria made attempts to reduce potential confounding factors such as those who had previously noted clinical change and those experiencing ongoing psychiatric disorders such as depression. However, this does not entirely control for all factors which may impact cognitive function such as stroke, which is prevalent in hospitalised PCS patients and may have gone unnoticed in hospital (Nannoni et al., 2021).

It is also important to highlight the sampling bias of the current study; participants represent a help-seeking group of individuals which suggests that rates of impairments were expected to be higher than the wider PCS population. Conversely, individuals with greater cognitive impairments may have been missed by failing to opt-in to the service due to difficulties completing questionnaires or changes in their care; some individuals may still be in hospital while others may have required supported living or care homes.

Furthermore, additional demographic information would have supported an understanding of the impact of chronic PCS. Other clinical variables such as medications prescribed while in hospital, whether individuals were in ICU or general wards, previous physical and psychiatric comorbidities as well as social variables such as time taken off work and relationships' status change, would have offered a more detailed characteristic description of the sample. This may have allowed more in-depth analysis of factors potentially impacting cognitive function. While the study reported on the rates of ventilation requirements, the need for supplemental oxygen was not reported, a factor which has been correlated with cognitive impairments in previous research (Almeria et al., 2020; Dondaine et al., 2022).

The conclusions are limited by the neuropsychological tests selected. However, in collaboration with a Consultant Clinical Neuropsychologist with significant experience in the

field, tests were selected by virtue of their relative appropriateness in clinical practice and availability of normative data. The statistical analysis may have benefitted from conducting a factor analysis to establish the factor structure of the chosen cognitive outcome domains, rather than determining these a-priori. Furthermore, while assessments are standardised, it is inevitable that variation existed across the delivery of these assessments. Similarly, room availability meant that variation existed in the time of assessments being conducted; fluctuations in cognitive ability in relation to fatigue and tiredness may have further impacted the reliability and validity of the assessments (Stebbins, 2007).

16.5 Future Research

From a methodological perspective, increased consistency and uniformity in the assessment tools utilised will support researchers and clinicians to make accurate conclusions regarding the characteristics of PCS patients. Longitudinal research is needed to assess the trajectory of difficulties. Similarly, research incorporating larger sample sizes with matched controls will facilitate a better understanding of the objective deficits or potentially lack thereof, among PCS patients.

The literature indicates that coping mechanisms mediate one's sense of coherence and quality of life (Lazarus & Folkman, 1984; Martz et al., 2007) and research, specifically in chronic illness populations, has confirmed this relationship (Eriksson & Lindström, 2007; Kristofferzon et al., 2018; Lo Buono et al., 2017; Poppe et al., 2013; Pusswald et al., 2012). It may be that coping is reduced in the current sample, leading to poorer quality of life. This relationship ought to be researched in the future. Additionally, the illness uncertainty in PCS patients relates to populations with medically unexplained illnesses or functional disorders. Negative health beliefs have been found to predict poor health outcomes in this population which should be a focus of future research in PCS populations (Glattacker et al., 2010;

Knoop et al., 2010; Sharpe et al., 2010). Ongoing research ought also to determine appropriate interventions for this emerging patient group.

16.6 Conclusions & Implications for Clinical Practice

Previously hospitalised PCS patients presenting to the MACH clinic demonstrated a range of ongoing psychological, cognitive and functional difficulties two years' post-infection which were impacting their daily lives. While the overall sample did not significantly differ from the normative mean across any cognitive assessment administered, there were patterns of low scores which indicated a primary attentional executive impairment. Further, while memory complaints were consistent with objective delayed memory assessments, there was no evidence of significant individual impairments with memory at the individual level. This led us to suppose that participants' interpretations of their cognitive difficulties can be explained in the context of impaired processing of complex information, aligning with patterns found on objective assessments. These findings offer guidance for neuropsychological clinical assessment and formulation when working with PCS patients; the integration of subjective and objective information is vital for a holistic understanding of a patient's presentation. Services providing support to PCS patients must consider the multifactorial aspect of this condition, aiming to reduce disability and increase overall well-being.

17.1 Bibliography

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18.1 Chapter Two Appendixes

18.1 Appendix A: Ethical Approval: IRAS Research Ethics Committee



North East - Newcastle & North Tyneside 1 Research Ethics Committee

NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Telephone: 020 7104 8255

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

21 October 2021

Miss Tessa Stanley
Trainee Clinical Psychologist
NHS Grampian
Department of Neuropsychology, Ashgrove House
Foresterhill Road
Aberdeen
AB252ZN

Dear Miss Stanley

Study title: Understanding cognitive function among individuals with post-COVID-19 syndrome
REC reference: 21/NE/0175
Protocol number: CAHSS2108/04
IRAS project ID: 302124

Thank you for your letter of 6th October 2021, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved on behalf of the PR sub-committee.

Confirmation of ethical opinion

On behalf of the Research Ethics Committee (REC), I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Good practice principles and responsibilities

The [UK Policy Framework for Health and Social Care Research](#) sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of [research transparency](#):

1. [registering research studies](#)
2. [reporting results](#)
3. [informing participants](#)
4. [sharing study data and tissue](#)

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral:

<https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/>

If you have not already included registration details in your IRAS application form, you should notify the REC of the registration details as soon as possible.

Approved documents

The documents reviewed and approved by the Committee are:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [PI Confirmation]		23 August 2021
IRAS Application Form [IRAS_Form_27082021]		27 August 2021
IRAS Application Form XML file [IRAS_Form_27082021]		27 August 2021
IRAS Checklist XML [Checklist_27082021]		27 August 2021
Non-validated questionnaire [Demographic Questionnaire, Version 1 23 August 2021]	1	23 August 2021
Organisation Information Document [Organisation_Information_Document_NonCommercial_Version 1 23 August 2021]	1	23 August 2021
Other [Summary of Neuropsychology Assessments, Version 1 23 August 2021]	1	23 August 2021
Other [CV Dr Maggie Whyte Aug21]	1	23 August 2021
Other [CT Confirmation]	1	23 August 2021
Other [EL Certificate - The University Court of the University of Edinburgh and subsidiary companies - NHE-15CA02-0013[55]]	1	23 August 2021
Other [TWIMC - Combined - The University Court of the University of Edinburgh and subsidiary companies - NHE-15CA02-0013[25]]	1	23 August 2021
Other [Good Clinical Practice Certificate]	1	25 January 2021
Other [Provisional Decision Responses Version 1 6 October 2021]	1	06 October 2021
Participant consent form [Consent Form, Version 1 23 August 2021]	1	23 August 2021
Participant information sheet (PIS) [Participant Information Sheet, Version 2 06 October 2021]	2	06 October 2021
Research protocol or project proposal [Protocol, Version 1 23 August 2021]	1	23 August 2021
Schedule of Events or SoECAT [Schedule of Events, Version 1 23 August 2021]	1	23 August 2021
Summary CV for Chief Investigator (CI) [CVTessa-Stanley, Version 1 23 August 2021]		23 August 2021
Summary CV for student [CVTessa-Stanley, Version 1 23 August 2021]	1	23 August 2021
Summary CV for supervisor (student research) [SAWRIKAR Vilas CV Version 1 23 August 2021]		23 August 2021

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:

<https://www.hra.nhs.uk/planning-and-improving-research/learning/>

**IRAS project ID: 302124
correspondence**

Please quote this number on all

With the Committee's best wishes for the success of this project.

Yours sincerely,

Pp. Miss Roma McGeehan

**Mr Paddy Stevenson
Chair**

Email:

Enclosures: "After ethical review – guidance for researchers" [\[SL-AR2\]](#)

Copy to: Miss Charlotte Smith

Lead Nation:
Scotland gram.nrspcc@nhs.scot

18.1.1 IRAS Research Ethics Committee – Approval of Amendment



North East - Newcastle & North Tyneside 1 Research Ethics Committee

NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

16 June 2022

Miss Tessa Stanley
Department of Neuropsychology
Ashgrove House,
Foresterhill Road,
Aberdeen
AB252ZN

Dear Miss Stanley,

Study title: Understanding cognitive function among individuals with post-COVID-19 syndrome
REC reference: 21/NE/0175
Protocol number: CAHSS2108/04
Amendment number: Substantial Amendment 1
Amendment date: 31 May 2022
IRAS project ID: 302124

The above amendment was reviewed at the meeting of the Sub-Committee of the Research Ethics Committee which was held in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Completed Amendment Tool [IRAS - 302124. Amendment 31 5 22 Amendment_Tool_v1_6_06Dec21]	1	31 May 2022
Participant consent form [Consent Form Version 2 27 May 2022]	2	27 May 2022
Participant information sheet (PIS) [Participant Information Sheet Version 4 27 May 2022]	4	27 May 2022
Research protocol or project proposal [Protocol Version 3 27 May 2022]	3	27 May 2022
Validated questionnaire [Psychological and Cognitive Change since COVID-19 (v1) 31 May 2022]	1	31 May 2022

