A Comprehensive Review on Investigations of Chronic Neuropsychological Impact of SARS-COV-2

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

This study meets ethical criteria by assuring, data confidentiality, integrity, proper attribution, and adherence to ethical guidelines for a rigorous and respectful evaluation.

Abstract

This review aims to provide a comprehensive knowledge on various long-term neuropsychological consequences of SARS-CoV-2. There are numerous pieces of evidence indicating that neuropsychological symptoms might continue long after the disease has ended.

This study synthesizes findings from a wide range of studies conducted worldwide and provides a thorough evaluation of research on the chronic neuropsychological impact of SARS-CoV-2. A total of 54 studies were included in the review. There were various types of studies including retrospective study, cross-sectional study, prospective study, case study, investigational study, survey study, observational study and longitudinal study. This review investigates the multidimensional nature of neuropsychological problems reported in people recovering from COVID-19 shedding information on cognitive deficits, attention problem, psychiatric issues, memory problem, olfactory disorder, anxiety, depression, insomnia, and neurological consequences that persist even after acute respiratory symptoms have subsided.

This comprehensive review adds to our growing understanding of the long-term effects of COVID-19 on the human brain by applying a wide range of tools and methods on the participants including PHQ-9, MMSE, MoCA, GAD-7, PCL-5, PSS-10, Brief-COPE, BRB-NT, IES-R, FSS, COMPASS-31, FAS etc. It emphasizes not only the current state of knowledge, but also the need for ongoing research to inform effective therapeutic interventions, rehabilitation strategies, and preventive measures to reduce the long-term neuropsychological burden on people recovering from SARS-CoV-2 infection.

Keywords: COVID-19, SARS-CoV-2, neuropsychological, neurological, cognitive, brain

Dedication

I want to dedicate my work to my parents who have been supporting me throughout my life.

Acknowledgement

First and foremost, I want to express my deepest gratitude to the almighty Allah who has blessed me to achieve my dream of studying Pharmacy at BRAC University.

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List of Acronyms

PTSD	Post-traumatic stress disorder
AURI	Acute upper respiratory infections
PTSS	Post-traumatic stress syndrome
RCE	Reduced cognitive efficiency
CG	Control group
OD	Olfactory dysfunction

Chapter 1

Introduction

1.1 Background

The severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 causes COVID-19 disease, and predominantly attacks the respiratory system. Moreover, SARS-CoV-2 can enter the central nervous system through a number of different pathways according to research, including the olfactory nerve and the circulation, generating inflammatory responses and potentially causing neuronal damage. Therefore, long-lasting neuropsychological symptoms such emotional instability, memory loss, and cognitive dysfunction may continue in those recovering from COVID-19 (He et al., 2023). Depression, anxiety, PTSD, insomnia, headache, and fatigue can also be persistent (Di Stadio et al., 2022; Fiabane et al., 2022; Fietsam et al., 2023)

Initially, the medical world was naturally focused on the respiratory features of COVID-19, but growing body of evidences highlight the complex interaction between SARS-CoV-2 and the central nervous system. This study explores the long-term neuropsychological consequences that SARS-CoV-2 infected persons face. Neuropsychological symptoms have been reported, ranging from mild cognitive deficits to severe neurological consequences, providing complex issues for both healthcare practitioners and affected persons in the post-acute phase of the illness. This study aims to contribute to a better understanding of the chronic neuropsychological impact of SARS-CoV-2 by conducting a thorough review of available literatures.

1.2 Research gap

Most of the available literatures primarily focuses on the neuropsychological consequences when the disease is in acute phase. Therefore, our knowledge of the virus's long-term and chronic neuropsychological consequences is still noticeably lacking.

Additionally, the majority of the literature that is now available focuses mostly on adults, paying insufficient attention to the possible long-term neuropsychological effects of SARS-CoV-2 infection on children and adolescents. Furthermore, a more nuanced examination of the various neuropsychological outcomes, including cognitive domains such as memory, attention, executive function, and emotional regulation, is required to fully comprehend the range of long-term implications. Moreover, potential processes underlying chronic neuropsychological sequelae must be investigated, including the role of persistent viral presence, neuroinflammation, and the interaction of pre-existing vulnerabilities and COVID-19-related variables.

Consequently, in order to improve our knowledge of the long-term neuropsychological effects of SARS-CoV-2 and to guide targeted therapies, long-term care plans, and public health policies for those impacted by the virus, a comprehensive review that addresses these gaps is essential.

1.3 Objective

This review aims to provide a comprehensive knowledge on various long-term neuropsychological consequences of SARS-CoV-2. There are three significant objectives of doing this review which are mentioned below:

Objective 1: Synthesize existing literatures

Review all of the available research and literature on the neuropsychological effects of SARS-CoV-2, with special attention to the long-term and chronic cognitive effects. An extensive synthesis of the state of the field's knowledge as of right now is the goal of this mission.

Objective 2: Evaluation of methodological approaches

Examine and evaluate the methods used in earlier research on the long-term neuropsychological effects of SARS-CoV-2.

Objective 3: Provide future recommendation and Clinical implications

Provide a concise summary and analysis of the results to produce significant clinical implications for researchers, legislators, and medical professionals and provide guidance for therapeutic approaches, recovery plans, and preventative actions to address and lessen the long-term cognitive effects of SARS-CoV-2.

1.4 Significance

The significance of conducting this review rests in its potential to give useful insights to numerous elements of public health, clinical practice, and scientific understanding.

This review study helps identify and characterize long-term cognitive impacts by summarizing existing literatures. Therefore, it will greatly advance our knowledge of the long-term neuropsychological effects of SARS-CoV-2.

Furthermore, healthcare providers need thorough understanding of the long-term neuropsychological effects of SARS-CoV-2 in order to make effective clinical decisions. Thus, this study can help healthcare practitioners recognize, diagnose, and manage the long-term cognitive effects of COVID-19 in patients. For those who experience persistent neuropsychological problems, this can help guide the development of tailored rehabilitation techniques.

Moreover, this study sets the foundation for future investigations by identifying gaps and limitations in current research, directing researchers to areas that require additional examination and methodological refinement.

