Dissertation

Long-COVID: Clinical Characteristics, Neural Correlates, and Intervention Approaches

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Graz, 21.10.2025 Manuel Leitner

Disclosures

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There are several co-authors who actively contributed to the results of the thesis and the publications. All co-authors have explicitly agreed to the use of their data in this thesis. Co-authors, their affiliations (at the time of the study), and their contributions are described below using the CRediT (Contributor Roles Taxonomy) system:

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Abbreviations and Definitions

ACE2 receptor: Angiotensin-Converting Enzyme 2 receptor

BMI: Body Mass Index

CBT: Cognitive Behavioral Therapy

CDC: Centers for Disease Control and Prevention

COVID-19: Coronavirus Disease 2019

CR: Cognitive Reserve

DMN: Default Mode Network

FC: Functional Connectivity

GM: Gray Matter

HBOT: Hyperbaric Oxygen Therapy

MERS-CoV: Middle East Respiratory Syndrome Coronavirus

MIS: Memory Index Score

MoCA: Montreal Cognitive Assessment

mRNA: Messenger Ribonucleic Acid

MS: Multiple Sclerosis

NASEM: National Academies of Sciences, Engineering, and Medicine

NICE: National Institute for Health and Care Excellence

PHEIC: Public Health Emergency of International Concern

rs-fMRI: Resting-State Functional Magnetic Resonance Imaging

RCT: Randomized Controlled Trial

SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

tDCS: Transcranial Direct Current Stimulation

VOC: Variants of Concern

VUM: Variants Under Monitoring

WHO: World Health Organization

WMH: White Matter Hyperintensities

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Zusammenfassung

Einleitung. Unter Long-COVID versteht man ein heterogenes Krankheitsbild, welches mehr als 200 Symptome umfasst und eine deutliche Belastung für Gesundheitssysteme weltweit darstellt. Selbst fünf Jahre nach Beginn der Pandemie ist das Wissen über die individuellen Auswirkungen, wirksame Behandlungsmethoden und die mit Long-COVID verbundenen Veränderungen im Gehirn noch immer begrenzt. ***Methoden.*** Diese Dissertation beinhaltet drei Studien, die darauf abzielten, (1) die Symptome, Belastungen und Auswirkungen von Long-COVID zu beschreiben, (2) strukturelle und funktionelle Gehirnveränderungen im Zusammenhang mit kognitiven Beeinträchtigungen - einem der häufigsten Symptome - zu untersuchen und (3) die Wirksamkeit eines tabletbasierten Trainingsprogramms als Intervention bei kognitiven und psychologischen Defiziten zu evaluieren. ***Ergebnisse.*** Die Ergebnisse verdeutlichen (1) die erheblichen Auswirkungen von Long-COVID auf das persönliche und berufliche Leben der Betroffenen, einschließlich einer Vielzahl unterschiedlicher Symptome, hoher psychischer Belastung und arbeitsbezogener Konsequenzen wie Einkommensverlust oder Arbeitsunfähigkeit. Darüber hinaus (2) zeigten sich signifikante funktionelle Veränderungen im Gehirn zwischen Patient:innen mit und ohne kognitiver Beeinträchtigung nach einer COVID-19 Infektion, insbesondere in Gehirnnetzwerken wie dem Default Mode Network (DMN), welches eine zentrale Rolle in verschiedenen mentalen Prozessen spielt. Außerdem (3) zeigen die Ergebnisse dieser Dissertation teilweise, dass tabletbasierte Trainingsprogramme subjektive kognitive Beschwerden und depressive Symptome lindern sowie die Gedächtnisleistung der Betroffenen unterstützen können. ***Schlussfolgerung.*** Diese Ergebnisse verdeutlichen das vielseitige Erscheinungsbild von Long-COVID und dessen erhebliche Auswirkungen auf das Leben der Betroffenen. Sie zeigen außerdem, wie wichtig ein tieferes Verständnis der neuronalen Mechanismen ist, welche den kognitiven und psychologischen Symptomen von Long-COVID zugrunde liegen. Künftige Forschung sollte darauf abzielen, reliable Biomarker zu identifizieren und maßgeschneiderte Interventionen zu entwickeln, um die Lebensqualität der Betroffenen zu verbessern.

Abstract

Introduction. Long-COVID is a highly heterogeneous condition that encompasses more than 200 symptoms and poses a significant burden on public health systems worldwide. Even five years after the pandemic, knowledge about its personal impact, effective treatment options, and brain alterations in affected individuals remains limited. ***Methods.*** Therefore, this thesis comprises three studies that aimed to (1) characterize the symptoms, burdens, and impacts of Long-COVID, (2) investigate structural and functional brain changes associated with cognitive impairment - one of the most frequently reported symptoms - and (3) explore the effectiveness of a tablet-based training program as a potential intervention for cognitive and psychological deficits. ***Results.*** The findings of this thesis underscore (1) the substantial impact of Long-COVID on patients' personal and professional lives, including a broad range of symptoms, high levels of psychological distress, and work-related consequences such as loss of income or inability to work. In addition, (2) significant functional brain alterations were observed between patients with and without cognitive impairment following COVID-19, especially in large-scale brain networks such as the default mode network (DMN), which plays an important role in various mental processes. Finally, (3) the findings of this thesis provide partial support for the use of tablet-based training programs to alleviate subjective cognitive complaints, reduce depressive symptoms, and support memory performance in affected individuals. ***Conclusion.*** These findings highlight the diverse clinical presentation of Long-COVID and its significant impact on those affected. Moreover, they underscore the need for a deeper understanding of the neuronal mechanisms underlying its cognitive and psychological symptoms. Future research should aim to identify reliable biomarkers and develop tailored, multimodal interventions to improve the quality of life for those affected.

Introduction

COVID-19 Overview

The year 2020 marks a radical event for people worldwide. With the outbreak of a novel coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2; SARS-CoV-2) in Wuhan, China, in December 2019, the lives of billions changed drastically from one day to the next. International media began reporting on a cluster of unknown pneumonia cases in Wuhan and immediately attempted to investigate the source of the illnesses [1, 2]. Shortly after the virus outbreak, the World Health Organization (WHO) declared COVID-19 (Coronavirus Disease 2019), a disease caused by SARS-CoV-2, a public health emergency on January 30, 2020. Subsequently, they declared COVID-19 a global pandemic on March 11, 2020 [3] (*Figure 1*), leading to unprecedented restrictions and constraints worldwide.

Although the pandemic and its consequences came as a surprise to many, coronaviruses were not new to humanity. This type of virus represents a group of viruses that can cause respiratory infections in humans, as seen with the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002/2003 [4] and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [5]. Even though these viruses also spread across multiple countries, the novel coronavirus SARS-CoV-2 was found to be particularly transmissible, causing respiratory disease in millions of people worldwide [6]. Although the genome of SARS-CoV-2 is around 79% identical to SARS-CoV and 50% to MERS-CoV [7], the emergence of this novel coronavirus led to a substantially larger number of rapidly infected individuals and fatalities within a short period, compared to other virus outbreaks [8]. As a result, SARS-CoV-2 posed a significant global public health threat.

Only weeks after the first confirmed case on December 8, 2019, the virus spread rapidly over multiple countries, with over 778 million confirmed COVID-19 cases reported worldwide (including 6.1 million cases in Austria) as of September 2025 [9]. One reason SARS-CoV-2 is so highly contagious and has caused so many illnesses worldwide is that it can be transmitted both before the onset of symptoms and by individuals with asymptomatic infections [10]. Since the rapid spread of the virus, researchers worldwide investigated the cause and origin of SARS-CoV-2, but its exact origin remains unresolved to this day. While some articles refer to a zoonotic origin of SARS-CoV-2, suggesting a potential transmission of viruses from animals (such as bats) to human populations [5, 11, 12], the WHO also investigated the possibilities that SARS-CoV-2 either first appeared in animal markets and was transmitted to humans via contaminated chilled products ("cold chain") as well as the possibility of a laboratory origin, most likely from the Wuhan Institute of Virology. However, even today, sufficient and reliable evidence to determine the origin of the virus is missing or not publicly accessible, as stated in an independent assessment of the origins of SARS-CoV-2 by the WHO in June 2025 [13].