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: <https://www.hra.nhs.uk/planning-and-improving-research/learning/>

IRAS Project ID - 302124:	Please quote this number on all correspondence
----------------------------------	---

Yours sincerely

pp. Miss Roma McGeehan

Mr Christopher Lewis
Chair

newcastlenorthtyneside1.rec@hra.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Miss Tessa Stanley

North East - Newcastle & North Tyneside 1 Research Ethics Committee

Attendance at Sub-Committee of the REC Meeting on 14 June 2022

Committee Members:

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Mr Christopher Lewis (Chair)	Consultant Plastic Surgeon	Yes	
Miss Hazel Jane Maines	Clinical Trials Coordinator	Yes	

Also in attendance:

<i>Name</i>	<i>Position (or reason for attending)</i>
Miss Roma McGeehan	Approvals Administrator

18.2 Appendix B: NHSG Research and Development Department

Research and Development Foresterhill House Annexe
Foresterhill
ABERDEEN
AB25 2ZB



Miss Tessa Stanley
NHS Grampian
Dept of Neuropsychology
Ashgrove House
Foresterhill
Aberdeen
AB25 2ZN

Date 23/06/2022
Our Ref 2021MH003E

Enquiries to Lynn Massie
Extension 53846
Direct Line 01224 553846
Email gram.randdpermissions@nhs.scot

Dear Miss Stanley

STUDY TITLE: Understanding cognitive function among individuals with post-COVID-19 syndrome
PROTOCOL NO: V3; 27.5.22
REC REF: 21/PR/1252
IRAS REF: 302124
AMENDMENT NO: SA01 31.5.22

We have been notified of the above amendment. This has been reviewed and we confirm that it does not alter local NHS Grampian R&D management permission subject to the conditions below:

You may only implement changes described in the amendment notice or letter.

You may only use the documents associated with this amendment if they have been approved by the REC.

Please also note that it remains the responsibility of the Sponsor/Chief Investigator to ensure that you, as PI, are notified of all amendments and provided with the correct documents.

Yours sincerely

Susan Ridge
Non Commercial Manager

cc. Dr Maggie Whyte
Sponsor

Documents provided to us are as listed below:

Participant Consent Form	V2	27.5.22
PIS	V4	27.5.22
Protocol	V3	27.5.22
Questionnaire (Psychological & Cognitive change since COVID-19)	V1	31.5.22

18.3 Appendix C: Psychological and Cognitive Changes Since Having Covid-19

Psychological and Cognitive Changes Since having COVID-19

Since being unwell with COVID-19 have you experienced any changes in:

	Never	Rarely	Sometimes	All of the time
<i>Mood</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Anxiety</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Attention</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Planning and organising ability</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Memory</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Has this affected your:

	Never	Rarely	Sometimes	All of the time
<i>Daily activities</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Work or Study</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Relationships</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please tell us about any changes you have experienced in these areas since having COVID-19.

18.4 Appendix D: Project Protocol



Non-CTIMP Study Protocol

Understanding cognitive function among individuals with post-COVID-19 syndrome.

Sponsor Details	University of Edinburgh College of Arts, Humanities and Social Sciences 55 George Square Edinburgh EH8 9JU Email: cahss.res.ethics@ed.ac.uk Tel: 0131 651 1619 Fax: 0131 242 9447
Protocol authors	Tessa Stanley
Chief Investigator	Miss Tessa Stanley
Sponsor number	CAHSS2108/04
REC Number	21/NE/0175
Version Number and Date	Version 3 Date: 27 May 2022

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operating Procedure

1 INTRODUCTION

1.1 BACKGROUND

COVID-19 began spreading across the globe in early 2020 and was declared a global pandemic in March 2020. A year later, there are increasing reports of people experiencing persisting complaints, including fatigue, neurological and cognitive difficulties. This ongoing experience of symptoms has come to be known as 'long-COVID' or post-COVID-19 syndrome, as defined by the National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (CGP) (2020). People with post-COVID-19 syndrome have described their cognitive difficulties as feeling mentally slow, hazy and struggling to sustain attention throughout the day. Cognitive difficulties affect our ability to remember to carry out tasks, maintain concentration and even have conversations with others. These aspects of daily living use cognitive processes such as memory, attention and complex mental skills called 'executive functions'. It is important for our healthcare systems to be able to identify and treat people with long-COVID for their cognitive difficulties, but first we need to understand what these are in more detail.

Reviewing the Neuropsychological Impact of other SARS-related syndromes

Research has shown damaging neurological and cognitive effects of previous human coronaviruses including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). A largescale study which reviewed acute and post-infectious cognitive impacts of SARS and MERS reported that more than 15% of individuals identified ongoing difficulties with concentration, memory, fatigue and insomnia (Rogers et al., 2020). Given that previous coronaviruses have resulted in individuals experiencing cognitive difficulties, there are concerns that survivors of COVID-19 may be at risk of developing similar difficulties.

Like other respiratory illnesses, COVID-19 can bring about lung complications such as pneumonia and even Acute Respiratory Distress Syndrome (ARDS). ARDS is when there is severely low blood oxygen in the body which can cause the brain to be starved of oxygen and this puts individuals at risk of developing cognitive difficulties. A study by Mikkelsen et al. (2012) reported that 55% of ARDS survivors displayed cognitive difficulties in the areas of memory, executive functioning, and our ability to use appropriate words in conversations 12 months after leaving hospital.

Cognitive Difficulties relating to HIV, Lyme Disease and Chronic Fatigue Syndrome

To explore the potential cognitive difficulties associated with COVID-19, it is useful to understand cognitive difficulties which have been described in other post-infectious and post-viral syndromes which share similar presentations, including HIV (human immunodeficiency virus), Lyme Disease and Chronic Fatigue Syndrome (CFS).

There is no definite cause of cognitive difficulties in HIV-1 infected individuals. However, like COVID-19, the central nervous system might be involved and many people, despite receiving antiretroviral therapy, develop cognitive disorders. There are frequently reported difficulties with attention, working memory, executive functioning and our ability to use appropriate words.

Lyme Disease can affect several systems in our bodies, such as the central nervous system which can cause inflammation of the brain (Fallon et al., 2010). Cognitive difficulties in individuals with Lyme Disease are reported with executive functioning and our memory for language. Problems with attention and the ability to think flexibly are also reported.

Fatigue is often reported following viral infections. Some research suggests that psychiatric disorders such as anxiety and depression worsen chronic fatigue symptoms. However, it is important to note that these psychological and psychiatric disorders i.e., anxiety and depression, are not the sole cause of chronic fatigue. There are various symptoms associated with chronic fatigue and up to 85% of individuals report cognitive difficulties (Komaroff, 1993). Cognitive difficulties are reported with attention, processing information, word finding and reaction times. Moreover, individuals with CFS and post-COVID-19 syndrome both describe their difficulties as being like 'brain fog'.

The similar cognitive difficulties among postinfectious and post-viral syndromes suggests that cognitive difficulties in patients with post-COVID-19 syndrome might include attention, memory and executive functions. While COVID-19 may result in cognitive difficulties for some people, not everyone who is infected will go on to develop these difficulties. As such, it is necessary to identify who is likely to report cognitive difficulties.

Current Research of Cognitive Difficulties & Post-COVID-19 Syndrome

The medium and long-term emotional and cognitive effects of COVID-19 are not fully known, though recent research has begun to explore this. A study by Jaywant et al. (2021) analysed the frequency and profile of cognitive difficulties in COVID-19 patients in the recovery phase; the majority (81%) displayed cognitive difficulties with specific problems in working memory, divided attention and the ability to think flexibly. However, the participants consisted of individuals receiving acute inpatient rehabilitation prior to discharge and cognitive assessments were undertaken 6.6 days (average) after patients' transfer from the acute hospital. This is not therefore a study analysing cognitive difficulties among post-COVID-19 syndrome, as defined by NICE-SIGN-RCGP (2020).

Another study by Hampshire et al. (2020) examined data from cognitive tests from 84,285 individuals who participated in the Great British Intelligence Test who had been infected with COVID-19. They similarly reported difficulties across multiple cognitive areas, including visual attention and verbal problem solving. Critically, the study used an online platform without a clinician to administer cognitive tests. The study also did not use the NICE-SIGN-RCGP (2020) definition of post-COVID-19 and relied on individuals' self-reported perceptions that they had recovered from COVID-19.