Chapter 2

Methods

2.1 Search strategy

A total of five databases were used for the literature search to find relevant articles: Scopus, PubMed, Springer, Google Scholar, and Science Direct. To search for papers about the neuropsychological effects of SARS-COV-2, the following keywords were used: “SARS-CoV-2”, “COVID-19”, “Post-COVID”, “Pandemic”, “Psychiatry”, “Neuropsychology”, “Cognitive impairment”, “Neurological investigations”, “Neuropsychological deficits”, “PTSD”, “Memory”, “Anxiety”, “Depression”, and “Fatigue”.

2.2 Inclusion and Exclusion Criteria

The articles met the following inclusion criteria: (1) articles describing the impacts of SARS-COV-2 on human neuropsychology, cognitive functioning, and various neuropsychological diseases; (2) original articles published between 2019 and 2023; (3) complete study with clear methods and outcome; (4) published in English; and (5) full-text accessible.

The following articles were excluded: (1) review; (2) systematic review; (3) meta-analysis; (4) vaccination studies; and (5) incomplete studies

2.3 Data Extraction

Searches of databases turned up a total of 4,132 articles. After reviewing the abstracts and titles, and removing duplicates, 461 articles were retained for additional screening. After applying all the exclusion criteria, 442 of them were deemed eligible for inclusion in the study. Finally, 54 of those were ultimately included in the systematic review after applying the inclusion criteria.

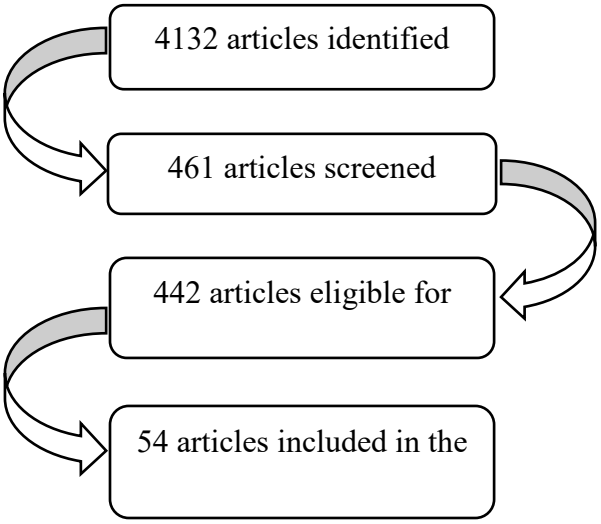

Figure 1: Flowchart representing the literature selection process

Chapter 3

Results

3.1 Study and Participant characteristics

In total, 54 articles were included in the final study with cross-sectional study being the most common (n= 14). Retrospective study (n= 5), prospective study (n= 7), case study (n= 3), investigational study (n= 4), survey study (n=3), observational study (n= 8), longitudinal study (n= 4) and other types of articles were also included in the study. The articles featured various categories of participants, with COVID-19 patients and survivors comprising the majority. Moreover, all the articles included in the study had human participants during or after the COVID-19 pandemic (Table 1).

Table 1: Types of studies and participants

Study type	Number of studies	Participant type	Number of participants	Reference
	05	Patients diagnosed with COVID-19 and AURI	134092	(Bohlken et al., 2022)
		Hospitalized COVID-19 patients with persistent neuropsychological deficits one-year post-release	07	(Ferrucci et al., 2023)

Study type	Number of studies	Participant type	Number of participants	Reference
Retrospective study		Neurological long COVID outpatient clinic attending patients	103	(Taruffi et al., 2023)
		COVID-19 survivors classified as at risk for or not at risk for brain disorders	152	(Fiabane et al., 2022)
		Hospitalized COVID-19 patients	891	(Nejad et al., 2021)
Prospective study	07	Post-COVID individuals with and without neurological symptoms	180	(Buoite Stella et al., 2022)
		COVID-19 patients with neurocomplications and controls	382	(Frontera et al., 2021)
		Hospitalized COVID-19 patients	451	(Frontera et al., 2022)
		Hospitalized COVID-19 patients with headache complaints	85	(Akıncı, 2023)

Study type	Number of studies	Participant type	Number of participants	Reference
		ICU and non-ICU COVID-19 patients	215	(Mattioli et al., 2022)
		Pregnant women with and without COVID-19	238	(G. k. Ahmed et al., 2022)
		Patients who were in the mild phase of COVID-19 disease	895	(Ismael et al., 2021)
Cross-sectional study	14	Healthcare workers and others	14945	(Jiang et al., 2023)
		Adolescents with COVID-19 infection 3-6 months before evaluation	31	(Tarantino et al., 2022)
		People with epilepsy (PWE) and caregivers during COVID-19 pandemic	590	(Cross et al., 2021)
		People with Multiple Sclerosis during COVID-19 pandemic	205	(Altunan et al., 2021)
		Patients with self-reported olfactory dysfunction due to COVID-19	152	(Di Stadio et al., 2022)

Study type	Number of studies	Participant type	Number of participants	Reference
		Participants who had mild, moderate or severe case of COVID-19 in the acute phase	102	(Voruz et al., 2022)
		COVID-19 patients and uninfected spouses of the patients	2005	(Liu et al., 2021)
		Adult COVID-19 survivors and healthy controls	170	(Abdelghani et al., 2022)
		COVID-19 patients and controls	93	(Douaud et al., n.d.)
		COVID-19 patients with cognitive symptoms three months after disease onset	50	(Delgado-Alonso et al., 2022)
		Participants with SARS-CoV-2 infection	2828	(Schneider et al., 2023)
		Participants diagnosed with COVID-19 previously	401	(M. Ahmed et al., 2022)

Study type	Number of studies	Participant type	Number of participants	Reference
		COVID-19 recovered patients	506	(Craparo et al., 2022)
		COVID-19 survivors with and without PTSD (post-traumatic stress disorder) symptoms	1108	(Xiao et al., 2023)
Case study	03	COVID-19 survivors with cognitive impairments at one-month follow-up.	73	(Palladini et al., 2022)
		A 23 year old man	01	(Gilio et al., 2022)
		A 76-year old male veteran with a historical diagnosis of mild cognitive impairment	01	(Okolichany et al., 2022)
Investigational study	04	Participants with and without post COVID-19 symptoms	49	(Fietsam et al., 2023)
		Post-COVID-19 patients with complaints of fatigue and control group	24	(Ortelli et al., 2021)