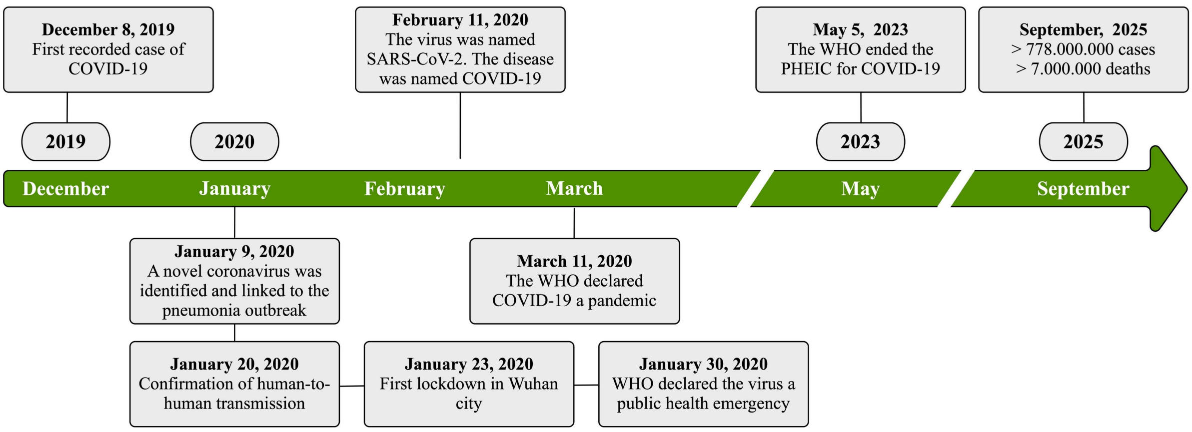
Even though the origin of SARS-CoV-2 remains unsolved, researchers gathered a large amount of information on coronaviruses and SARS-CoV-2 itself. Coronaviruses belong to the family *Coronaviridae* and are positive-strand RNA viruses [14, 15] that can be found in several animal species such as bats or pangolins [16]. They have crown-like surface glycoprotein projections, which is why the virus was named "Coronavirus" (from Latin „corona", meaning crown) [17]. In general, coronaviruses are divided into four genera: Alphacoronaviruses, Betacoronaviruses, Gammacoronaviruses, and Deltacoronaviruses. The well-known coronaviruses that caused outbreaks such as SARS, MERS, and COVID-19 belong to a subgroup of Betacoronaviruses [5, 11, 15]. The SARS-CoV-2 virion consists of several structural proteins, including the spike protein, nucleocapsid protein, membrane protein and envelope protein [18]. Notably, SARS-CoV-2 infects human cells mainly via the spike protein (S protein), which binds to angiotensin-converting enzyme 2 (ACE2) receptors and allows the virus to enter host cells [19, 20]. ACE2 receptors can be found in several tissues and organs throughout the human body, such as the gut, brain, lung or heart [21, 22]. Hence, this might be one reason why symptoms following infection with the virus are so diverse and vary in severity.

The first symptoms people faced after an infection with the coronavirus included, but were not limited to, fever, cough, fatigue, and dyspnea (shortness of breath) [23, 24]. Although patients initially showed symptoms of a viral pneumonia, a huge variety of other symptoms were reported by infected individuals within the next years of the pandemic, as for instance, anosmia or ageusia (loss of smell or taste), headache, diarrhea or nausea [25]. While the majority of those infected were able to recover from the illness without needing professional medical help, some needed to get transferred to a hospital, with a high mortality rate of up to 17% of those critically ill patients [26].

Hospitalization and mortality rates varied significantly over time as new variants emerged, and the first vaccines became publicly available [27]. Over time, the virus mutated as it spread among humans. In many cases, mutations have little impact on infection or mortality rates; however, some mutations can cause substantial concerns [28]. The most significant variants, as labeled by the WHO, include Alpha (strain B.1.1.7), Beta (strain B.1.351), Gamma (strain P.1), Delta (strain B.1.617.2), and Omicron (B.1.1.529) [29]. As significant variants of concern (VOC), the alpha variant was first detected in the UK (09/2020), followed by the beta variant in South Africa (10/2020), the gamma variant in Brazil (11/2020), the delta variant in India (12/2020) and the omicron variant in South Africa (11/2021) [20]. Since then, new variants emerged and are monitored with respect to their transmissibility and their impact on disease severity.

Furthermore, about a year after the first reported cases of COVID-19, vaccines were approved and became publicly available, including mRNA vaccines (e.g., *Comirnaty* by Pfizer-BioNTech and *Spikevax* by Moderna) and viral vector vaccines (e.g., *Vaxzevria* by Oxford-AstraZeneca and *Janssen* by Johnson & Johnson). Data from the last years demonstrate that vaccination was associated with a significant reduction of COVID-19-related hospital admissions and mortality rates worldwide [27, 30-34], which enabled a turning point in the course of the coronavirus crisis. Nevertheless, as of 2025, countries all over the world are still dealing with the private, social, and economic consequences of the pandemic.

Figure 1. Significant events associated with the COVID-19 outbreak from December 2019 to September 2025



Note. COVID-19: Coronavirus disease 2019; PHEIC: public health emergency of international concern; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization [35]

COVID-19 in Austria

In Austria, the high number of confirmed COVID-19 cases triggered several lockdowns, which lasted weeks or months and led to curfews, travel bans, the closure of public spaces, school and university restrictions, and the postponement of medical procedures. In addition, the pandemic caused a high rate of unemployment and an economic collapse. Until September 2025, approximately 6.1 million cases of COVID-19 were reported in Austria, with around 22.500 fatalities, corresponding to a mortality rate of around 0.4% [9]. Although this number seems relatively low, the fatality rate was significantly higher before vaccines became publicly available worldwide (highest rate: 5.9% in April 2020) [30, 36]. From a psychological perspective, the Austrian population suffered from increased levels of loneliness, especially among older adults during the COVID-19 pandemic [37], and from high levels of psychological distress, including depressive symptoms and anxiety [38-40]. These negative health consequences were not only present during governmental lockdowns, but also after restrictions were suspended [39] and led to a significant decrease in quality of life of those affected [41].

Nevertheless, the availability of COVID-19 vaccines led to the first vaccinations in Austria on December 27, 2020. Following this, the growing immunity in the population led to the official end of COVID-19 as a Public Health Emergency of International Concern (PHEIC) on May 5, 2023 [42]. However, although the acute danger of the pandemic was brought under control in Austria and worldwide, various long-term health challenges emerged. Some individuals never fully recovered from COVID-19 or developed new symptoms after their initial infection subsided. This lasting condition is referred to as "Long-COVID", "long haulers", "Post-COVID-19 condition (PCC)" or "Post-COVID syndrome (PCS)" [43].

Post-COVID-19 Condition (Long-COVID)

Early studies used different terms to describe persistent or newly developed symptoms following an acute SARS-CoV-2 infection based on the duration of symptoms [43]. The terminology published by the National Institute for Health and Care Excellence (NICE) suggested the terms „*acute COVID-19*" for symptoms lasting up to 4 weeks, „*ongoing symptomatic COVID-19*" for symptoms of COVID-19 from 4 weeks up to 12 weeks, and „*Post-COVID-19*" for symptoms that develop during or after COVID-19 and extend beyond 12 weeks [44]. According to the clinical recommendations by the NICE, „*Long-COVID*" encompasses both ongoing symptomatic COVID-19 (symptoms 4-12 weeks) and Post-COVID-19 syndrome (symptoms existing for ≥ 12 weeks). However, as of 2025, there is still no consensus on the precise definition of Long-COVID [45, 46]. The majority of studies published today refer to the definition by the WHO (a) or NASEM (b; National Academies of Sciences, Engineering, and Medicine), which define this complex condition as follows:

a. Post-Covid-19 condition (Long-COVID) is defined as "the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation" [47, 48].
b. "Long COVID (LC) is an infection-associated chronic condition (IACC) that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems" [49].