Individual Differences Associated with Cognitive Functioning in Post-COVID-19 Syndrome

There are several other factors which will be important in understanding who is at greater risk of experiencing cognitive difficulties among people with post-COVID-19 syndrome. The Hampshire et al. (2020) study demonstrated that increasing levels of respiratory care, ranging from being at home to being in hospital on ventilators,

negatively impacted peoples' overall cognitive scores. This is also the case among SARS survivors and in those requiring mechanical ventilation for critical illness.

On the other hand, the recent post-hospitalisation COVID-19 study (PHOSP-COVID, 2021) analysed information collected via questionnaires on emotional, physical and cognitive outcomes of 1077 COVID-19 patients discharged from hospital in 2020. People were categorised into four groups depending on the severity of scores from their outcome measures. However, interestingly, the severity of outcomes was not related to being on mechanical ventilation. This led the researchers to conclude that severity of ongoing emotional, physical and cognitive difficulties are a result of mechanisms independent of mechanical ventilation.

Cognitive difficulties reported by individuals following hospitalisation with COVID-19 may also be affected by many different psychological and social-psychological factors, including anxiety, depression, being in hospital, witnessing staff wearing PPE, visitor restrictions and the global trauma impact.

The present research study hopes to explore the potential cognitive difficulties among patients with post-COVID-19 syndrome. The information gathered from this research may help us understand more about some of the cognitive difficulties patients experience with long-COVID which could help create the best possible treatment for future patients with long-COVID.

1.2 RATIONALE FOR STUDY

According to the Office for National Statistics, an estimated 1.1 million people in the UK community reported experiencing long-COVID while an estimated 674,000 people reported that their symptoms have negatively impacted on their ability to undertake their day-to-day activities. The Scottish Government has set out the 'Framework for supporting people through Recovery and Rehabilitation during and after the COVID-19 Pandemic' which has a core focus on the rehabilitation of individuals. A major problem faced by healthcare professionals in organising outpatient services to treat this emerging patient group is that the associated symptoms, particularly cognitive symptoms, have not yet been clearly defined or measured. Of particular focus for the current research are ongoing cognitive symptoms associated with COVID-19. People with long-COVID have described these cognitive difficulties as feeling mentally slow, hazy and struggling to sustain attention throughout the day. As such, the present study is primarily concerned with understanding the potential cognitive difficulties among COVID-19 survivors. The information gathered from this research may help us understand more about some of the cognitive difficulties patients experience with long-COVID which could help create the best possible treatment for future patients with long-COVID.

While preliminary evidence exists showing the potential role of COVID-19 infection in cascading illness extension in domains of cognitive functioning, no research studies have used objective assessment methods to study cognitive difficulties among patients with post-COVID-19 syndrome. As such, no clear profile of cognitive difficulties has been established for this patient group using object measures with relevant comparisons to normative data. The analysis of the broader literature related to cognitive difficulties following postinfectious and post-viral syndromes also indicated that not all infected patients will progress to experiencing cognitive decline. No research exists examining potential individual factors related to cognitive difficulties to help identify which patients are more vulnerable to cognitive decline

than others within this patient group. The research is driven by two empirical questions: (i) examine the types of difficulties in cognitive functioning reported among patients with post-COVID-19 syndrome and (ii) what factors related to age, sex, ethnicity, anxiety, depression, fatigue, emotional and psychological distress, quality of life, length of stay in hospital and being ventilated are associated with different types of difficulties in cognitive functioning among patients with post-COVID-19 syndrome. In order to do this, the research study will analyse outcome measures individuals complete during a mental health screening clinic as well as information from cognitive assessments. The procedure will be explained in more detail below.

The present study does not seek to present causal inferences between hospitalisation with COVID-19 and cognitive difficulties, but rather to explore the potential cognitive difficulties among patients with post-COVID-19 syndrome. The information gathered from this research may help us understand more about some of the cognitive difficulties patients experience with post-COVID-19 syndrome which could help create the best possible treatment for future patients with post-COVID-19 syndrome.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To examine the types of difficulties in cognitive functioning among patients with post-COVID-19 syndrome.

2.1.2 Secondary Objectives

To examine what factors related to age, sex, ethnicity, anxiety, depression, fatigue, emotional and psychological distress, quality of life, length of stay in hospital and being ventilated are associated with different types of difficulties in cognitive functioning among patients with post-COVID-19 syndrome.

3 STUDY DESIGN

Design (Please see Study Flowchart below).

The current study is linked with another study (IRAS 297003) taking place in a newly funded COVID-19 Mental Health Screening Clinic within NHS Grampian. This service is led by Liaison Psychiatry with input from the Multi-Disciplinary Team (MDT). The data collected as part of the current study will draw from data collected as part of the COVID-19 Mental Health Screening Clinic.

Protocol

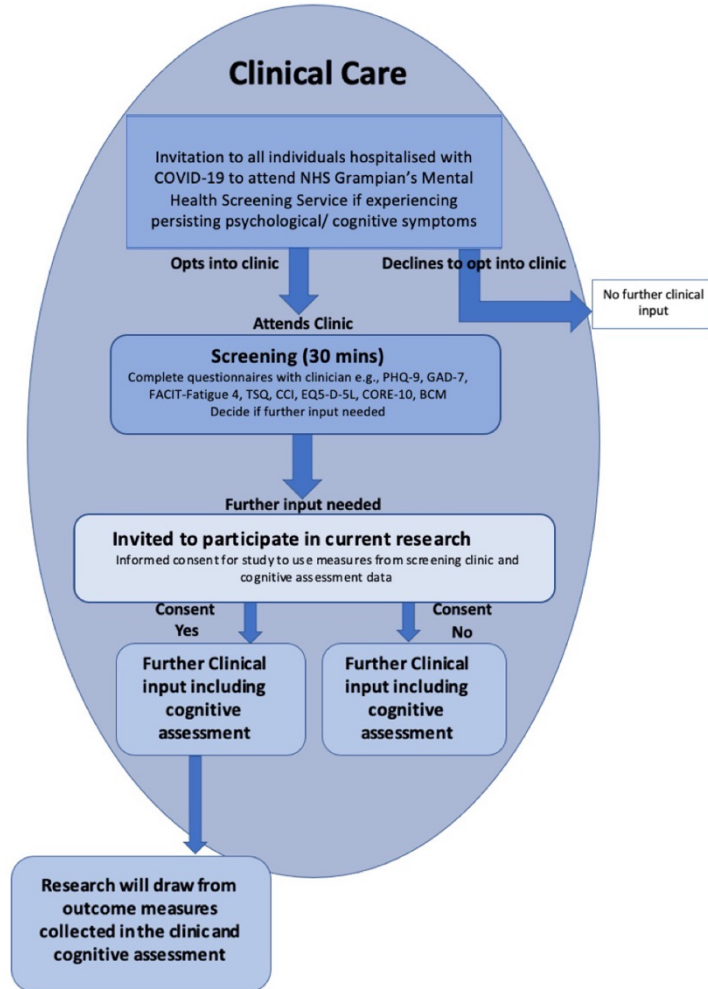
At the point where individuals are offered to participate in the current research, they will have already attended a 30 minute screening appointment with either a psychologist or psychiatrist. This screening appointment will have been conducted via Attend Anywhere (NearMe). This step is associated with the linked study (IRAS 297003). By the end of the screening clinic, participants will have completed the following questionnaires:

- Patient Health Questionnaire (PHQ-9)
- Generalised Anxiety Disorder (GAD-7)
- Cognitive Change Index (CCI)
- The Trauma Screening Questionnaire (TSQ)
- Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue)
- Clinical Outcomes in Routine Evaluation ten item measure (CORE-10)
- EuroQol 5-dimensions (EQ5-D-5L)
- Bespoke Cognitive Measure (BCM; Psychological and Cognitive Changes since having COVID-19)

During this screening appointment, if they indicate that they are experiencing cognitive difficulties via the Cognitive Change Index and/or verbally to the treating clinician, they will be offered further clinical input with a clinician to complete cognitive assessments which is part of routine clinical care. If they opt-in to engage with cognitive assessment and meet the research's criteria, they will be advised of the current research. As the 30 min screening appointment is via NearMe, individuals will be sent a Patient Information Sheet in the post so they can digest the information in their own time. This will be sent via admin in the clinic. The Participant Information Sheet will have the Chief Investigator's contact details in case the participants have any questions regarding the research. Participants who attend their appointment for further clinical cognitive assessment will again be advised of the current research with the Participant Information Sheet as well as verbally, and provided with an informed consent form. The consent form will explain that the current research wishes to analyse the questionnaires they completed during the screening clinic as well as their cognitive assessments. Individuals will have the option to decline involvement in the study by indicating this to the clinician in the clinic. Individuals will still be offered further clinical input with a psychologist or psychiatrist regardless if they agree to participate in the study and the cognitive assessments will not be retained and stored within the dataset for the current study. Participants will be verbally advised as well as via the information sheet that declining to participate in the current study will not interfere with receiving further clinical care.