Study type	Number of studies	Participant type	Number of participants	Reference
		COVID-19 patients with severe, moderate, and mild forms of disease	110	(Voruz et al., 2023)
		Non-hospitalized mild and moderate COVID-19 patients	107	(Abdel Azim & Osman, 2021)
Survey study	03	CADASIL patients during the COVID-19 pandemic	135	(Reyes et al., 2023)
		COVID-19 recovered patients with mild to severe forms of disease experience	1584	(Thomason et al., 2022)
		Adults aged ≥18 years during the extended lockdown in Victoria, Australia	1157	(Czeisler et al., 2021)
		Convalescent COVID-19 patients undergoing pulmonary rehabilitation	63	(Moretta et al., 2022)
		Healthcare workers at 3 and 12 months post-pandemic	410	(Cyr et al., 2022)

Study type	Number of studies	Participant type	Number of participants	Reference
Observational study	08	COVID-19 survivors included in ME/CFS+ (myalgic encephalomyelitis / chronic fatigue) and ME/CFS- group	37	(Mantovani et al., 2021)
		COVID-19 survivors with neurological manifestations	60	(Chaumont et al., 2022)
		Physically functional COVID-19 patients and controls without infection	60	(do Carmo Filho et al., 2022)
		Long COVID patients with cognitive impairment complains and healthy controls (HC)	34	(Manganotti et al., 2023)
		Health care workers (HCWs) in China.	171	(Chen et al., 2020)
		COVID-19 survivors and healthy controls (HCs)	145	(He et al., 2023)
Longitudinal study	04	COVID-19 patients discharged from hospital	329	(Sun et al., 2023)

Study type	Number of studies	Participant type	Number of participants	Reference
		COVID-19 patients who received hospital care for acute infection	21	(Diana et al., 2023)
		Adult participants with epilepsy during 2020 and 2021 lockdown period	193	(Gander et al., 2023)
		COVID-19 positive patients and controls	252	(Johnson et al., 2022)
Retrospective and prospective study	01	Patients with COVID-19 pneumonia diagnosis	41	(Pellitteri et al., 2022)
Multidisciplinary approach	01	Children with COVID-19 and respiratory tract infection and matched controls	50	(Troitskaya et al., 2022)
Online study	01	Adolescents aged 12–18 with SARS-CoV-2 infection and matched controls	684	(Yilmaz Kafali et al., 2022)
Monocentric study	01	Participants with laboratory confirmed COVID-19 and subjective olfactory dysfunction (OD)	102	(Prem et al., 2022)

Study type	Number of studies	Participant type	Number of participants	Reference
Analysis of two year retrospective cohort studies	01	COVID-19 and other respiratory infected patients	2568874	(Taquet et al., 2022)
Population based cohort study	01	COVID-19 survivors and controls	299968	(Park et al., 2021)

3.2 Outcomes of each study type

The outcome of each and every included study is shown in Table 2. The overall outcome under each type of study is demonstrated below:

Retrospective study

All five of the included studies had nearly identical neuropsychological findings (Table 2). A study found that the overall rate of mild cognitive disorder (MCD) was much greater in COVID-19 patients than in AURI (acute upper respiratory infection) patients (Bohlken et al., 2022). Two of the studies demonstrated that COVID-19 patients displayed poor verbal memory, memory impairment, poor processing speed, deficits in attentive and executive functions (Ferrucci et al., 2023; Taruffi et al., 2023). Presence of depression and anxiety among the participants were found (Fiabane et al., 2022; Taruffi et al., 2023). Neurological manifestations like headache, memory impairment, vertigo, sleeplessness, hyposmia / anosmia, and hypogeusia were common among COVID-19 patients (Nejad et al., 2021).

Prospective study

Post-COVID individuals had neurological symptoms like myalgia/asthenia, headache, hyposmia / hypogeusia, dizziness, sleep problems, and brain fog/cognitive loss (Buoite Stella et al., 2022). One of the studies revealed that six months after being hospitalized with COVID-19, more than 90% of patients showed abnormalities in functional outcomes, cognitive impairment, ADLs, anxiety, depression and sleep (Frontera et al., 2021). Cognitive, and neuropsychiatric outcomes got worsened 12 months after COVID-19 hospitalization (Frontera et al., 2022). A study found out that majority of the COVID-19 patients had taste/smell dysfunction, and patients with headaches had increased smell/taste issues (Akıncı, 2023). Another study revealed that ICU COVID-19 patients are more susceptible to develop cognitive deterioration and neurological deficits (Mattioli et al., 2022). Pregnant women with COVID-19 had more psychiatric issues than women without COVID-19, with the exception of post-traumatic stress disorder (G. k. Ahmed et al., 2022). Symptoms of depression, anxiety, and post-traumatic stress were recorded at clinically significant levels in patients who were in the mild phase of COVID-19 disease (Ismael et al., 2021).

Cross-sectional study

Almost all of the 14 included studies demonstrated that majority of the COVID-19 patients and/or survivors had cognitive impairment and various psychological issues (Table 2). Depression, anxiety, headache and attention and concentration issues were very common among the participants. (Abdelghani et al., 2022; Craparo et al., 2022; Delgado-Alonso et al., 2022; Di Stadio et al., 2022; Tarantino et al., 2022). Other common issues reported by the participants include anosmia, hyposmia, fatigue, memory problem, and impaired executive function (Abdelghani et al., 2022; M. Ahmed et al., 2022; Delgado-Alonso et al., 2022; Di Stadio et al., 2022; Schneider et al., 2023). A study showed that during the pandemic, healthcare workers experienced tremendous stress and Severe psychosomatic symptoms in China (Jiang et al., 2023). A study found that psychological distress was much higher in people

with epilepsy compared to the caregivers (Cross et al., 2021). Cognitive impairment, anxiety, depression and fatigue were higher in COVID-19 patients and / or survivors compared to controls (Abdelghani et al., 2022; Douaud et al., n.d.)