For the purposes of this dissertation, I refer to the definition provided by the WHO. According to the most recent WHO data (February, 2025), approximately 6% of individuals who have had COVID-19 will develop Long-COVID, with a declining risk compared to the early phase of the pandemic [50]. However, the number may be substantially higher, with various studies suggesting a global prevalence of 10-20% among infected individuals [51-54], or even as high as 36-40% [55-57]. This heterogeneity in the prevalence estimates may be explained by several factors, including the criteria used to define Long-COVID, the time of assessment, the virus variant, risk factors and the vaccination status of individuals [58, 59].

Notably, there is high heterogeneity between studies [60], and not all individuals have the same risk to develop Long-COVID, as several risk factors have been defined for this condition. Factors such as female sex [60-62], higher age [53, 57, 60, 61, 63], a high body mass index (BMI) [62, 64-66], and pre-existing comorbidities [60] increase the risk for Long-COVID. In addition, also psychological factors such as anxiety [53], depression [64], or sleep [53, 64] seem to play a crucial role in this complex condition. Importantly, most of these risk factors are modifiable and can therefore be targeted by psychological research and interventions. In addition, vaccination has been shown to have a strong protective effect, as vaccinated individuals exhibit a significantly lower risk of developing Long-COVID compared to unvaccinated individuals [61, 66-70]. This protective effect seems to be particularly strong for those vaccinated with mRNA vaccines as compared to viral vector-based vaccines [61]. Furthermore, a higher dose of vaccines (e.g., two doses compared to one dose) increases efficacy [67, 68, 71, 72]. Some patients even benefit from getting vaccinated when they already exhibit Long-COVID symptoms [67, 73], although studies on this topic are still controversial. Hence, vaccination both before and after a SARS-CoV-2 infection may reduce the risk of developing Long-COVID and therefore represents one of the most effective protective strategies to date [67, 71, 74].

To better understand this condition, research has focused on the underlying mechanisms and the nature of Long-COVID. Although the exact pathophysiology of Long-COVID remains unclear [58, 75], several hypotheses were proposed, including virus persistence, gut inflammation, microbiome disturbance, a reactivation of latent viruses, as well as immune and endothelial dysregulation [58]. The post-acute viral persistence theory suggests that viral fragments can persist in specific organs and tissues for weeks or months [76], and various other studies found an association between inflammation markers and immune dysfunction with Long-COVID [77, 78]. Other studies suggest that SARS-CoV-2 infection may trigger reactivation of latent viruses, such as Epstein-Barr virus (EBV) [76, 78-80] or propose a disruption of the gut microbiome [78, 81, 82], as Long-COVID was linked to alterations within the microbiome [78, 83, 84]. Finally, multiple studies showed that SARS-CoV-2 can impair endothelial function [85, 86], which might result in an increased cardiovascular risk even years after a SARS-CoV-2 infection [87]. However, the clinical picture of Long-COVID is highly heterogeneous, and therefore no single pathophysiological mechanism can be determined for the variety of symptoms, as the mechanisms responsible for this condition seem to be complex and intertwined [75, 78]. This fact also complicates research attempting to find a biomarker, as up to now, no reliable biomarkers or tests to diagnose Long-COVID are available [58].

Common Symptoms of Long-COVID

Individuals suffering from Long-COVID can present with single symptoms, multiple symptoms or various diagnoseable conditions, with any organ system affected [88]. Furthermore, children and adults can be affected, regardless of their demographics [63]. Notably, this condition can emerge after severe, mild, or even asymptomatic SARS-CoV-2 infection [49, 89], although severe acute illness was shown to increase the risk of developing Long-COVID [90]. Moreover, symptoms can either continue from the time of infection or might emerge after the infection subsided (e.g., weeks or months after "recovery"). The range of symptoms and their severity levels is wide [49], as more than 200 different symptoms have been linked to Long-COVID [52, 88].

The most common symptoms include memory problems [91], muscle weakness [55], breathlessness [55, 56, 60], headache [92], loss of smell/taste [56, 91, 92], concentration difficulties [91], fatigue [56, 60, 90, 92], and overall cognitive difficulties [60]. Interestingly, symptoms seem to be relapsing or fluctuating [93], meaning they may improve on some days but worsen on others. Additionally, symptoms can vary widely between individuals, and may even result in severe functional impairment, which limits patients' ability to engage in day-to-day activities [94]. About 1 out of 5 individuals is unable to work or left/lost their job due to their illness [94]; others reported loss of income (about 37% [93]) or an inability to perform usual activities anymore (about 64% [93]). Moreover, data from 2024 further indicates that Long-COVID has a major impact on patients' quality of life [95-97]. This includes a high prevalence of depression and anxiety among Long-COVID patients (23%; 95% CI [20%, 26%]) as well as a high prevalence of sleep disorders (45%; 95% CI [37%, 53%]) [98].

Finally, as mentioned above, Long-COVID has a significant impact on cognitive abilities in many individuals, as cognitive dysfunction represents one of the most frequently reported symptoms [99, 100]. Numerous studies reported impairments in various cognitive domains, including working memory [101-105], reaction time [105], executive function [101, 103-106], short-term memory [105], verbal fluency [104], and attention [101, 106] following both acute COVID-19 and in patients with Long-COVID. Moreover, brain fog represents one of the most frequently reported symptoms [107-109], referring to a form of cognitive dysfunction that may include difficulties finding words, memory impairment (e.g., forgetfulness), fatigue, as well as attention and concentration difficulties [107, 109]. This term became increasingly popular to describe cognitive dysfunction in Long-COVID [107]. Notably, these symptoms can occur regardless of the severity of the initial infection, as both hospitalized and non-hospitalized individuals may develop cognitive impairments after their SARS-CoV-2 infection [99]. The variety of symptoms often leads to a reduced quality of life and decreased work function in those affected [99, 110], hence posing a significant burden on both patients and healthcare systems. To better understand these symptoms, neuroimaging methods such as magnetic resonance imaging (MRI) have been used to gain insights into this complex condition.

Long-COVID-Associated Brain Alterations

Although Long-COVID probably affects millions of people worldwide, the structural and functional brain alterations related to this condition are, to date, insufficiently investigated and scientifically not yet fully understood. Some studies investigated Long-COVID brain alterations overall, without focusing on specific symptoms. One of these studies suggests that patients, compared to healthy controls, exhibit reduced gray matter (GM) volume in limbic, cerebellar and cortical brain areas [111]. Most studies so far, however, focused on brain alterations (structural and functional) with respect to specific persistent symptoms, which seems plausible given the wide range of symptoms and the heterogenous clinical picture of this condition. Among the most frequently reported symptoms are fatigue, headache, and cognitive impairment [49, 92, 112], to mention just a few. With respect to fatigue, one study comprising 50 patients suffering from fatigue post-infection showed decreased volumes and shape deformations of the left thalamus, pallidum and putamen in patients compared to a healthy control group [113]. Headache was found to be associated with lower cortical thickness and cortical GM volume compared to healthy subjects in brain areas including the inferior frontal cortex and the fusiform cortex [114] and post-covid cognitive impairment was linked to increased cortical thickness in frontal [104, 115] and temporal brain regions [115].