Cognitive assessment will take approximately 1 hour 15 minutes. This is all part of routine clinical care. The current research project is asking for an additional 5mins (max) to complete a demographic questionnaire. Participants are being asked for permission to allow the current project to analyse their data which they will complete as part of routine clinical practice. Time from consent to dissemination of findings would be the last contact with the research. How long participants will be involved in the research will depend on when they attend their cognitive assessment appointment but the research will run for 18 months and participants can choose to join the study at any time. Dissemination of findings to participants will likely be in July 2023.

Study Flowchart



4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

The single group of participants will consist of individuals aged 18 and over, who were previously hospitalised with COVID-19 within NHS Grampian. Participants will be identified as eligible for the current research study during the screening service if they self-identify as experiencing cognitive difficulties either via the Cognitive Change Index (CCI) and/or through

clinical interview. All participants who indicate that they are experiencing ongoing cognitive difficulties and who meet the inclusion criteria will be offered to participate in the current research.

The estimated sample size required is 74. At the time of writing, 1259 patients have been identified as being hospitalised with COVID-19 within NHS Grampian.

The study will run for 18 months, participants can choose to join the study at any time during this period. The research will only be conducted on one site being NHS Grampian.

4.2 INCLUSION CRITERIA

1. Detail participant inclusion criteria Individuals aged 18 and over who were previously hospitalised with COVID-19 within NHS Grampian, and, who have self-identified as having persisting cognitive difficulties as assessed by the Cognitive Change Index during clinical assessment.
2. Individuals who meet the criteria for 'post-COVID syndrome', as defined by NICE-SIGN-RCGP (2020) as 'signs and symptoms that develop during or after an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by an alternative diagnosis'.

4.3 EXCLUSION CRITERIA

1. Detail participant exclusion criteria Individuals with a Learning Disability, as classified by ICD-10.
2. Individuals with a previous moderate/ severe brain injury or previous brain injury with clinically noted cognitive change.
3. Individuals with a diagnosis of dementia.
4. Individuals with severe sensory, visual or hearing impairment which might interfere with testing.
5. Individuals with a dependency on alcohol or recreational drugs.
6. Individuals not able to engage with questionnaires or cognitive assessment due to a limited level of English ability such as English not being their first language.
7. Individuals lacking capacity, as assessed by the treating clinician.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Individuals who indicate cognitive difficulties either via the Cognitive Change Index and/or during the screening clinic will be offered further clinical assessment. If participants opt-in to receiving further clinical assessment, and meet the study criteria, they will be advised of the current research study by their treating clinician/ direct care team.

The direct care team will have a copy of inclusion/ exclusion criteria in order to identify who will be offered involvement in the research based on their medical records. Only members of the direct care team will have access to patient records.

Any participants thought not to have capacity to consent will not be approached.

Current measures maintaining confidentiality for patients that are in place within the Neuropsychology service will be applied to those patients that will be approached to be offered the opportunity to take part in the current research.

5.2 CONSENTING PARTICIPANTS

Individuals will be given a Participant Information Sheet sent to them in the post following the screening clinic. Individuals will therefore have time to read and digest the information prior to attending their cognitive assessment appointments where the treating clinician will again, go over the patient information sheet with participants before taking informed consent. The consent form will be read through with each participant to ensure it is understood properly what the consent is being given for. An opportunity to ask questions will be given and further time to consider participation if that is needed at that point.

By taking part in the research, individuals are consenting to the research being able to analyse the questionnaires completed during the screening clinic and the cognitive assessments. Informed consent will be taken by the clinician conducting the cognitive assessment.

5.2.1 Withdrawal of Study Participants

Participants who decide to take part, are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care they receive. Taking part in this research will not interfere or prevent individuals receiving appropriate clinical input now, or in the future. As participation in the research study is anonymous, it will not be possible to withdraw data.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

This project will have three stages (please refer to Study Matrix below for more detail):

Stage 1: Preparation/ Development Phase.

At this stage study sponsorship and ethical agreement will be sought. Cognitive assessments will be carefully selected by the Chief Investigator and Clinical Supervisor/ Clinical Neuropsychologist, Dr Maggie Whyte.

Stage 2: COVID-19 Mental Health Screening – Linked Study (IRAS: 297003).

At the point where individuals are offered to participate in the current research, they will have already attended a 30 minute screening appointment within the COVID-19 Mental Health Screening Service within NHS Grampian. Their screening appointment will have been conducted via Attend Anywhere (NearMe) with either a Clinical Psychologist or a Psychiatrist.

By the end of the screening clinic, participants will have completed the following questionnaires:

- Patient Health Questionnaire (PHQ-9)
- Generalised Anxiety Disorder (GAD-7)
- Cognitive Change Index (CCI)
- The Trauma Screening Questionnaire (TSQ)
- Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue Scale)
- Clinical Outcomes in Routine Evaluation ten item measure (CORE-10)
- EuroQol 5-dimensions (EQ5-D-5L)

- Psychological and Cognitive Changes since having COVID-19 (Bespoke Cognitive Measure; BCM)

During the screening appointment, if they indicate that they are experiencing cognitive difficulties via the Cognitive Change Index and/or verbally to the treating clinician, they will be offered further clinical input with a clinician to complete cognitive assessments, which is part of routine clinical care. If they opt-in to receive this cognitive assessment and meet the research's criteria, they will be advised of the current research. As the 30 min screening appointment is via NearMe, individuals will be sent a Patient Information Sheet in the post so they can digest the information in their own time. This will be sent via admin in the clinic. The Participant Information Sheet will have the Chief Investigator's contact details in case the participants have any questions regarding the research. Participants will be verbally advised as well as via the information sheet that declining to participate in the current study will not interfere with receiving further clinical care. They will be made aware that they will still be offered further clinical input regardless if they agree to participate in the research and the cognitive assessments will not be retained and stored within the dataset for the current study. See the Study Flowchart in section 3.2 and the Study Matrix in section 3.3 for full details of the measures included.

Stage 3: Cognitive Assessment.

Participants who attend their appointment for further clinical cognitive assessment will again be advised of the current research with the Participant Information Sheet as well as verbally, and provided with an informed consent form. The consent form will explain that the current research wishes to analyse the questionnaires they completed during the screening clinic as well as their cognitive assessments. Individuals will have the option to decline involvement in the study by indicating this to the clinician in the clinic. Individuals will still be offered further clinical input with a psychologist or psychiatrist regardless if they agree to participate in the study and the cognitive assessments will not be retained and stored within the dataset for the current study. Participants will be verbally advised as well as via the information sheet that declining to participate in the current study will not interfere with receiving further clinical care. They will be made aware that they will still be offered further clinical input regardless if they agree to participate in the research and the cognitive assessments will not be retained and stored within the dataset for the current study.

Participants will be asked to complete a demographic sheet which will ask for their age, sex, ethnicity, length of stay in hospital, whether they were ventilated and if they have a previous head injury.

The cognitive assessments will be administered by an experienced clinician and overseen by Dr Maggie Whyte, Consultant Clinical Neuropsychologist. Cognitive assessment will take a maximum of 1 hour 15 minutes (including instructions) and offered over several sessions, depending on the individuals' needs. As per routine clinical procedures, testing can also be stopped and re-scheduled at any point depending on their needs. The cognitive assessments will take place face-to-face in an outpatient clinic within NHS Grampian.

Individuals will be advised that they will be contacted by a clinician from the Department of Neuropsychology to discuss the results from their cognitive assessments and plan further treatment, if required. Data collected to date will be analysed and written up for Tessa Stanley's doctoral thesis.

Study Matrix

	Stage 1	Stage 2	Stage 3
	Study Preparation	COVID-19 Mental Health Screening (Linked Study IRAS: 297003)	Cognitive Assessment
Apply for permissions e.g. sponsorship, ethics	*		
R&D Approval	*		
Select Cognitive Assessments	*		
Informed Consent			*
Demographic Questionnaire			*
Patient Health Questionnaire (PHQ-9)		*	
Generalised Anxiety Disorder (GAD-7)		*	
Cognitive Change Index (CCI)		*	
The Trauma Screening Questionnaire (TSQ)		*	
Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue Scale)		*	
Clinical Outcomes in Routine Evaluation ten item measure (CORE-10)		*	
EuroQol 5-dimensions (EQ5-D-5L)		*	
Bespoke Cognitive Measure (BCM; Psychological and Cognitive Changes since having COVID-19)		*	
Wechsler Test of Adult Reading (WTAR)			*
California Verbal Learning Test, Third Edition. (CVLT-3)			*
The Logical Memory subtest of the Wechsler Memory Scale, 4th Edition (WMS-IV)			*
Rey-Osterrieth Complex Figure Test (ROCF)			*
Digits Backwards & Forwards Span from the Wechsler Memory Scale, 4th Edition (WMS-IV)			*
Elevator Counting & Elevator Counting with Distraction subtests of the Test of Everyday Attention (TEA)			*
Verbal Fluency Subtest of the Delis-Kaplan Executive Functioning System (D-KEFS)			*
Zoo Map Subtest of the Behavioural Assessment of Dysexecutive Syndrome (BADS)			*
Colour Trails Test			*

7 DATA COLLECTION

Please refer to the Study Matrix

Primary Outcomes

The primary outcome is to examine the types of difficulties in cognitive functioning among patients with post-COVID-19 syndrome. Cognitive functioning will be assessed using several cognitive tests which assess a range of cognitive abilities, including: pre-morbid functioning, memory, attention, executive functioning and processing speed. These are listed and described in detail below. The treating clinician will collect the data as measures completed are part of routine clinical care. Individuals will be supported to complete all measures and will be offered shorter appointments over several sessions, depending on the needs of the individuals. Moreover, testing can be stopped at any time and individuals can re-arrange another appointment, depending on their needs. For example, if they are becoming fatigued or are struggling with their concentration.