Case study

One of the three included studies showed that the global cognitive functioning had been effected significantly by the CRT program including improvement in verbal fluency and executive functions on quality of life (Palladini et al., 2022). A study revealed that patient had normal cognitive profile but increased anxiety and depression and the patient had improved dysesthesia, motor, and cognitive issues after four months of therapy (Gilio et al., 2022). A study found that psychosocial conditions may reduce cognitive and functional decline in older COVID-19 patients (Okolichany et al., 2022).

Investigational study

A total of four studies were included (Table 2). A study found that the symptomatic patients had more fatigue, pain, poor quality of life, and perceived fatigability, but not objective fatigability (Fietsam et al., 2023). Another study found that when compared to healthy controls, patients had significantly increased levels of fatigue, apathy, executive deficits, impaired cognitive control, and neuropsychological difficulties (Ortelli et al., 2021). Moreover, one study revealed that every COVID-19 patient experienced neurological symptoms within 10 days of the epidemic where headache predominated Other symptoms include fatigue, myalgia, anomalia/dysgeusia, and dizziness (Abdel Azim & Osman, 2021). One of the included studies revealed that lack of cognitive flexibility was observed in the intermediate group, while poor verbal performance in episodic memory tasks was observed in the severe group (Voruz et al., 2023).

Survey study

According to one of the three included survey studies, depressive episode, post-traumatic and stressor related disorder manifestations were significantly present in 9% of the studied patients (Reyes et al., 2023). Another study claimed that due to COVID-19, 25% of the surveyed patients had memory or cognitive issues, and 19.4% of them complained of persistent mood symptoms (Thomason et al., 2022). Moreover, anxiety, depression, and suicidal thoughts were prevalent and adverse mental health symptoms were more common in young adults, unpaid caregivers, disabled people, and psychiatric or sleep disorder patients (Czeisler et al., 2021).

Observational study

A total of eight observational studies were included (Table 2). The most common problem observed among the included study participants were cognitive impairment, anxiety, depression, and post-traumatic stress disorder (PTSD) (Chaumont et al., 2022; Chen et al., 2020; He et al., 2023; Mantovani et al., 2021; Moretta et al., 2022). Additionally, fatigue, poor sleep quality, problems in smell and taste, and reduced executive functioning were also reported (Chaumont et al., 2022; He et al., 2023; Manganotti et al., 2023; Mantovani et al., 2021; Moretta et al., 2022). Moreover, a study claimed that About 50% of the sample had Reduced cognitive efficiency (RCE) in spatial and linguistic long-term memory and executive functioning (Moretta et al., 2022). Furthermore, those with symptoms similar to ME/CFS-(myalgic encephalomyelitis / chronic fatigue) reported poorer sleep quality, more fatigue, pain, depression, and subjective cognitive complaints (Mantovani et al., 2021). However, one study found that visuomotor reaction time (RT) and VRT (variability of reaction time) were both longer for COVID-19 patients at discharge, and omission mistakes were more common, compared to controls (do Carmo Filho et al., 2022). A study revealed that Health care workers who treated patients with COVID-19 reported higher rates of stress and chronic stress related disorders (Chen et al., 2020).

Longitudinal study

One of the four included studies revealed that, the COVID-19 survivors' probable PTSD (post-traumatic stress disorder) dropped dramatically over a year and women with respiratory sequelae were more likely to develop chronic PTSD (Sun et al., 2023). Moreover, a study found out that at t0, 50% of COVID-19 patients demonstrated cognitive impairment, predominantly verbal memory. Depression and PTSD impacted 30% of patients and were linked to attentional executive function which declined over time (Diana et al., 2023). Furthermore, one study showed that those who test positive for COVID-19 are more likely to experience a rise in depression symptoms once the quarantine is lifted when compared to controls (Johnson et al., 2022).

Other studies

There were seven other types of study included. The rate of insomnia increased after COVID-19, and the prevalence of insomnia disorder was significantly higher among COVID-19 survivors compared to the control group (Park et al., 2021; Pellitteri et al., 2022). Furthermore, children with Post-COVID19 syndrome were found to have a higher prevalence of cognitive disorders such as executive dysfunction, attention deficit, and memory impairment compared to the control group (Troitskaya et al., 2022). The CAPE-Positive Frequency/Stress scores were higher in SARS-CoV-2 than in CG (Yilmaz Kafali et al., 2022). According to a monocentric study, SARS-CoV-2 infection is associated with persistent olfactory dysfunction (OD) (Prem et al., 2022). An analysis of two-year retrospective cohort studies revealed that 2 years after COVID-19 infection, cognitive impairments, dementia, psychotic illnesses, and seizures increased. Although children had no risk of mood or anxiety disorder, they had other risk factors (Taquet et al., 2022).

3.3 Methods & Results

Table 2 represents the various kinds of investigational tools and methods used in the included studies along with the main results and findings from the included studies.

Table 2: Investigation tools/methods and results

Study type	Investigation tools/methods	Main results	Reference
Retrospective study	Disease Analyzer database (IQVIA), conditional Poisson regression models, Kaplan-Meier curves propensity score matching, ICD-10 codes, McNemar tests and Wilcoxon signed-rank tests	The overall rate of mild cognitive disorder was much greater in COVID-19 than in AURI (acute upper respiratory infection) patients, with the exception of those aged 70 and older.	(Bohlken et al., 2022)
	Brief Repeatable Battery of Neuropsychological Tests (BRB-NT	Patients initially displayed poor verbal memory, processing speed, visual attention, and learning, but visual-spatial learning fully recovered after one year, with some experiencing verbal memory problems,	(Ferrucci et al., 2023)

Study type	Investigation tools/methods	Main results	Reference
		processing and visual attention inadequacies, and concentration issues.	
	A complete neuropsychological evaluation using a standardized battery	Neuropsychological assessment showed memory impairment, depressive mood, deficits in attentive and executive functions, and a high level of anxiety in participants.	(Taruffi et al., 2023)
	Patient Health Questionnaire-9 (PHQ-9), Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Generalized Anxiety Disorder-7 (GAD-7), Impact of Event Scale-Revised (IES-R)	Both groups of post COVID19 patients had mild to moderately frequent symptoms of depression, anxiety, and PTSD.	(Fiabane et al., 2022)
	Analysis of neurological manifestations and demographic characteristics	Neurological manifestations like headache, memory impairment, vertigo, sleeplessness, hyposmia/ anosmia, hypogeusia were	(Nejad et al., 2021)