Beyond structural imaging, resting-state functional magnetic resonance imaging (rs-fMRI) offers one approach to identifying functional markers for diseases, which might be used to assess treatment response, monitor disease progression, or allow for an early identification of diseases [116, 117]. This approach measures brain activity when individuals are not engaged in a specific task but simply lying in the scanner, and examines which brain regions are functionally connected, i.e., showing correlated increases or decreases in activity over time. Some studies have focused on alterations in large resting-state brain networks (defined as a widely spread, but functionally related, brain regions that exhibit synchronized activity even in the absence of tasks, in contrast to task-fMRI [118]) in patients with Long-COVID. As a result, studies indicate changes (i.e., hypo- or hyperconnectivity within brain networks as compared to healthy controls) in the salience network [119], the dorsal attention network [120-122], the default mode network (DMN) [119, 121-124], the executive control network [119], and the sensorimotor network [122] following COVID-19. For instance, altered DMN connectivity was found to be linked to cognitive performance in patients with Long-COVID [123]. Results, however, are difficult to interpret, as both hypo- and hyperconnectivity between (parts of) resting state networks were reported [125]; therefore, more studies are warranted. Finally, the plurality of symptoms and the lack of a reliable biomarker to adequately diagnose the condition suggest that a multidisciplinary approach is vital for both diagnosing and reducing the symptom burden in these patients.

Therapy Options

Due to the heterogeneity and complexity of Long-COVID and its symptoms, non-invasive and safe treatment options targeting Long-COVID are rare and remain challenging, even five years after the pandemic started [58, 126]. Furthermore, as the condition can affect multiple organ systems and over 200 different symptoms have been associated with Long-COVID [52, 88], a single treatment approach is unlikely to be effective for all patients [58]. However, I will highlight a few treatment approaches that might be promising for some individuals, particularly regarding specific, frequently reported, symptoms.

From a pharmaceutical perspective, studies indicate a reduced risk of developing Long-COVID in patients receiving *metformin* during their acute illness, a medication primarily used to treat type 2 diabetes mellitus [127, 128]. With respect to patients already suffering from Long-COVID, various pharmaceutical drugs including *sulodexide* (antithrombotic effects) [129], *ivabradine* (reduces the heart rate) [130], *cortexin* (claimed to have neuroprotective effects) [131], *actovegin* (enhances glucose absorption and oxygen uptake in tissue) [132], *vortioxetine* (antidepressant effect) [133], *glucosaminyl muramyl dipeptides* (immunomodulatory properties) [134] as well as systemic and probiotic enzymes (supporting digestion and metabolism) [135] yielded promising results, although these treatments target different symptoms. It is therefore likely that specific pharmaceutical medications are effective only for treating particular Long-COVID symptoms rather than the condition as a whole.

Systematic investigations also indicate a positive effect of physical activity interventions on Long-COVID recovery [136, 137]. One Austrian study reported a significant improvement of symptoms such as fatigue, functional status (used to measure functional limitations following COVID-19 [138]), and quality of life after attending an interdisciplinary pulmonary rehabilitation, including physical activity such as endurance, strength, and muscle training [139]. Moreover, another study found improvements in muscular strength, perceived health (physical and mental), cardiopulmonary parameters as well as in anxiety and depression after a multidisciplinary physical and psychological rehabilitation program [140]. Finally, also aerobic endurance training performed as either interval training or moderate continuous training seems to improve the physical exercise capacity in patients with Long-COVID [141].

Another therapy approach involves the use of hyperbaric oxygen therapy (HBOT). Hyperbaric oxygenation refers to the inhalation of 100% oxygen under elevated ambient pressure. This leads to increased oxygen levels in the tissue and may activate regenerative processes, including mast cell proliferation, mobilization, anti-inflammatory effects, and inhibition of inflammatory signaling pathways [142, 143]. Two studies, for instance, reported a significant improvement of Long-COVID patients' fatigue, cognition (e.g., attention, executive function), verbal function [144], emotional well-being, pain and other domains after 10 sessions of HBOT [142]. Another study using HBOT also reported improved sleep quality and quality of life as well as reduced pain in patients suffering from Long-COVID [145].

Preliminary data also suggest a positive effect of non-invasive brain stimulation on Long-COVID, especially regarding Long-COVID-related fatigue [146]. One study by Santana and colleagues (2023) [147] indicated a positive effect of transcranial direct current stimulation (tDCS) on fatigue, anxiety, and quality of life in patients with persistent Long-COVID symptoms. Transcranial direct current stimulation describes a brain stimulation method used to modulate cortical excitability [148]. This method was used in another study in which patients also experienced a positive effect on their physical fatigue and on depressive symptoms after eight sessions of tDCS [149]. However, it is worth to note that other studies could not replicate that active tDCS was superior compared to sham tDCS (a placebo condition) [150].

Finally, computerized rehabilitation programs have been evaluated for their effectiveness in alleviating Long-COVID symptoms, especially cognitive symptoms. Although these programs have been tested in various populations before, including patients with diabetes [151], Parkinson's disease [152], and stroke [153], only a few studies evaluated their effectiveness for Long-COVID. Up to now, options to alleviate cognitive impairment following COVID-19 are highly limited, although it represents one of the most common debilitating symptoms post-infections [154], especially in the domains of memory, executive function, processing speed, and attention [100]. One study by Samper-Pardo and colleagues (2023) used a telerehabilitation approach (ReCOVery App) to improve cognitive and mental health outcomes but did not find any significant effects between their intervention and control group [155]. Another study aimed to alleviate cognitive dysfunction in patients suffering from cognitive impairment after COVID-19 and found promising effects [156]. However, as no control group was available, the results of this study should be interpreted with caution [156]. The lack of home-based computerized training options, which could be particularly beneficial for patients with fatigue, as they are location-independent and can be used at patients' own pace, limits the ability to draw reliable conclusions and highlights the need for further research.

Hypotheses

As described above, Long-COVID represents a heterogeneous condition, lacking a standardized definition and comprises a broad variety of symptoms. This significantly limits our ability to diagnose and effectively treat Long-COVID. Despite Austria's strong healthcare system, more Long-COVID rehabilitation centers closed after the pandemic was no longer declared a PHEIC (public health emergency of international concern). Even when considering conservative estimates of the number of people living with Long-COVID (6%, [50]), hundreds of thousands of individuals may be affected by at least some lingering symptoms in Austria. In order to contribute to the existing literature on a) the variety of Long-COVID symptoms and their impact on the personal and professional lives of those affected, b) structural and functional brain alterations in patients living with Long-COVID, and c) therapeutic options, particularly computerized training programs, to alleviate these debilitating symptoms, I dedicated my PhD thesis to shedding light on these complex questions.

Study 1: My first research aim was to characterize the health impact and burden of Long-COVID in Austria and other German-speaking countries. Especially during the early phase of the COVID-19 pandemic, it was essential to identify the disease course (e.g., asymptomatic, mild, severe), hospitalization rates, the frequency of symptoms during the acute infection and their persistence after the initial infection subsided, as well as how these symptoms were experienced by those affected. Additionally, I aimed to examine the consequences of Long-COVID on participants' private and professional lives (e.g., changes in mood and stress resistance) and to assess the impact of COVID-19 vaccination on symptoms and outcomes.