Cognitive Change

Cognitive Change Index (CCI) (Saykin et al. 2006)

The CCI is a 20-item, self-report tool measuring perceived cognitive decline across domains of memory, executive function and language. Other measures including the Cognitive Failures Questionnaire and the Everyday Memory Questionnaire were considered, although the CCI was chosen following consultation with the Consultant Clinical Neuropsychologist. The language is accessible, facilitating ease of completion. The CCI has shown high internal consistency $\alpha=0.96$ (Rattanabannakit et al., 2016). This measure will be used as part of the initial screening process to determine whether cognitive difficulties are present.

Premorbid Functioning

Wechsler Test of Adult Reading (WTAR; Wechsler, 2001)

This is a measure of pre-morbid functioning as vocabulary strongly correlates with overall ability level and is relatively unaffected by most non-aphasic brain disorders (Lezak et al., 2012). 50 irregular words are presented and individuals' ability to correctly pronounce them suggests prior knowledge of them. The WTAR was co-normed among a US and UK sample for ages 16-89 years.

Memory

California Verbal Learning Test, Third Edition. (CVLT-3; Delis et al., 2017)

This measures both immediate and delayed memory abilities. The examiner reads List A words 5 times, followed by an interference List B. Participants engage in 'free' and cued recall of List A items. Thereafter, there is a 20 minute 'long delay' which measures recall of List A under the same two conditions of 'free' and 'cued'. The measure was created to assess the use of semantic associations when learning words and as a screen for memory impairments. The 3rd edition was standardised on a large sample of adults (ages 16-90) based on the 2015 US Census data.

The Logical Memory subtest of the Wechsler Memory Scale, 4th Edition (WMS-I; Wechsler, 2009).

This test measures verbal memory and learning. Individuals are told a story and they are required to recall as much as possible immediately and after a 20–30-minute delay. The test is sensitive to detect subtle memory changes among individuals with mild cognitive impairment (Lezak et al., 2012).

Rey-Osterrieth Complex Figure Test (ROCFT; Osterrieth, 1944; Rey, 1941)

This primarily measures visual memory and visual-spatial constructional ability. Participants are shown a complex figure and asked to copy it, then the original image is removed. Participants complete an immediate recall followed by a delayed recall of 20-30 minutes. Internal reliability coefficients (Cronbach alpha (α)) for copy condition is greater than $\alpha = 0.60$, and greater than $\alpha = 0.80$ for both immediate and delayed recall conditions (Strauss et al., 2006).

Digits Backwards & Forwards Span from the Wechsler Memory Scale, 4th Edition (WMS-IV; Wechsler, 2009)

This will measure working memory (Lezak et al., 2012).

Attention

Elevator Counting & Elevator Counting with Distraction subtests of the Test of Everyday Attention (TEA; Robertson et al., 1994, 1996)

These two subtests are widely used clinically and are ecologically valid measures of sustained and selective attention (Robertson et al, 1996). During elevator counting, individuals establish which imagined floor they are on by counting a series of seven strings of tones. Elevator with distraction requires individuals to count the same pitched tones from the previous test while ignoring higher pitched distractor tones. This replicates the auditory distractions individuals hear in daily life.

Executive Function

Verbal Fluency Subtest of the Delis-Kaplan Executive Functioning System (D-KEFS; Delis et al., 2001)

Verbal fluency measures an individual's ability to produce fluent speech as well as 'executive' aspects of verbal behaviour including cognitive flexibility (Lezak et al., 2012). Assessment of this includes letter, category fluency with switching. Fluency tests have demonstrated sensitivity to acute deficits following mild-traumatic brain injury (mTBI) (Belanger et al., 2005).

Zoo Map Subtest of the Behavioural Assessment of Dysexecutive Syndrome (BADS; Wilson et al., 1996)

The Zoo Map subtest will measure planning abilities. Participants have two attempts to plan a route through a zoo while adhering to sets of rules and varying amount of instructions. Penalties are imposed for rule breaks and lack of speed. The test demonstrates adequate discriminant and ecological validity (Norris & Tate, 2000; Wilson et al., 1996).

Processing Speed

Colour Trails Test (D'Elia et al., 1996)

This test will assess processing speed as well as non-verbal aspect of sustained and divided attention. Participants are asked to connect digits within circles in ascending numerical order, beginning with 1 to 25. In Part 2, participants connect digits within circles with alternate colour and completion times are recorded for each trial. Adult version is for ages 18-89. Normative data is based on a sample of 1528 healthy volunteers across various ethnicities (D'Elia et al., 1996).

Secondary Outcome: The secondary outcome is to examine what factors related to age, sex, ethnicity, anxiety, depression, fatigue, emotional distress, length of stay in hospital and

being ventilated are associated with different types of difficulties in cognitive functioning among patients with post-COVID-19 syndrome.

Demographic Questionnaire

The demographic information will gather information related to age, sex, ethnicity, length of stay in hospital and whether the individual was ventilated or not. The demographic sheet will also ask if participants have had a previous head injury.

Mood

Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001)

The PHQ-9 is a self-report measure assessing depression severity, which parallels the 9 symptoms used to diagnose Major Depressive Disorder according to the DSM-IV criteria, with higher scores indicating more severe symptoms. It is recommended by NICE (2011) and used in a variety of populations both clinically and in research. It has good internal consistency ($\alpha = 0.86-0.89$) (Kroenke et al., 2001).

Generalised Anxiety Disorder-7 (GAD-7; Spitzer et al., 2006)

This standardised measure was originally developed to monitor Generalised Anxiety Disorder and is also recommended by NICE (2011). It is routinely utilised in primary care and mental health services to monitor reported symptoms; higher scores indicate more severe symptoms.

Fatigue

Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-4; Hewlett et al., 2011)

This is a 13-item tool designed to assess fatigue and tiredness and its effect on daily functioning in several chronic illnesses. It has demonstrated good reliability and validity across populations and in long-term conditions such as MS, cancer and neurologic disorders (Hewlett et al., 2011).

Emotional Distress

Trauma Screening Questionnaire is a 10-item tool which asks individuals to record the presence, or absence of PTSD symptoms over the past week. The measure has been validated across various populations and is reported to have good sensitivity in assessing PTSD symptoms (Brewin, 2005; Walters et al., 2007).

Psychological Distress

Clinical Outcomes in Routine Evaluation ten item measure (CORE-10; Connell & Barkham, 2007)

The CORE-10 is a short-form of the Clinical Outcomes in Routine Evaluation Outcome Measure CORE-OM (Barkham et al. 2001, 2005; Evans et al. 2002). The CORE10 captures 'psychological distress' and comprises 10 items relating to the domains of symptoms (anxiety, depression, physical and trauma), life functioning and risk to self. The psychometric properties of the CORE10 have shown it to have good internal reliability with an alpha for the overall scale of 0.82 (CI 0.79-0.85) (Connell & Barkham, 2007).

Quality of Life

EuroQol 5-dimensions (EQ5-D-5L; van Reenen M, Oppe M, 2015).

The EQ5-D-5L will be used to measure Quality of Life, which consists of items classified into five dimensions: mobility, selfcare, usual activity, pain/discomfort, and anxiety/depression. The EQ5-D-5L is one standard measurement scale for QoL. On the thermometer-like scale

(EQ VAS), individuals describe how good or bad they feel by marking the scale from 0 to 100 where 0 is the worst possible health and 100 is the best possible health, thus generating the EQ VAS individual self-estimated health condition, defined as the VAS score.