Study type	Investigation tools/methods	Main results	Reference
		common among COVID-19 patients.	
Prospective study	COMPASS-31 questionnaire, neuropsychological evaluation	97 patients had neurological symptoms (myalgia/asthenia, headache, hyposmia / hypogeusia, dizziness, sleep problems, brain fog/cognitive loss), whereas 83 patients had additional post-COVID sequelae.	(Buoite Stella et al., 2022)
	Telephone Montreal Cognitive Assessment, the modified Rankin Scale (mRS), activities of daily living (ADLs; Bar-thel Index) and Neuro-QoL batteries	Six months after being hospitalized with COVID-19, more than 90% of patients showed abnormalities in functional outcomes, cognitive impairment, anxiety, depression and sleep.	(Frontera et al., 2021)
	The modified Rankin Scale (mRS), the Barthel Index, the telephone Montreal Cognitive Assessment (t-MoCA), Neuro-QoL batteries	51% of the patients reported major life pressures at 12 months. Life stressors made functional, cognitive, and neuropsychiatric outcomes worse 12 months after COVID-19 hospitalization.	(Frontera et al., 2022)

Study type	Investigation tools/methods	Main results	Reference
	Evaluation of clinical COVID-19 features and the characteristics and course of the patients' headaches	65.3% of patients had taste/smell dysfunction, with 25.9% still had it 3 months later. Three months after hospital discharge, 20% had headaches, which increased smell/taste issues.	(Akıncı, 2023)
	Extensive cognitive evaluations and neurological exams	Results showed that ICU patients had poor results in neuropsychological tests and they are more susceptible to develop cognitive deterioration and neurological deficits.	(Mattioli et al., 2022)
	STAI (State-Trait Anxiety Inventory), EPDS (Edinburgh Postnatal Depression Scale), PCL-5 (PTSD Checklist for DSM-5)	Women with COVID-19 had more psychiatric issues than women without COVID-19, with the exception of post-traumatic stress disorder. The most significant issues were anxiety and depression.	(G. k. Ahmed et al., 2022)
	Generalized Anxiety Disorder-7 (GAD-7), Patient Health	Symptoms of depression, anxiety, and post-traumatic stress were recorded at clinically significant levels.	(Ismael et al., 2021)

Study type	Investigation tools/methods	Main results	Reference
	Questionnaire-9 (PHQ-9), PCL-C scale		
Cross-sectional study	Perceived Stress Scale-10 (PSS-10) and Psychosomatic Symptom Scale (PSSS)	During the pandemic, healthcare workers experienced tremendous stress and Severe psychosomatic symptoms in China.	(Jiang et al., 2023)
	A telehealth procedure, a checklist and a battery of multiple standardized measures	The majority of participants had depression and anxiety. 58% of patients experienced long-COVID symptoms, mostly headache and concentration issues.	(Tarantino et al., 2022)
	A survey form about access to health services, impact of COVID-19, and 6- item Kessler Psychological Distress Scale (K-6)	Psychological distress was much higher in people with epilepsy compared to the caregivers. 57% of PWE and 27% of caregivers suffered serious psychological discomfort.	(Cross et al., 2021)
	Coping with Experienced Problems Scale (Brief-COPE), Perceived stress scale	The pandemic saw many patients use religious coping, strategic planning, and acceptance. Twenty-three had stellar PSS scores. LowProgression Status	(Altunan et al., 2021)

Study type	Investigation tools/methods	Main results	Reference
	(PSS) and Quality of Life scale (SF-12)	Scale patients used the acceptance strategy more.	
	Headache scale, Mini Mental State Examination (MMSE), Cognitive assessment, Olfactometry, Nasal endoscopy and self-reported measures	The patients reported headaches, cognitive fog, anosmia, hyposmia, parosmia/cacosmia, and a mix of the two. Patients with mental clouding and headaches had increased anosmia and hyposmia.	(Di Stadio et al., 2022)
	A battery of neuropsychological, olfactory, fatigue, psychiatric, dyspnoea, and quality of life tests and questionnaires	In nosognosic subjects the self-reported psychiatric symptoms, fatigue and dyspnea were higher with poor quality of life. However, unconsciousness of olfactory recognition deficit was higher in anosognosic patients.	(Voruz et al., 2022)
	Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) & a Chinese version of the Telephone Interview of Cognitive Status-40 (TICS-40)	The percentage of cases exhibiting both longitudinal cognitive deterioration and current cognitive impairment was higher in patients with severe COVID-19 compared to non-	(Liu et al., 2021)

Study type	Investigation tools/methods	Main results	Reference
		severe COVID-19 patients and controls.	
	Montreal Cognitive Assessment (MoCA), Structured Clinical Interview for DSM-5 Axis I Disorders (SCID-5), Hospital Anxiety Depression Scale (HADS)	COVID-19 survivors had more cognitive impairment and higher anxiety and depression levels than controls. The visou-executive skills, delayed recall, attention and language, were mostly impacted.	(Abdelghani et al., 2022)
	The Chalder Fatigue Scale (CFQ-11), Montreal Cognitive Assessment (MoCA), the Cambridge Neuropsychological Test Automated Battery (CANTAB)	Overall CFQ-11 scores were higher in the COVID-19 group compared to the control group. Neuropsychological performance did not vary significantly across groups.	(Douaud et al., n.d.)
	A battery of neuropsychological scales and tests, including those for	Patients demonstrated impaired cognitive function, particularly in areas of executive function, episodic memory, visuospatial	(Delgado-Alonso et al., 2022)