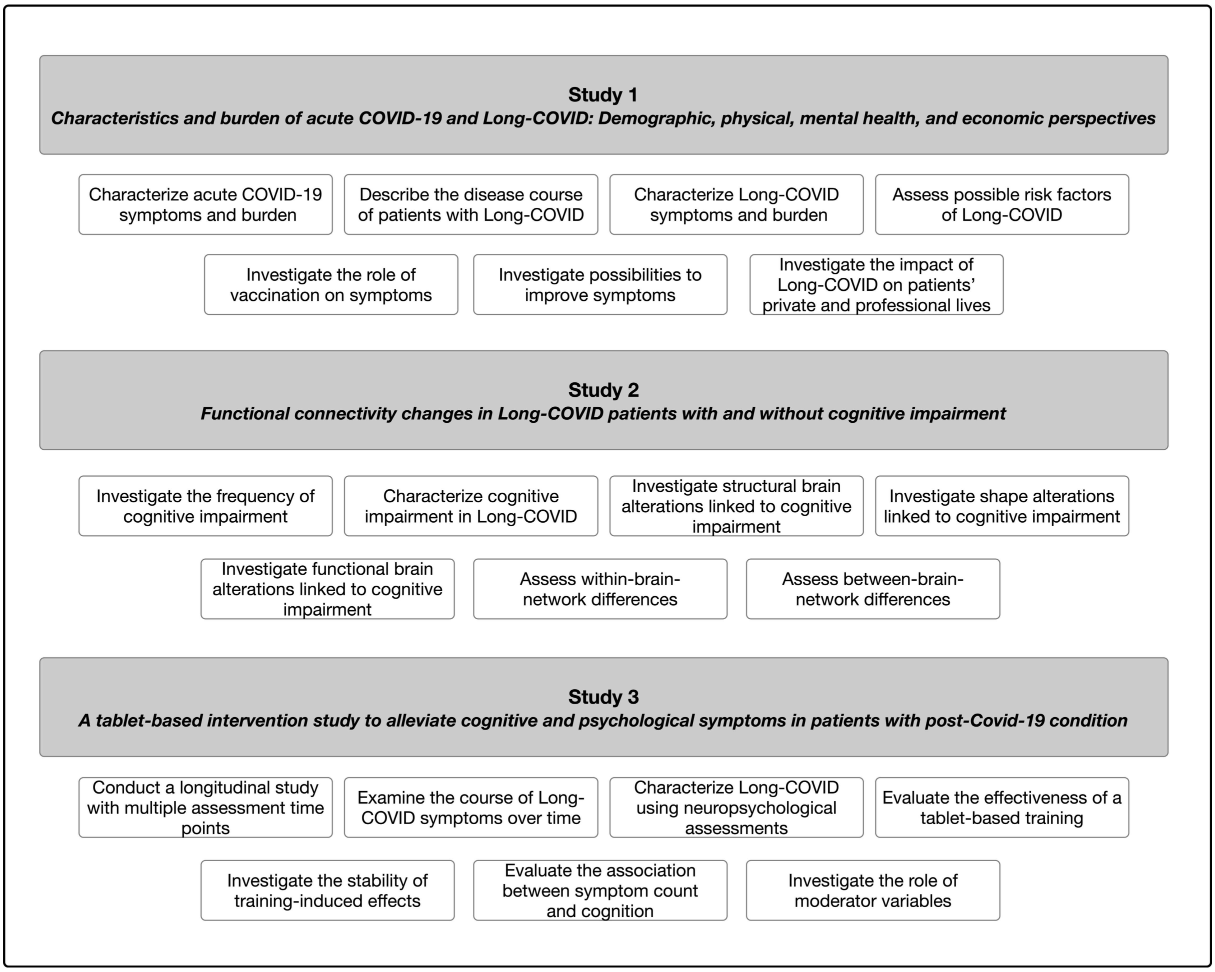
Study 2: My second research question focused on structural and functional brain alterations that are associated with Long-COVID. Magnetic resonance imaging (MRI) represents a crucial tool for investigating this question and helps to highlight changes within the brain associated with Long-COVID. I therefore focused on a specific symptom cluster (cognitive impairment) and investigated both structural and functional brain alterations associated with it. In particular, I compared Long-COVID patients with and without cognitive impairment and aimed to highlight how they differ in large resting-state networks. These findings may help future studies to detect cognitive impairment at an early stage or to identify important mechanisms underlying cognitive decline or improvement in training studies.

Study 3: Finally, my third and final research focus went beyond identifying symptoms, burden and brain alterations. Within a longitudinal study, I aimed to alleviate cognitive symptoms and improve the quality of life of those affected. Therefore, I focused on validating a tablet-based training program which was developed for patients with Long-COVID. The training program consisted of various exercises, such as cognitive tasks and relaxation techniques, tailored to improve cognition and mental health of people with Long-COVID. Over the course of one year, I carried out comprehensive neuropsychological assessments to assess cognition and mental health and to evaluate the effectiveness of the intervention program.

Discussion

As described above, this thesis focused on several important aspects of Long-COVID, a highly heterogeneous condition encompassing a wide range of symptoms, which can have a significant impact on those affected. *Figure 2* illustrates the structure of this work.

Figure 2. Overview of the three studies conducted as part of this dissertation, highlighting their specific goals



Note. Study 1, 2 and 3 can be accessed through [157], [158], and [159], respectively.

a) Study 1, Long-COVID symptom characterization: we examined the prevalence and burden of symptoms (both during acute COVID-19 and Long-COVID), hospitalization rates, extramural examinations, Long-COVID symptom progression, vaccination rates, as well as the impact of Long-COVID on patients' private and professional lives. We also explored potential risk factors and differences between genders as well as between vaccinated and unvaccinated individuals. Our primary aims were to identify which symptoms do occur frequently and need to be targeted first, how they are perceived (i.e., their burden), what impact they have on patients' lives, and which psychological approaches (e.g., training programs) may help to treat or at least alleviate these symptoms.

b) Study 2, Neural correlates of cognitive dysfunction in Long-COVID: In a second study, we investigated structural and functional brain alterations that are linked to cognitive impairment in patients with Long-COVID. Our findings highlight that cognitive complaints are a major issue in this condition and are associated with alterations/disruptions in relevant resting-state networks. These findings may assist future studies in identifying patients' cognitive complaints and assessing their responsiveness to cognitive interventions and might provide first indications of a functional biomarker in the brain that is associated with cognitive impairment in this condition.

c) Study 3, Efficacy of tablet-based training programs in Long-COVID: In a final study, we aimed to alleviate cognitive symptoms and improve mental health outcomes in those affected by providing a tablet-based intervention that included cognitive, relaxation, and physiotherapy exercises. The intervention was tailored for patients living with Long-COVID, particularly those experiencing cognitive complaints. This study contributes to the growing body of research on computerized training programs aimed to improve quality of life in Long-COVID patients and highlights the advantages that are associated with such training programs, such as, for instance, location-independence.

The findings from this dissertation offer insights into several aspects of Long-COVID:

Insights into Symptoms, Burden and Impact of COVID-19 and Long-COVID

One of our first research questions was related to the number and burden of symptoms during both acute COVID-19 and Long-COVID, which provided a guide for which symptoms are crucial to be treated and focused on. In addition, our study was one of the first studies that not only investigated the wide range of symptoms themselves, but also their burden on affected individuals.

Insights into COVID-19

Consistent with previous studies [93, 160], Study 1 (conducted between March 2022 and May 2022) confirmed that, during their initial infection, most patients suffered from respiratory symptoms such as dry cough, runny nose, or shortness of breath (dyspnea), as well as fatigue and various cognitive problems (e.g., brain fog, memory problems). A very similar symptom pattern emerged in Study 3, conducted between October 2022 and November 2023, in which participants most frequently reported exhaustion and fatigue, an altered sense of taste or smell, headache, and respiratory symptoms like sore throat and dyspnea during their initial SARS-CoV-2 infection. It is, however, essential to note that over 200 symptoms associated with Long-COVID have been identified [52, 88], and that both the type and frequency of symptoms varied slightly with the emergence of different variants of the virus [161, 162]. For instance, symptoms related to the nose (e.g., runny nose, blocked nose, sneezing) were reported more frequently during the predominance of Alpha and Delta variants, whereas the Omicron variant was associated with a decrease in the incidence of smell or taste impairments [162].

In our studies, most individuals reported that they felt sick for about 1-2 weeks (*Mdn* = 11-15 days for Study 1, and *Mdn* = 6-10 days for Study 2) and that they had an asymptomatic (6.0%), mild (74.3%), or severe (19.7%) disease course (Study 1). Although no specific guidelines were provided on how to classify the severity of the initial infection in Study 1, these results were comparable to those of a study conducted early in the course of the pandemic [35]. Furthermore, 7.8% of participants in Study 1 and 5.0% in Study 3 required hospitalization, indicating that hospitalization rates were relatively high but comparable between the two studies. However, due to the high rate of immunity worldwide, hospitalization rates are currently (September 2025) significantly lower [9], rendering acute SARS-CoV-2 infections less of a public health concern today. Hence, COVID-19 remains an ongoing health issue but no longer constitutes a public health emergency of international concern (PHEIC) [42].