Subjective Report of Psychological and Cognitive Changes since COVID-19

Psychological and Cognitive Changes since having COVID-19 (Bespoke Cognitive Measure BCM)

This measure was developed by Consultant Clinical Neuropsychologist, Dr Maggie Whyte as a brief way to capture an individual's perceived changes since having COVID-19. The measure offers a free text box which the other measures don't allow. This offers the individuals the opportunity to write freely an account of their perceived changes since having COVID-19. This will allow for subjective reports of peoples' experiences to be reported.

7.1 Source Data Documentation

Outcome measures as part of the COVID-19 Mental Health Screening Service linked study will either be completed electronically or via paper. Where patients have opted for completion via paper questionnaire, study data from questionnaires will be input onto an excel database by the treating clinician matched with a unique Audit identifier. This will be completed by the clinician within the screening service. All data will be input via NHS computer with triple password protection - laptop pin, NHS G log on and password protected excel sheet and will be stored on secure servers within NHS Grampian - this data will be completely anonymised with a unique audit identifier (UAI).

When the cognitive assessments are completed, the clinician will fill in a cognitive assessment summary sheet, which again, is part of routine clinical practice. This sheet documents all the scores from the assessments with no identifiable information, just the scores. The clinician will add the UAI to the sheet, make a copy and give it to the researcher. The original cognitive summary sheet will be retained according to NHSG policies and procedures as part of the patients notes which is routine clinical practice. The copy will be destroyed appropriately after the data has been input into the excel sheet. This ensures that no personal, identifiable information will be accessed by the researcher. The researcher will then input the scores into a password protected excel sheet, similarly stored on NHS computers which are fire-walled and password protected.

Case Report Forms

Document the type of case report forms which will be used, including any electronic data collection procedures.

8 DATA MANAGEMENT

8.1.1 Personal Data

Several measures of emotional and cognitive outcomes will be collected as part of the research. All of this data will be anonymised.

8.1.2 Data Information Flow

Any personal data will be stored as per routine clinical practice procedures, Data Protection Act and NHS Grampian Confidentiality policy. All data will be anonymised before it is accessed by the researcher.

8.1.3 Transfer of Data

Data collected or generated by the study will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

8.1.4 Data Controller

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site)

8.1.5 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Sample size was calculated using the G*Power online statistical calculator (Faul, Erdfelder & Buchner, 2009). Effect size was estimated to be medium ($f^2=0.15$) for regression models (Cohen, 1988). The calculation included 9 predictor variables (age, sex, ethnicity, anxiety, depression, fatigue, emotional distress and length of stay in hospital and presence or absence of ventilation), an alpha level of 0.05, and statistical power of 0.95 (Cohen, 1992; Green, 1991). The total sample size is estimated to be 74.

The research will run for 18 months and participants can choose to join the study at any time. At the time of writing, 1259 patients have been identified as being hospitalised with COVID-19 within NHS Grampian. Anecdotally, from GPs and other clinicians, many individuals are eager to receive support for their experience of post-COVID-19 syndrome. The PHOSP-COVID study (2021) reported 17% prevalence of cognitive impairment in a sample of 1077 patients discharged from hospital following COVID-19, as assessed by the Montreal Cognitive Assessment.

9.2 PROPOSED ANALYSES

The data will be analysed using IBM SPSS V22, or equivalent. Demographic information will be explored via descriptive statistics. Data analyses will be conducted to understand cognitive difficulties among individuals according to the research aims:

Research Aim 1: To understand the patterns of cognitive difficulties among patients with post-COVID-19 syndrome, participants' performance scores on cognitive assessments will be converted to z-scores and compared to normative data of each cognitive test. The frequencies of scores will be examined. For cognitive measures, 'mild/borderline' will be defined as 1 SD below the mean of the normative sample while 'impaired' will be defined as scoring 2 SD or more below the mean of the normative sample. This classification has been used in another study examining

cognitive functioning in patients with post-COVID-19 syndrome (Jaywant et al., 2021).

Research Aim 2: To understand what individual characteristics are associated with cognitive difficulties within the post-COVID-19 cohort, a cross-sectional correlational analysis will be adopted. The researcher will utilise regression methodology where measures of cognitive function will be represented as the DV, while individual characteristics (age, sex, ethnicity, anxiety, depression, fatigue, PTSD symptoms, psychological distress, quality of life and disease severity) will represent the IVs. A multiple regression model will be computed per cognitive domain. Appropriate corrections to statistics will be applied.

10 RISKS

The research will incorporate measures and cognitive assessments which have been developed through theory and have been validated and utilised in multiple clinical populations and so we do not anticipate any ethical issues when using these measures with patients with post-COVID-19 syndrome. It is unlikely any harm will come to participants during this research.

Ethical Issues

Neuropsychological Assessment

Implementing the measures and cognitive assessments are not associated with any significant risk, although there is a low risk that individuals will become anxious and/or distressed. To manage this risk, individuals primary source of support will be their treating clinician who will provide mental health support as part of routine clinical care. Moreover, there will be a clinical psychologist available within the screening service to support participants if and when required. If a participant feels that they would like additional support due to any issues raised then they can speak to the clinician present. Participants will be given the contact number for the COVID-19 clinic where they can access support (Monday-Friday) from a Psychologist/ Psychiatrist to give advice and sign posting. Participants attending the clinic will have an assigned mental health professional who can assist with management of psychological distress and assess risk.

Participant Burden & Effort

Completing cognitive assessment requires mental effort on behalf of the participant. However, the cognitive assessment is routine clinical practice and participants will not be required to complete anything additional, minimising participant burden. Cognitive assessments were carefully selected with the supervision of the field supervisor, Dr Maggie Whyte, Consultant Clinical Neuropsychologist, with the additional consideration of participant burden.

Post-COVID-19 syndrome has been associated with fatigue. Engagement with neuropsychological testing will require both mental and physical effort which has the potential to increase fatigue. To mitigate this risk, experienced clinicians who are aware of the impact of fatigue on effort and cognitive performance will be administering the neuropsychological testing as part of routine clinical practice.

Moreover, testing will be conducted over several, shorter sessions, if necessary, depending on the individuals' preferences and needs (e.g., difficulties with concentration, fatigue etc.). Testing can also be stopped at any point and re-scheduled depending on the individuals' needs.

COVID-19

At the time of writing, COVID-19 remains a public health crisis which has the potential to affect any individual involved with the study. The pandemic is a dynamic situation, associated with several risks of new 'waves' of infection and restrictions on people's movements. However, NHS Scotland continues to facilitate a vaccination programme and governmental restrictions are easing, enabling participants to travel and attend the clinic. The clinic will continue to follow Government and NHS Grampian's COVID safety measures including social distancing, window ventilation, hand gelling, pre-COVID checks etc.

Travel and Inconvenience

Engaging in the research will involve no additional inconvenience to participants. They will be attending the clinic to complete cognitive assessments as part of routine clinical care and travel to their appointments is part of this. Data analysis for the project will continue until November/ December 2023 to give individuals ample time to attend the clinic and engage in neuropsychological assessment at a time convenient to them.

All participants will complete the measures via routine clinical practice and the data will be compared to normative samples, which means there will be no withholding treatment for a control group, offsetting this possible ethical issue.

11 OVERSIGHT ARRANGEMENTS

11.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met. The Chief Investigator has undertaken Good Clinical Practice Training.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the treating clinician (qualified delegated person) and will cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant will be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant will be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF).

12.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

12.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

12.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

12.2.5 GCP Training

The Chief Investigator has undertaken Good Clinical Practice Training.

12.2.6 Confidentiality

All records will be kept in a secure storage area with limited access in an NHS Grampian Building where entry is gained with staff ID badges. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study.

The researcher will not have access to the any identifiable information. No identifiable information will be requested via the questionnaires. Questionnaires collected via the COVID-19 Mental Health Screening Service will be entered along with a unique audit identifier to allow the clinic to match information with the patient for clinical use, however the researchers will not be matching the UAI with patient records.

Cognitive assessment data and demographic info will be input into secure excel database with the individual's unique audit identifier. The researcher will then be able to match the cognitive assessment data with the questionnaire data via the unique audit identifier. As such, the researcher will never access any patient identifiable information. The link between the study number and participant's personal data will not be made.

Cognitive assessments will be stored as per Data Protection Act and NHS Grampian Confidentiality policies as these assessments are part of routine clinical care. They will be stored in a locked filing cabinet within the Department of Neuropsychology, Ashgrove House, Aberdeen Royal Infirmary, Aberdeen. When the cognitive assessments are completed, the treating clinician will fill in a cognitive assessment summary sheet, which again, is part of routine clinical practice. This sheet documents all the scores from the assessments with no identifiable information, just the raw scores. The clinician will add the UAI to the sheet, make a copy and give it to the researcher. The demographic questionnaire will be matched with the UAI and given to the researcher as well. The scores will then be input into secure excel database stored on NHS computers which are fire-walled and password protected. The copy of the cognitive summary sheet will then be destroyed appropriately after the data has been input into the excel sheet.