Study type	Investigation tools/methods	Main results	Reference
	fatigue, depression, anxiety, sleep, and smell.	processing, and attention-concentration.	
	Somatic Symptom Disorder scale, Patient Health Questionnaire, Generalized Anxiety Disorder scale, and Fatigue Assessment Scale	Half of the patients reported ongoing symptoms, and some believed they had a daily life impairment which was most strongly correlated with self-reported fatigue, dyspnea, and poor focus.	(Schneider et al., 2023)
	The Memory Complaint Questionnaire (MACQ), a binary logistic regression model, Statistical analysis	About 20% of people with COVID-19 developed various memory issues within a year. Despite this, no link between memory issues and COVID-19 severity was found.	(M. Ahmed et al., 2022)
	Hospital anxiety and depression scale, Personality inventory for DSM-5 brief form, Toronto alexithymia scale-20, Impact of event scale-revised,	The presence of elevated levels of alexithymia, dissociation, anxiety, and sadness has been found to be indicative of the likelihood of experiencing post-traumatic stress disorder symptoms in COVID-19 recovered participants.	(Craparo et al., 2022)

Study type	Investigation tools/methods	Main results	Reference
	Dissociative experience scale-ii		
	Propensity scorematching (PSM), Pittsburgh Sleep Quality Index, Demographics questionnaire, Perceived Social Support Questionnaire, the Resilience Style Questionnaire, the Peace of Mind Scale, the Impact of Events Scale-Revised, the Fatigue Scale-14, the Short Version of COVID-19 Stigma Scale	The study revealed four potential risk factors: a more severe case of COVID-19 infection, chronic fatigue, social isolation due to COVID-19, and poor sleep quality.	(Xiao et al., 2023)
Case study	Cognitive remediation therapy (CRT), a neuropsychological screening test, the Brief Assessment of Cognition	The global cognitive functioning had been effected significantly by the CRT program including improvement in verbal fluency and executive functions on quality of life.	(Palladini et al., 2022)

Study type	Investigation tools/methods	Main results	Reference
	in Schizophrenia, and a mixed model ANOVA		
	Neuropsychological evaluation, a course of psychoanalytic psychotherapy and targeted physical therapy	Patient had normal cognitive profile but increased anxiety and depression. The patient improved dysesthesia, motor, and cognitive issues after four months of therapy.	(Gilio et al., 2022)
	A battery of cognitive tests and self-report measures	The results of the pre- and post-COVID tests showed no discernible pattern of cognitive changes. Better psychosocial conditions may reduce cognitive and functional decline in older COVID-19 patients.	(Okolichany et al., 2022)
Investigational study	Fatigue Severity Scale (FSS), Visual Analog Scale for pain (VAS), Fatigue Assessment Scale (FAS), and the EQ-5D-5L	The symptomatic patients had more fatigue, pain, poor quality of life, and perceived fatigability, but not objective fatigability.	(Fietsam et al., 2023)
	Montreal Cognitive Assessment, Apathy	When compared to healthy controls, patients had	(Ortelli et al., 2021)

Study type	Investigation tools/methods	Main results	Reference
	Evaluation Scale, Beck Depression Inventory, Fatigue Rating Scale, Fatigue Severity Scale, Frontal Assessment Battery, computerized tasks	significantly increased levels of fatigue, apathy, executive deficits, impaired cognitive control, and neuropsychological difficulties.	
	Neuropsychological tests, olfactory tests, psychiatric and respiratory questionnaires	A lack of cognitive flexibility was observed in the intermediate group, while poor verbal performance in episodic memory tasks was observed in the severe group.	(Voruz et al., 2023)
	Data collection using a questionnaire	Every COVID-19 patient experienced neurological symptoms within 10 days of the epidemic where headache predominated Other symptoms include fatigue, myalgia, anomalia/dysgeusia, and dizziness.	(Abdel Azim & Osman, 2021)
Survey study	French version of both the Montgomery and	Among the patients 9% had a depressive episode. Additionally,	(Reyes et al., 2023)

Study type	Investigation tools/methods	Main results	Reference
	Asberg Depression Rating Scale and the Weiss Impact of Event Scale, Euro-QoL, a specific questionnaire	posttraumatic and stressor-related disorder manifestations were also significantly present in 9% of the patients.	
	Detailed medical and psychosocial information from the participants	Due to COVID, 25% of patients said they had memory or cognitive issues, and 19.4% of them complained of persistent mood symptoms.	(Thomas on et al., 2022)
	Surveys and multivariable Poisson regression models	Anxiety, depression, and suicidal thoughts were prevalent. Adverse mental health symptoms were more common in young adults, unpaid caregivers, disabled people, and psychiatric or sleep disorder patients.	(Czeisler et al., 2021)
Observational study	Self-report questionnaires to assess psychological distress and quality of life, and a standardized	The study participants had high rates of depression, anxiety, and PTSD. About 50% of the sample had Reduced cognitive efficiency (RCE) in spatial and linguistic	(Moretta et al., 2022)

Study type	Investigation tools/methods	Main results	Reference
	neuropsychological assessment battery	long-term memory and executive functioning.	
	Validated questionnaires for the assessment of psychological distress and burnout	At three and twelve months, burnout and anxiety remained same while PTSD and depression decreased.	(Cyr et al., 2022)
	Neuropsychiatric and neuropsychological assessment scales and test batteries.	Those with symptoms similar to ME/CFS- reported poorer sleep quality, more fatigue, pain, depression, and subjective cognitive complaints.	(Mantovani et al., 2021)
	3-level version of the EuroQol five dimension scale, Montreal Cognitive Assessment Blind, Hospital Anxiety and Depression Scale, 35- item version of Cognitive Difficulties Scale	Six months following the acute phase, half of the patients still had some degree of impairment and poor quality of life. The most common neuropsychiatric effects were cognitive impairment, anxiety and depression, and problems with smell and taste.	(Chaumont et al., 2022)
	Continuous Visual Attention Test (CVAT)	Visuomotor reaction time (RT) and VRT (variability of reaction time) were both longer for	(do Carmo

Study type	Investigation tools/methods	Main results	Reference
		COVID-19 patients at discharge, and omission mistakes were more common, compared to controls.	Filho et al., 2022)
	Neuropsychological assessment of attentive and executive functions, Fatigue Severity Scale (FSS), Montreal Cognitive Assessment (MoCA)	The patients had a much lower MoCA adjusted score than the controls. Most patients' neuropsychological evaluations of their executive skills revealed below average performance. The vast majority of these individuals had very high levels of fatigue.	(Mangan otti et al., 2023)
	Multiple psychological evaluation scales	As compared to HCW in the low-risk group, individuals in the high-risk group were more likely to be diagnosed with posttraumatic stress symptoms (PTSS). Health care workers who treated patients with COVID-19 reported higher rates of stress and chronic stress-related disorders.	(Chen et al., 2020)
	Questionnaires for neuropsychiatric evaluation and Cognitive	Even 15 months after being released from the hospital, survivors of COVID-19 continue	(He et al., 2023)