Nevertheless, several factors still pose a risk for a severe and concerning disease course. Our findings (Study 1) indicate that higher age and BMI were associated with a longer duration of acute illness, with high BMI further linked to a greater disease severity. This suggests that both factors are not only risk factors for developing Long-COVID, as described above, but also for experiencing a longer and more severe acute illness, which itself increases the risk of developing Long-COVID [163, 164].

Since Study 1 was conducted between March and May 2022 and Study 3 was conducted between October 2022 and November 2023, it is very likely that individuals were infected with all different variants of concern (VOC) during that period. This suggests that the symptoms reported by participants are linked to the variant that was predominant during this time but were still similar in their overall emergence. Although much research focused on COVID-19 symptoms during the early phase of the pandemic, the drastic decline in publications on acute COVID-19 by September 2025 indicates a decreasing relevance of acute SARS-CoV-2 infections for the public health system. Nevertheless, the symptoms listed by major national and international organizations, such as the CDC (Centers for Disease Control and Prevention) and the WHO (World Health Organization), still include fever, cough, fatigue, and sore throat [165, 166], similar to the symptoms reported in our studies. However, due to the high global vaccination rate, immunity from prior infections, and the emergence of new variants, the overall severity of acute infections decreased [167]. Finally, as of September 2025, the XFG variant, currently classified as a variant under monitoring (VUM) by the WHO [9], is predominant [168], but so far, no significant changes in symptoms or disease severity have been reported.

Study 1 also contributes to the current body of literature on COVID-19 by showing that vaccinated individuals experience a significantly shorter duration of acute COVID-19 illness. This finding is particularly important, as a long and severe disease course has been identified as a risk factor for developing Long-COVID [169]. These results are supported by several other studies, showing that vaccinated individuals, as compared to unvaccinated ones, were less likely to report severe COVID-19 [170], had lower viral loads, and experienced milder disease courses when infected with the Alpha or Delta variants [171]. Nevertheless, while the duration of such acute infections with SARS-CoV-2 seems to be relatively short in general (typically around 1-2 weeks) and can be managed significantly better due to the development of medication such as Remdesivir (Veklury) [172] or Nirmatrelvir/Ritonavir (Paxlovid) [173], some individuals still do not fully recover after their infection. This is also supported by our study: Although most individuals (74.3 %) rated their acute infection as mild in Study 1 or reported being vaccinated prior to their first SARS-CoV-2 infection (50.0%, Study 3), they nevertheless developed Long-COVID. This is especially concerning, because although severe infection is a known risk factor for Long-COVID [174], even individuals with mild or asymptomatic infections are at risk of developing persistent symptoms [175, 176]. Additionally, the persistent psychological and physical effects of COVID-19 are expected to become an increasing concern in the next years [177], as information about the pathogenesis, potential biomarkers, and treatment of Long-COVID remains limited.

Insights into Long-COVID

To address a limitation of Study 1, that is, not including the Post-COVID-19-Functional-Status Scale [138], a tool to measure the full range of functional outcomes following COVID-19, we showed that patients' functional status deteriorated significantly from pre- to post-COVID in Study 3 ($p < .001$; results not reported in the paper). These results are crucial because they demonstrate that even individuals without a prior history of physical or mental illness can be significantly debilitated after an infection with SARS-CoV-2. While patients reported no functional limitations at all before their infection with SARS-CoV-2 (functional status of 0), they exhibited functional limitations (e.g., feeling the need to reduce or even avoid usual activities or needing time to spread these duties over a longer time as a result of symptoms, pain, anxiety, or depression [138]) in one of our studies. These functional limitations, however, resolved over time, suggesting a gradual improvement in functioning, which was also present in other studies and offers hope for patients still struggling with lingering symptoms following COVID-19 [178, 179].

As described in Study 1, the onset of these symptoms mostly occurred within the first two weeks post-infection. Interestingly, we observed an earlier onset of Long-COVID symptoms in vaccinated compared to unvaccinated individuals. Although this finding has not been reported in previous studies, it may suggest that vaccination induces a more immediate inflammatory response after infection, possibly leading to an earlier onset of symptoms, or that vaccinated individuals are more vigilant and health-conscious, resulting in earlier reporting of these symptoms. Another reason could be that vaccinated individuals were infected with different virus variants than those unvaccinated before their first infection, which might have led to a different onset of Long-COVID symptoms post-infection. Regardless of that, most patients reported fatigue, exhaustion, memory problems, brain fog and dyspnea as their most prevalent lingering symptoms, similar to the symptoms reported by patients in Study 3, which included fatigue, exhaustion, memory impairments, brain fog, and muscle pain. These findings are consistent with previous studies on Long-COVID symptoms [92].

While the type and frequency of symptoms was assessed previously, our study was the first to also investigate the individual burden associated with these symptoms. The symptoms with the highest burden, ranked from high to low, were fatigue, exhaustion, discomfort after physical exertion, sleep alterations, altered sense of taste and smell, and cognitive dysfunction. Overall, women reported a higher number of symptoms than men in Study 1, and a similar trend was observed in Study 3. Additionally, previous studies indicate that female sex is a risk factor for developing Long-COVID [55, 60, 61].

Finally, in Study 1, patients reported that their symptoms were associated with significant limitations in their daily lives. In line with a previous study [93] and replicated in our research, these limitations include work-related changes (e.g., inability to work or being unable to work full-time), increased sick leave, substantial financial losses, dependence on relatives or external organizations for daily activities, as well as alterations in sexual life, stress tolerance, and mood.

Furthermore, an interesting finding from Study 1 was that most patients reported a deterioration of symptoms after physical (70.2%) or mental (52.1%) activities, while at the same time reporting that they believe that breathing (65.4%), movement/physical (80.4%), and cognitive (72.1%) exercises may help them to alleviate their burden. Although these results may seem contradictory at first, they might suggest that pacing, i.e., focusing on energy management to prevent feeling overwhelmed and to avoid symptom exacerbation, represents a crucial factor of interventions designed to improve Long-COVID symptoms [180]. In fact, training programs that can be conducted from a patient's home and at their own pace, regardless of location, appear particularly promising and beneficial for patient populations in which pacing represents an important component of symptom management. Moreover, fatigue and extreme exhaustion often prevent patients from participating in outpatient and long-duration therapies.

Finally, a large proportion of patients (53.6%) perceived their symptoms as fluctuating, suggesting that symptom severity varies throughout the day or week, consistent with findings from a previous study [93]. However, since patients reported using cognitive, movement, and breathing exercises at their own pace to improve symptoms, these elements were incorporated into our tablet-based training study, described in more detail later.

Insights on Long-COVID Prevention

Vaccination was found to be a key factor in preventing Long-COVID [27, 30-34], although no single factor can completely eliminate the risk of developing this condition. This is evident in both Study 1 and Study 3 of this thesis, in which 45.3 % and 50.0% of participants, respectively, were vaccinated prior to SARS-CoV-2 infection, but still developed Long-COVID. However, those vaccinated prior to their infection reported a shorter duration of acute COVID-19 in both Study 1 and Study 3. While this finding is promising in terms of reducing the acute illness burden, the number of Long-COVID symptoms patients experienced did, however, not differ significantly between groups. Nevertheless, vaccination is highly effective in reducing the risk of developing Long-COVID in the first place and may represent one of the most effective strategies developed to date [68]. This highlights the importance of primary prevention of Long-COVID (avoiding the occurrence of Long-COVID) through vaccination. However, previous studies pointed out that misinformation regarding COVID-19 vaccines can significantly increase vaccine hesitancy (i.e., individuals who believe false information about vaccines are less likely to get vaccinated) [181]. Future studies that aim to decrease the risk of developing Long-COVID should therefore start at this point and develop psychological programs and public information campaigns to reduce vaccine hesitancy on a global basis.

Another important finding is that a higher BMI was associated with a more severe disease course and longer illness duration during acute COVID-19 (Study 1 and Study 3) and was also identified as a risk factor of developing Long-COVID in previous works [62, 64-66, 92]. Therefore, our results suggest that future psychological interventions should incorporate physical exercises and motivational strategies as part of primary prevention, especially for individuals with a high BMI. In addition, as severe COVID-19 disease courses, which are one of the key risk factors for Long-COVID, become less frequent with increasing immunity, a more positive outlook for future Long-COVID incidence rates can be expected. Finally, although lingering symptoms have a severe impact on the lives of those affected, at least some of the most frequently reported and burdensome symptoms may be alleviated through psychological interventions described later in this thesis.