Demographic forms will be stored in a locked filing cabinet within the Department of Neuropsychology. Consent forms will be stored separately in locked filing cabinet within the Department of Neuropsychology.

12.2.7 Data Protection

All Investigators and study site staff involved with this study will comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) and NHS Grampian's Confidentiality policy with regard to the collection, storage, processing and disclosure of personal information. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality.

Computers used to collate the data will have limited access measures via usernames and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place.

STUDY CONDUCT RESPONSIBILITIES

12.3 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.4 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

- (a) the safety or physical or mental integrity of the participants of the trial; or
- (b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the sponsor (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.6 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.7 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the sponsor have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and sponsor within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.8 INSURANCE AND INDEMNITY

The sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the -sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

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- (maf), multi-dimensional fatigue inventory (mfi), pediatric quality of life
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18.5 Appendix E: Participant Information Sheet



THE UNIVERSITY
of EDINBURGH

Participant Information Sheet

Research: Understanding Cognitive Functioning Among Individuals with Post-COVID-19 Syndrome

Chief Investigator: Tessa Stanley

Introduction

This sheet is about research that is happening in NHS Grampian. It gives some information to help you decide if you want to take part or not. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, such as your GP and relatives, if you wish. If you have any questions, please get in touch with members of the research team, Tessa Stanley or Dr Maggie Whyte on **01224 559352**. We are happy to answer any questions you have and would like to thank you for taking the time to read this information.

What is this research about?

COVID-19 began spreading across the globe in early 2020 and was declared a global pandemic in March 2020. A year later, there are increasing reports of people experiencing persisting complaints, including fatigue, neurological and cognitive symptoms. This ongoing experience of symptoms has come to be known as 'long-COVID' or post-COVID-19 syndrome. People with long-COVID have described these cognitive difficulties as feeling mentally slow, hazy and struggling to sustain attention throughout the day.

Cognitive difficulties affect our ability to remember to carry out tasks, maintain concentration and even have conversations with others. These aspects of daily living use cognitive processes such as memory, attention and complex mental skills called 'executive functions'. It is important for our healthcare systems to be able to identify and treat people with long-COVID for their cognitive difficulties, but first we need to understand what these are in more detail.

This research project hopes to understand which cognitive difficulties people with long-COVID are experiencing. People who have attended NHS Grampian's COVID-19 Screening Clinic and who have self-reported cognitive difficulties will be offered a cognitive assessment, as part of routine clinical practice. Routine clinical practice means that everyone who reports difficulties with their cognition will be offered these tests, regardless of if they are participating in the research or not.

To understand if there are any similar cognitive difficulties among people with long-COVID, this research project is asking for your consent to analyse the assessments which you complete as part of routine clinical practice. We also wish to analyse the demographic information you complete to try to understand if these factors will affect your cognitive abilities. The demographic information we

would like to analyse includes your fatigue levels, anxiety, depression, emotional & psychological distress, quality of life, ethnicity, sex, how long you were in hospital for and if you were ventilated or not. We would also like to understand your perspective about the psychological and cognitive changes you experienced since having COVID. We hope that analysing this information will contribute to an improved understand of the impact of COVID-19.

Length of Involvement Time

You will not be required to provide any additional time other than attending your appointments which is part of routine clinical practice.

Why have I been invited to take part?

You have been asked because you have indicated that you are experiencing cognitive difficulties after being infected with COVID-19. You, along with other people who have been infected with COVID-19, and, who are still experiencing difficulties with their cognition will be asked for permission to analyse the assessment information.

Do I have to take part?

No. It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. Taking part in this research will not interfere or prevent you receiving appropriate clinical input now, or in the future. Please note that as participation in the research study is anonymous, it will not be possible to withdraw your data.

What will happen to me if I take part?

As part of this research, you will not have to do anything other than attend your routine clinical appointments. All the measures you complete in NHS Grampian's COVID-19 Screening Clinic and the cognitive assessments are part of your routine clinical care. The only additional item we will ask you to complete for the research project is a demographic questionnaire which you can fill in with a clinician during your cognitive assessment appointment which will take 2 minutes. The demographic questionnaire will ask for your age, sex, ethnicity, how long you were in hospital for and whether you were ventilated or not.

By taking part in the research, you are consenting to us analysing the questionnaires you completed during the screening clinic and your cognitive assessments. All your information will be anonymised. We would also like to report anonymised quotations from the questionnaire which captured your perspective on the psychological and cognitive changes you noticed after having COVID-19. You can complete a consent form with your clinician at your cognitive assessment appointment.

What are the possible disadvantages and risks of taking part?

The research involves analysing data from the assessments you complete as part of routine clinical practice so is not likely any harm will come to you if you take part.

If at any time you become distressed or upset during routine clinical practice, there will be a psychologist or a psychiatrist available to support you if, and when required. If you feel concerned or

upset about any issue raised during the course of the research, you can also talk to Tessa Stanley or Dr Maggie Whyte on 01224 559352. They will be happy to discuss any concerns you may have.

What are the possible benefits of taking part?

There are no direct benefits, but the information gathered from this research may help us understand more about some of the cognitive difficulties patients experience with long-COVID which could help create the best possible treatment for future patients with long-COVID.

Will my taking part in this research be kept confidential?

All the information we collect during the course of the research will be kept confidential and there are strict laws which safeguard your privacy at every stage.

The research process is organised so that all data which is collected about you will be anonymised and kept completely confidential, which means the research team will never be able to identify you. Your information will be coded before the research team analyse it so no personal details will be available from the questionnaires and cognitive assessments alone. Any personal information you discuss during routine clinical practice is kept separate from the research data and will never be given to the research team. Procedures for storing data are compliant with the Data Protection Act (2018) and NHS Grampian Confidentiality Policy. Electronic data will be stored on NHS computer servers, computers are password protected as per local NHS board policy. You can stop being part of the research at any time, without giving a reason. Please note that as participation in this research study is anonymous, it will not be possible to withdraw your data.

Once we have finished the research, 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 research.

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.

Anonymised data from the study will be stored for a minimum of 3 years and may be used in future ethically approved research.

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

You can find out more about how we use your information here:

- At <https://www.ed.ac.uk/records-management/privacy-notice-research>
- by asking one of the research team
- by sending an email to the University of Edinburgh Data Protection Officer at dpo@ed.ac.uk

What will happen to the results of the research?

The research will initially be published as a thesis as part of the University of Edinburgh's Doctorate in Clinical Psychology. The results of the research will also be made into a leaflet and a poster explaining the findings. You will be given the opportunity to receive a summary of the findings if you wish. We may also publish the results in scientific journals and present the results at conferences. This will likely be made available in September 2023. We will make sure no-one can work out who you are from the written findings.

Who is organising and funding the research?

The project is part of Tessa Stanley's training as part of the Doctorate in Clinical Psychology at the University of Edinburgh. The research has been sponsored by The University of Edinburgh and organised by the Department of Clinical Neuropsychology at Aberdeen Royal Infirmary. There is no additional funding in place for this research.

Who has reviewed the research?

The Northeast - Newcastle & North Tyneside 1 Research Ethics Committee, which has responsibility for scrutinising NHS research proposals, has reviewed this research and raised no objections from the point of view of research ethics. It is a requirement that all relevant research records are made available for scrutiny by monitors from NHS Grampian, whose role is to check that the research is properly conducted and the interests of those taking part are protected.

Contact for Further Information

If you have any questions, you can contact Dr Maggie Whyte or Tessa Stanley on 01224 559352.

You can also email the research team at gram.neuropsych@nhs.scot

If you would like to speak to someone independent of the research, please contact Dr Jackie Hamilton on 01224 559352.

If you have a concern about any aspect of this research, you should ask to speak to the researchers who will do their best to answer your questions [01224 559352]. If you remain unhappy and wish to complain formally, you can do this via NHS Grampian complaints procedure. Contact details for the services are provided below.

NHS Grampian: The Feedback Service is open during the office hours of Monday to Friday 9am to 5pm. You can contact them via post: NHS Grampian Feedback Service, Summerfield House, 2 Eday Road, Aberdeen, AB15 6RE. Tel: 0345 337 6338. E-mail gram.nhsgrampianfeedback@nhs.scot

Alternatively, you can complete a Feedback Card which can be found throughout NHS Grampian at clinics and practices (please tick the Complaint box on the card to confirm you wish to make a formal complaint).

You can also access www.hra.nhs.uk/information-about-patients to find out more about how we use your information.

- Thank you for taking the time to read about this research!
- If you wish to take part, please complete the accompanying consent form.
- If you do not wish to participate, please dispose of the forms as you see fit.