Study type	Investigation tools/methods	Main results	Reference
	assessment using a digital, gamified tool	to exhibit signs of cognitive impairment, particularly in executive function.	
Longitudinal study	Primary-Care PTSD screening questionnaire, 9-item Patient Health Questionnaire, modified British Medical Research Council dyspnea scale, EuroQol five dimension five-level questionnaire, and the 7-item Generalized Anxiety Disorder	The COVID-19 survivors' probable PTSD dropped dramatically over a year. Non-severe patients improved in all four PTSD clusters at 12 months, while severe patients only improved in numbing and re-experiencing. Women with respiratory sequelae were more likely to develop chronic PTSD.	(Sun et al., 2023)
	Neuropsychological testing, and memory, attention and executive function tests, as well as questionnaires on depression, PTSD, psychological health, and quality of life	At t0, 50% of COVID-19 patients demonstrated cognitive impairment, predominantly verbal memory. Depression and PTSD impacted 30% of patients and were linked to attentional executive function which declined over time.	(Diana et al., 2023)

Study type	Investigation tools/methods	Main results	Reference
	Telemedicine, a 14- part questionnaire	Researchers observed no statistically significant difference between the two strictest lockdowns in terms of seizure control or lifestyle characteristics.	(Gander et al., 2023)
	Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7 (GAD-7), Bergen Insomnia Scale (BIS)	Those who test positive for COVID-19 are more likely to experience a rise in depression symptoms once the quarantine is lifted when compared to controls.	(Johnson et al., 2022)
Retrospective and prospective study	Clinical interviews, self-administered questionnaires, and neurological examinations	The rate of insomnia increased after COVID-19, and abnormalities in T1 and T2 scores for anxiety, depression, and PTSD were seen in a sizeable percentage of patients.	(Pellitteri et al., 2022)
Multidisciplinary approach	Neuropsychological testing that include assessments of Praxis, Gnosis, Memory, Motor attention and Thinking	Children with Post-COVID19 syndrome were found to have a higher prevalence of cognitive disorders such as executive dysfunction, attention deficit, and	(Troitskaya et al., 2022)

Study type	Investigation tools/methods	Main results	Reference
		memory impairment compared to the control group.	
Online study	The Pittsburg Sleep Quality Index (PSQI), Generalized Anxiety Disorder (GAD-7), Patient Health Questionnaire (PHQ9), and the Community Assessment of Psychic Experiences-42 (CAPE-Pos)	The CAPE-Positive Frequency/Stress scores were higher in SARS-CoV-2 than in CG, while the GAD-7 Total and PSQI Total scores were lower. Additional risk factors for having at least one CAPE-Pos "often" or "almost always" present were smoking, GAD-7, and PHQ9 scores.	(Yilmaz Kafali et al., 2022)
Monocentric study	Chemosensory test, 27-item Candy Smell Test, psychophysical testing, Taste Strips Test, and importance of olfaction (IOQ) and olfactory-specific quality of life (QOD) questionnaires	According to the study, SARS-CoV-2 infection is associated with persistent olfactory dysfunction (OD). The majority of patients, as confirmed by thorough smell tests, had OD within the range of hyposmia.	(Prem et al., 2022)
Analysis of two year	Data extraction (fromTriNetX electronic health records network),	2 years after COVID-19 infection, cognitive impairments, dementia, psychotic illnesses,	(Taquet et al., 2022)

Study type	Investigation tools/methods	Main results	Reference
retrospective cohort studies	propensity-score matching, and statistical analyses	and seizures increased. Although children had no risk of mood or anxiety disorder, they had other risk factors.	
Population based cohort study	Data extraction from the National Health Insurance Service (NHIS) COVID-19 database and statistical analysis	The prevalence of insomnia disorder was significantly higher among COVID-19 survivors compared to the control group.	(Park et al., 2021)

3.4 Discussion

Summary of the findings

This systematic review was conducted to find out the chronic neuropsychological impact of SARS-COV-2. We studied 54 articles that included 3035612 participants (Table1).

We observed that participants had experienced various neuropsychological problems due to COVID-19. The most common issues included cognitive impairment, attention problem, deficits in executive functions, depression, anxiety, memory problem, post-traumatic stress disorder, olfactory disorder, headache, psychiatric issues, fatigue, cognitive fog, anosmia, hyposmia, insomnia, concentration problem, and many other neuropsychological problems were also observed in some of the participants (Table 2).

There are many direct and indirect mechanisms that might be associated with SARS-COV-2 neuropsychological problems but the mechanism is unclear (Bohlken et al., 2022; Ferrucci et al., 2023). However, a study claimed that long-OVID-19 patients may experience headache, cognitive, and olfactory impairment due to neuroinflammation brought on by SARS-CoV-2 infection (Di Stadio et al., 2022).

Common Investigational tools/methods

The Brief Repeatable Battery of Neuropsychological Tests (BRB-NT): A battery of neuropsychological tests used to measure cognitive impairments in participants (Ferrucci et al., 2023).

The Patient Health Questionnaire-9 (PHQ-9): A 9 item questionnaire which measured depression in participants (Fiabane et al., 2022).

The Generalized Anxiety Disorder-7 (GAD-7): An anxiety measurement tool used to measure anxiety level of the participants (Fiabane et al., 2022).

The Impact Event Scale-Revised (IES-R): This tool was used to measure post-traumatic stress disorder (PTSD) in participants (Fiabane et al., 2022)

The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA): Both of these tools were used for the assessment of the cognitive functioning of the participants (Fiabane et al., 2022).

The Composite Autonomic Symptom Scale 31 (COMPASS-31): A questionnaire that is a commonly used instrument for evaluating symptoms of autonomic nervous system failure (Buoite Stella et al., 2022).