Insights on Brain Alterations Associated with Cognitive Impairment in Long-COVID

As described in the Introduction of this thesis, both structural and functional brain alterations have been linked to Long-COVID in general, as well as to specific symptoms associated with it. Several of these alterations have also been linked to cognitive dysfunction in this condition. Investigating brain changes related to specific symptoms in Long-COVID, for instance using fMRI, is essential, as it provides insights into the underlying mechanisms of this condition and helps to identify potential treatment options. Moreover, fMRI results may contribute to diagnosing functional decline (e.g., cognitive impairment) even before overt behavioral symptoms manifest and can also be used to evaluate the efficacy of a certain treatment, based on the assumption that effective interventions lead to more “normalized” patterns of functional connectivity within the brain [117]. Finally, such findings may serve as objective biomarkers that demonstrate actual changes (functional or structural) in the brain, rather than being dismissed as "just" subjective experiences. Since cognitive complaints such as memory problems or brain fog were reported as one of the main symptoms of Long-COVID in both previous research [182-184] and in Study 1, we aimed to look more deeply into the underlying structural and functional mechanisms associated with it.

In Study 2, we specifically focused on a group of patients with significant cognitive impairment compared to another group of patients without severe cognitive dysfunction. Cognitive dysfunction was defined as scoring significantly below the population norm ($T < 35$), according to the respective test manuals, in at least one cognitive domain (attention, executive functions, memory, or verbal fluency). This approach, however, had two limitations: first, the group allocation (patients with vs. without cognitive dysfunction) may be considered as somewhat arbitrary, although it was consistent with several other studies [185-187] and allowed for a comparison between extreme groups, which was necessary considering the small sample size of the study. Second, our sample consisted only of individuals with at least subjective cognitive complaints, since this was a requirement to be eligible for participation in the subsequent training study (Study 3), from which sample the fMRI analyses were conducted. However, not all patients showed severe cognitive complaints on neuropsychological tests. Similar findings have been reported in previous studies, showing that subjective cognitive complaints are not necessarily correlated with objective (i.e., measurable) cognitive deficits [110, 188], but still represent a high subjective burden for those affected. Finally, since our analyses were limited to patient groups (with and without severe cognitive dysfunction), this study (Study 2) lacked a healthy control group.

As one of the first studies to examine both structural and functional brain alterations in Long-COVID patients with and without severe cognitive impairment, we observed significant within- and between-network functional differences, but no structural differences (i.e., subcortical brain region volumes) between groups. Specifically, Long-COVID patients with severe cognitive impairment exhibited significantly higher functional connectivity (FC) of the Default Mode Network (DMN) with the a) posterior supramarginal gyrus (right), b) angular gyrus (right), and c) temporo-occipital part of the middle temporal gyrus (right). In addition, between-network analyses revealed stronger functional correlations ("edge strength") between the ventral stream network and the occipital pole in this group, compared to patients without severe cognitive impairment. In contrast, we found no volumetric differences or differences in the number of white matter hyperintensities (WMH) between groups.

As previous studies linked cognitive dysfunction to DMN alterations in conditions such as multiple sclerosis [189, 190], Parkinson's disease [191], and Long-COVID [123, 192], our findings align with these results, suggesting that the DMN plays a central role in cognitive impairment across various disorders. These results are further supported by findings of increased FC involving the DMN in patients with Long-COVID compared to healthy controls [119], as well as by another study reporting increased DMN connectivity in individuals with subjective cognitive decline [193]. The DMN is typically most active at rest but downregulated during task engagement [194]. Our findings indicate that baseline connectivity (measured during rest in the MRI scanner) of the DMN is altered in Long-COVID patients with cognitive impairment. This altered connectivity differences may hinder efficient switching between networks when cognitive demands arise and may consequently contribute to the observed cognitive deficits. In addition, increases in FC may reflect an inefficient compensatory mechanism, suggesting that the additional effort made by the brains of those with Long-COVID and severe cognitive deficits is insufficient to restore normal brain function [119].

This is consistent with other studies, as hyperconnectivity across diverse brain regions, in general, was found to indicate a common response to neurological disruption [195]. In the present study, the increased DMN connectivity was observed with brain regions involved in phonological decision-making and reading [196, 197], memory retrieval, inhibition, higher-order motor control [198, 199], as well as language processing and semantic cognition [200]. As a result, the enhanced connectivity with areas primarily outside the DMN observed in our sample may reflect a disruption of normal default-mode dynamics in individuals with cognitive impairment; probably indicating maladaptive processes.

With these findings, our study provides valuable insights beyond the previously conducted studies, as most prior studies focused on comparing Long-COVID patients to healthy controls rather than examining brain alterations within the Long-COVID population itself. This, however, also represents a significant limitation, as connectivity changes cannot be attributed to Long-COVID directly in the absence of a healthy control group. Additionally, future research should investigate other networks relevant for cognition, such as the salience network, frontoparietal network, and dorsal attention network. Importantly, studies should not only assess cognition on a general level (as done in our study) but also consider analyses based on specific cognitive domains (e.g., comparing patients with versus without attention deficits).

Moreover, we also observed a surprising finding: Long-COVID patients with significant cognitive impairment exhibited higher FC between the ventral stream network and the occipital pole compared to those without severe cognitive deficits. This increased coupling between primary visual and higher visual areas might indicate less flexible visual information processing, as basic visual regions were overly strong connected to the ventral stream. Such hyperconnectivity could reflect an inefficient process not yet reported in the literature. Both the ventral stream and occipital pole are essential for object recognition and shape perception [201], and one study has also linked the visual network to cognitive performance [202]. Our findings align with these studies and suggest that regions within the visual network may contribute to cognitive impairments, particularly in domains such as visual attention and memory [203].

Finally, we found no structural differences between the two patient groups. This emphasizes the importance of using not only structural but also functional MRI, suggesting that functional alterations might emerge even before structural atrophy is detectable. Although our findings revealed altered brain connectivity in Long-COVID patients with cognitive impairment, it is important to note that causal interpretations are limited due to the cross-sectional study design and the lack of both a healthy control group and experimental manipulation [117]. Future research in the upcoming years will further reveal whether cognition-related maladaptive changes in the brain (as observed in our Study 2) can be reversed (i.e., "normalized") or modified through cognitive training (as implemented in Study 3).

Insights into the Treatment of Long-COVID

As the exact cause of Long-COVID remains unclear and symptoms vary widely, a symptom-oriented therapeutic approach appears promising given the current state of knowledge. With respect to Long-COVID, fatigue is among the most frequently reported symptoms (Study 1 and Study 3). As fatigue is also common in other conditions such as multiple sclerosis (MS) or cancer (cancer-related fatigue), it has been targeted by various psychological interventions in different populations. These interventions include psychoeducation [204, 205], energy management [206], cognitive behavioral therapy (CBT) [207], mindfulness [208, 209], and relaxation [210, 211], and should also be applied to patients living with Long-COVID. The high rates of fatigue reported in our studies (97.4% in Study 1 and 40.0% in Study 3) further underscore the relevance of these intervention programs.

Another important finding (Study 1) is that cognitive impairment was reported as one of the most burdensome lingering symptoms. This is consistent with the results of Ceban and colleagues [154] and Möller and colleagues [212], who reported that one in five patients with Long-COVID exhibit cognitive impairments three or more months after SARS-CoV-2 infection. However, training options targeting cognitive impairment in Long-COVID remain scarce, highlighting the need to development cognitive intervention programs. Therefore, Study 3 of this thesis aimed to alleviate cognitive dysfunction and improve the quality of life of affected patients by providing a comprehensive tablet-based training program.