18.6 Appendix F: Submission Guidelines for the Journal of Neuropsychology

10/04/2023, 15:33

Journal of Neuropsychology: Author Guidelines



3. Manuscript Categories and Requirements
4. Preparing the Submission
5. Editorial Policies and Ethical Considerations
6. Author Licensing
7. Publication Process After Acceptance
8. Post Publication
9. Editorial Office Contact Details

1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

New submissions should be made via the [Research Exchange submission portal](#). You may check the status of your submission at any time by logging on to submission.wiley.com and clicking the “My Submissions” button. For technical help with the submission system, please review our FAQs or contact submissionhelp@wiley.com.

All papers published in the *Journal of Neuropsychology* are eligible for Panel A: Psychology, Psychiatry and Neuroscience in the Research Excellence Framework (REF).

Data protection:

By submitting a manuscript to or reviewing for this publication, your name, email address, and affiliation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognize the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at <https://authorservices.wiley.com/statements/data-protection-policy.html>.

Preprint policy:

This journal will consider for review articles previously available as preprints. Authors may also post the submitted version of a manuscript to a preprint server at any time. Authors are requested to update any pre-publication versions with a link to the final published article.

2. AIMS AND SCOPE

The Journal of Neuropsychology publishes original contributions to scientific knowledge in neuropsychology including:

- clinical and research studies with neurological, psychiatric and psychological patient populations in all age groups
- behavioural or pharmacological treatment regimes
- cognitive experimentation and neuroimaging
- multidisciplinary approach embracing areas such as developmental psychology, neurology, psychiatry, physiology, endocrinology, pharmacology and imaging science

The following types of paper are invited:

- papers reporting original empirical investigations
- theoretical papers; provided that these are sufficiently related to empirical data
- review articles, which need not be exhaustive, but which should give an interpretation of the state of research in a given field and, where appropriate, identify its clinical implications
- brief reports and comments
- case reports
- fast-track papers (included in the issue following acceptance) reaction and rebuttals (short reactions to publications in JNP followed by an invited rebuttal of the original authors)
- special issues.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

- Research papers should be no more than 6000 words (excluding the abstract, reference list, tables and figures). Multiple citations for a single point are usually duplicative and authors are urged to cite the best reference. In exceptional cases the Editor retains discretion to publish papers beyond this length where the clear and concise expression of the scientific content requires greater length (e.g., explanation of a new theory or a substantially new method). Authors must contact the Editor prior to submission in such a case.
- Brief communications are short reports of original research or case reports. They are limited to a maximum of 1500 words (excluding the abstract, reference list, tables and figures) and have a total of up to three tables or figures, and no more than 10 references.
- Theoretical or review articles are full-length reviews of, or opinion statements regarding, the literature in a specific scientific area. They should be no more than 4000 words (excluding the abstract, reference list, tables and figures) and have no more than 45 references. Multiple citations for a single point are usually duplicative and authors are urged to cite the best reference. In exceptional cases the Editor retains discretion to publish papers beyond this length where the clear and concise expression of the scientific content requires greater length (e.g., explanation of a new theory or a substantially new method). Authors must contact the Editor prior to submission in such a case.
- Please refer to the separate guidelines for [Registered Reports](#).
- All systematic reviews must be pre-registered and an anonymous link to the pre-registration must be provided in the main document, so that it is available to reviewers. Systematic reviews without pre-registration details will be returned to the authors at submission.

4. PREPARING THE SUBMISSION

Free Format Submission

Journal of Neuropsychology now offers free format submission for a simplified and streamlined submission process.

Before you submit, you will need:

- Your manuscript: this can be a single file including text, figures, and tables, or separate files – whichever you prefer. All required sections should be contained in your manuscript, including

abstract, introduction, methods, results, and conclusions. Figures and tables should have legends. References may be submitted in any style or format, as long as it is consistent throughout the manuscript. If the manuscript, figures or tables are difficult for you to read, they will also be difficult for the editors and reviewers. If your manuscript is difficult to read, the editorial office may send it back to you for revision.

- The title page of the manuscript, including a data availability statement and your co-author details with affiliations. (*Why is this important? We need to keep all co-authors informed of the outcome of the peer review process.*) You may like to use this template for your title page.

Important: the journal operates a double-anonymous peer review policy. Please anonymise your manuscript and prepare a separate title page containing author details. (*Why is this important? We need to uphold rigorous ethical standards for the research we consider for publication.*)

- An ORCID ID, freely available at <https://orcid.org>. (*Why is this important? Your article, if accepted and published, will be attached to your ORCID profile. Institutions and funders are increasingly requiring authors to have ORCID IDs.*)

To submit, login at <https://wiley.atyponrex.com/journal/JNP> and create a new submission. Follow the submission steps as required and submit the manuscript.

If you are invited to revise your manuscript after peer review, the journal will also request the revised manuscript to be formatted according to journal requirements as described below.

Revised Manuscript Submission

Contributions must be typed in double spacing. All sheets must be numbered.

Cover letters are not mandatory; however, they may be supplied at the author's discretion. They should be pasted into the 'Comments' box in Editorial Manager.

Parts of the Manuscript

The manuscript should be submitted in separate files: title page; main text file; figures/tables; supporting information.

Title Page

You may like to use [this template](#) for your title page. The title page should contain:

- A short informative title containing the major key words. The title should not contain abbreviations (see Wiley's best practice SEO tips);
- A short running title of less than 40 characters;
- The full names of the authors;
- The author's institutional affiliations where the work was conducted, with a footnote for the author's present address if different from where the work was conducted;
- Abstract;
- Keywords;
- Data availability statement (see Data Sharing and Data Accessibility Policy);
- Acknowledgments.

Author Contributions

For all articles, the journal mandates the CRediT (Contribution Roles Taxonomy)—more information is available on our [Author Services](#) site.

Abstract

Please provide an abstract which gives a concise statement of the intention, results or conclusions of the article. The abstract should not include any sub-headings.

- Abstracts for Research Papers should not exceed 250 words.
- Abstracts for theoretical or review articles should not exceed 250 words.
- Abstracts for brief communications should not exceed 80 words.

Keywords

Please provide appropriate keywords.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

Main Text File

As papers are double-anonymous peer reviewed, the main text file should not include any information that might identify the authors.

Manuscripts can be uploaded either as a single document (containing the main text, tables and figures), or with figures and tables provided as separate files. Should your manuscript reach revision stage, figures and tables must be provided as separate files. The main manuscript file can be submitted in Microsoft Word (.doc or .docx) or LaTeX (.tex) format.

If submitting your manuscript file in LaTeX format via Research Exchange, select the file designation “Main Document – LaTeX .tex File” on upload. When submitting a LaTeX Main Document, you must also provide a PDF version of the manuscript for Peer Review. Please upload this file as “Main Document - LaTeX PDF.” All supporting files that are referred to in the LaTeX Main Document should be uploaded as a “LaTeX Supplementary File.”

LaTeX Guidelines for Post-Acceptance:

Please check that you have supplied the following files for typesetting post-acceptance:

- PDF of the finalized source manuscript files compiled without any errors.
- The LaTeX source code files (text, figure captions, and tables, preferably in a single file), BibTeX files (if used), any associated packages/files along with all other files needed for compiling without any errors. This is particularly important if authors have used any LaTeX style or class files, bibliography files (.bbl, .bst, .blg) or packages apart from those used in the NJD LaTeX Template class file.
- Electronic graphics files for the illustrations in Encapsulated PostScript (EPS), PDF or TIFF format. Authors are requested not to create figures using LaTeX codes.

Your main document file should include:

- A short informative title containing the major key words. The title should not contain abbreviations;
- Acknowledgments;
- Abstract without any subheadings;
- Up to seven keywords;
- Main body: formatted as introduction, materials & methods, results, discussion, conclusion;
- References;
- Tables (each table complete with title and footnotes);
- Figure legends: Legends should be supplied as a complete list in the text. Figures should be uploaded as separate files (see below)
- Statement of Contribution.

Supporting information should be supplied as separate files. Tables and figures can be included at the end of the main document or attached as separate files but they must be mentioned in the text.

- As papers are double-anonymous peer reviewed, the main text file should not include any information that might identify the authors. Please do not mention the authors' names or affiliations and always refer to any previous work in the third person.
- The journal uses British/US spelling; however, authors may submit using either option, as spelling of accepted papers is converted during the production process.

References

This journal uses APA reference style; as the journal offers Free Format submission, however, this is for information only and you do not need to format the references in your article. This will instead be taken care of by the typesetter.

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figures

Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted.

[Click here](#) for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc.

[Click here](#) for Wiley's FAQs on supporting information.

Note: if data, scripts, or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

General Style Points

For guidelines on editorial style, please consult the [APA Publication Manual](#) published by the American Psychological Association. The following points provide general advice on formatting and style.

- **Language:** Authors must avoid the use of sexist or any other discriminatory language.
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