The 6-item Kessler Psychological Distress Scale (K-6): A tool that measured the psychological state of the participants (Cross et al., 2021).

The Perceived Stress Scale-10 (PSS-10): PSS-10 was used as a measurement tool of perceived stress among the participants (Jiang et al., 2023).

PTSD Checklist for DSM-5 (PCL-5): Post-traumatic stress disorder (PTSD) in mothers was assessed using a 20-item scale called the PTSD Checklist for DSM-5 (PCL-5) (G. k. Ahmed et al., 2022).

Brief-COPE: A 28-item self-report tool called Brief-COPE was created to assess how well and poorly people handle stressful life events (Altunan et al., 2021).

The Fatigue Assessment Scale (FAS) and the Fatigue Severity Scale (FSS): These two tools were used to evaluate fatigue and perceived fatigue (Fietsam et al., 2023).

The Chalder Fatigue Scale (CFQ-11): A tool that measured the severity of fatigue and its extent (Douaud et al., n.d.).

The Hospital anxiety and depression scale (HADS): This 14 item tool was used to assess depression and anxiety among participants with various physical pathologies (Craparo et al., 2022).

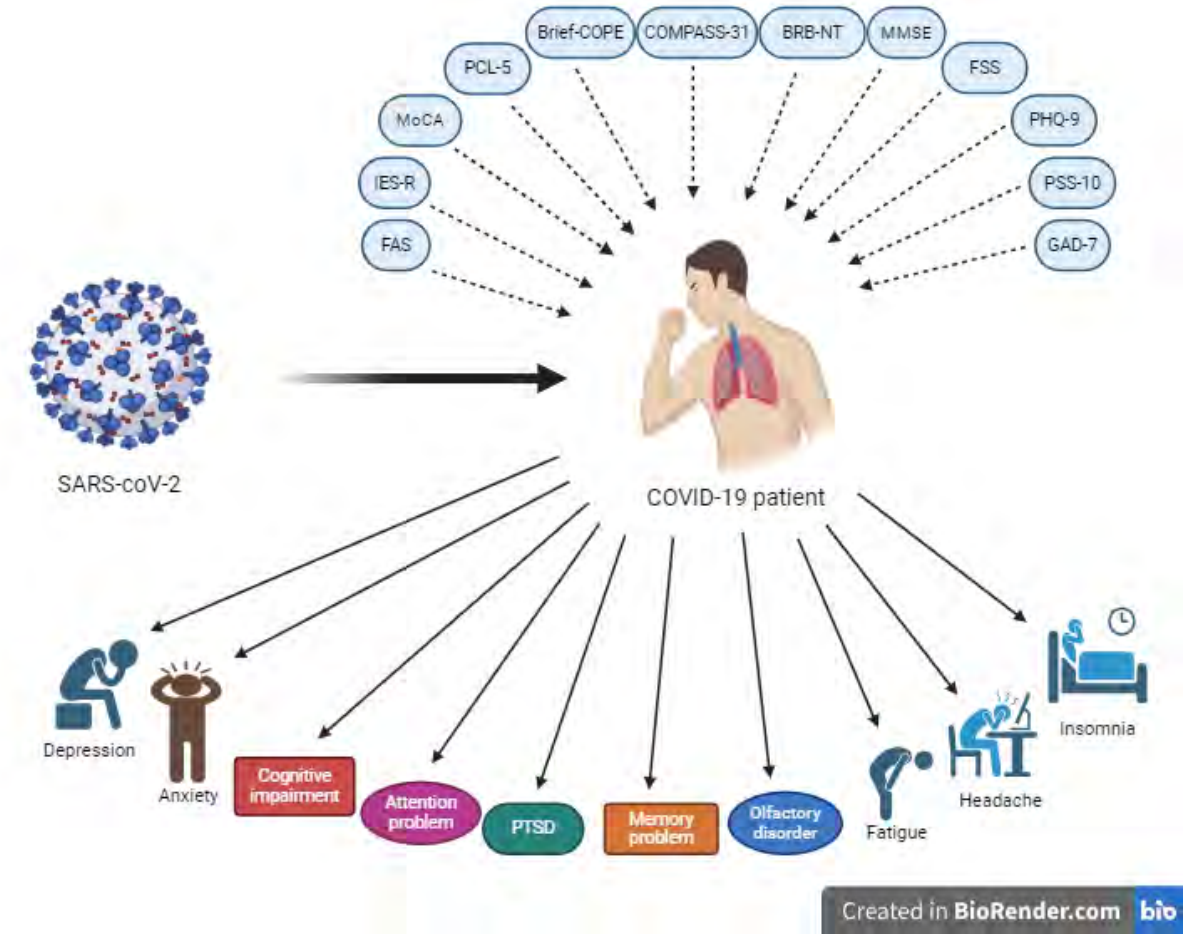

Figure 2: Common Investigational tools used and common problems in participants

Chapter 4

Conclusion

To conclude, the investigation into the chronic neuropsychological impact of SARS-CoV-2 has yielded essential knowledge about the enduring effects of COVID-19 on the human brain. The wide range of neuropsychological symptoms experienced by COVID-19 patients highlights how the virus may affect mental and cognitive functioning. This review presents information that suggests long-term neurological problems, emotional disruptions, and chronic cognitive impairments may endure after the acute respiratory symptoms resolve.

However, as the exact pathophysiology of the virus effecting the neuropsychological domains are not clearly understood till now, the management of mental health of post-COVID patients remain a challenge for the healthcare professionals. To obtain a more thorough and nuanced picture of the long-term neuropsychological impacts of SARS-CoV-2, future research with longer follow-up periods and standardized methodology would be essential.

4.1 Limitation

A significant limitation of our review is the existing literature, which is primarily composed of relatively short-term studies with variable follow-up periods and diverse techniques. Another limitation of our study lies in the variety of study populations, which includes differences in age, comorbidities, and pre-existing health disorders.

4.2 Future Recommendation

In order to enable a more comprehensive knowledge of the long-lasting cognitive consequences of the virus, future research endeavors should seek to solve these limitations by means of long-term, well planned studies that include a wider range of COVID-19 cases.

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