As patients in Study 1 reported that they would likely benefit from cognitive, breathing, and movement exercises, the tablet-based training program of Study 3 incorporated cognitive training (e.g., targeting attention/reaction time, memory, and executive functions) as well as elements of physiotherapy and relaxation. To prevent fatigue and overexertion, various difficulty levels were implemented. Additionally, to overcome limitations of previous studies, which often did not include a control group [156], we conducted a randomized-controlled trial (RCT) as part of this thesis. This study is among the few that used computerized training programs, such as tablet-based training, for patients with Long-COVID.

Our findings showed a strong reduction in subjective cognitive complaints as well as depressive symptoms. Furthermore, we found that performance in the "Montreal Cognitive Assessment Memory Index Score" (MoCA MIS), a simple measure of memory performance, remained stable in the intervention but declined in the control group. These findings are consistent with previous studies reporting improvements in cognition and quality of life following cognitive training [156, 213].

A reduction in subjective cognitive complaints after taking part in computerized interventions has been reported in previous research [214], which is important because cognitive complaints are among the most common problems after COVID-19 [182]. Moreover, our finding, demonstrating that tablet-based training can also improve mental health by reducing depressive symptoms, is particularly important, as approximately one in four individuals with Long-COVID experience mental health problems such as stress, anxiety, and depression [215]. Our finding that memory performance in the MoCA-MIS remained stable in the intervention group appears plausible as well: One previous study [93] and Study 1 indicated that symptoms tend to fluctuate over time. Taking part in the intervention group may have counteracted such fluctuations in memory performance, yielding a stable memory score in the intervention group, but not in the control group. Future studies should emphasize the clinical relevance of improvements (e.g., whether patients are better able to manage daily life demands) rather than focusing solely on neuropsychological test outcomes. This limitation might be addressed through qualitative interviews and represents a crucial direction for future research.

Our findings suggest that tablet-based intervention programs targeting cognitive and mental symptoms in Long-COVID are at least partially effective in alleviating specific symptoms, since no improvements in other domains were found in our study. However, these improvements do not appear to be stable over time, as our results show a significant effect only in the pre-to-post analysis, but not when a follow-up assessment (three months after the end of the training program) was included. This suggests that training-induced effects may not be stable over time (i.e., longer and more intense training may be required), or that also the control group, even without training, shows improvement over time (which is consistent with previous studies on symptom improvement [178, 179, 216]). Although some patients may experience symptom improvement even without training (spontaneous remission/recovery), it is critical to provide treatment to achieve symptom improvement as quickly as possible given the substantial personal and professional impact of Long-COVID, as demonstrated in Study 1. In addition, Study 3 suggests a negative association between the number of persistent symptoms and memory performance - an effect that became stronger (and thus more severe) with longer disease duration in Long-COVID. This indicates that a higher number of symptoms may be linked to reduced/impaired memory function, and that a long, untreated disease duration exacerbates this impact on memory performance.

Overall, these findings warrant further research on the stability of training-induced effects, the optimal training duration, and the impact of long disease duration on cognitive performance. The lack of treatment studies on cognitive dysfunction highlights the urgent need for more research in this area.

Finally, future research should also focus on two important aspects: resilience and cognitive reserve (CR). Resilience, defined as the ability to adapt well in the face of trauma, stress, adverse life events or major challenges, represents a malleable and trainable life skill associated with positive outcomes [217, 218]. Additionally, patients with Long-COVID, on average, exhibit low resilience [219], which is further associated with depression [220], anxiety

[221], and perceived stress [222] - all highly prevalent among individuals living with Long-COVID [215, 223, 224]. These findings are consistent with the results from Study 3, which showed that approximately one-fifth of individuals living with Long-COVID experienced anxiety (22.5%) or depression (30.0%). Resilience training programs for individuals affected by Long-COVID could therefore be particularly valuable.

Cognitive reserve, on the other hand, refers to the brain's ability to adapt and compensate, helping explain why some individuals maintain cognitive abilities and daily functioning better than others despite aging, brain changes, or damage (e.g., insult). CR was studied in various populations, including individuals with schizophrenia, bipolar disorder, and depression [225], traumatic brain injury [226], Alzheimer's disease [227] or those with Mild Cognitive Impairment [228]. Proxies of CR were shown to be associated with a reduced risk of depressive symptoms [229, 230], anxiety [230], and stress [231]. Costas-Carrera and colleagues (2022) found high levels of CR to be protective against severe cognitive dysfunctions following a COVID-19 infection [232] and CR might also influence post-COVID patient's memory, language, and executive functions [106]. Finally, in individuals who survived and recovered from COVID-19, higher levels of CR were shown to be a protective factor against the development of depressive symptoms [233], as well as against symptoms of psychological distress [230]. Future studies aimed at enhancing both resilience and CR in the Long-COVID population are therefore warranted.

Conclusion

For many, COVID-19 belongs to the past, yet for others, its shadow remains ever present: This thesis aimed to provide an overview of the symptoms and impact of Long-COVID, explore the brain alterations underlying cognitive dysfunction in this condition, and ultimately provide a treatment option with the goal of improving the daily lives and well-being of the large number of individuals living with Long-COVID.

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RESEARCH ARTICLE

Characteristics and burden of acute COVID-19 and long-COVID: Demographic, physical, mental health, and economic perspectives

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Abstract

Background

COVID-19 infection and its associated consequence, known as long-COVID, lead to a significant burden on the global healthcare system and limitations in people's personal and work lives. This study aims to provide further insight into the impact of acute and ongoing COVID-19 symptoms and investigates the role of patients' gender and vaccination status.

Methods

416 individuals (73.9% female) between the ages of 16 and 80 years (*M* = 44.18, *SD* = 12.90) with self-reported symptoms of long-COVID participated in an online survey conducted between March and May 2022.

Results

6.0%, 74.3%, and 19.7% of all respondents reported having had an asymptomatic, mild, or severe acute illness, respectively. Out of all participants, 7.8% required hospitalization. The most prevalent symptoms during the acute infection (*Mdn* = 23.50 symptoms, *IQR* = 13–39) included fatigue, exhaustion, cough, brain fog, and memory problems. The median long-COVID disease duration was 12.10 months (*IQR* = 2.8–17.4). Among 64 inquired long-COVID symptoms (*Mdn* = 17.00 symptoms, *IQR* = 9–27), participants reported fatigue, exhaustion, memory problems, brain fog, and dyspnea as the most common ongoing symptoms, which were generally experienced as fluctuating and deteriorating after physical or cognitive activity. Common consequences of long-COVID included financial losses (40.5%), changes in the participants' profession (41.0%), stress resistance (87.5%), sexual life (38.1%), and mood (72.1%), as well as breathing difficulties (41.3%), or an increased drug intake (e.g., medicine, alcohol; 44.6%). In addition, vaccinated individuals exhibited a shorter acute illness duration and an earlier onset of long-COVID symptoms. In general, women reported more long-COVID symptoms than men.

Conclusion

Long-COVID represents a heterogeneous disease and impacts multiple life aspects of those affected. Tailored rehabilitation programs targeting the plurality of physical and mental symptoms are needed.

Introduction

Since the World Health Organization (WHO) declared the coronavirus disease a global pandemic in March 2020, over 770 million confirmed cases [1] of COVID-19 have been recorded so far (11/2023). Although roughly 80% suffer a mild or moderate illness [2], some are at risk of a severe disease course, requiring intensive medical attention [3]. During the acute phase of an infection, symptoms typically encompass, but are not limited to, fever, cough, fatigue, dyspnea, or muscle aches [4, 5].

As the rate of infections remains elevated, the number of patients with persisting symptoms is increasing as well, leading to a significant amount of sickness rates and ongoing health challenges. Although there is a tremendous amount of heterogeneity in the definition of long-COVID in interventional studies [6], health experts defined the permanence of symptoms beyond four weeks after an initial infection subsided as long-COVID [7, 8]. Long-COVID includes both ongoing symptomatic COVID-19 (4–12 weeks) and the post-COVID-19 syndrome (+12 weeks) [9]. As persisting/ongoing symptoms such as cognitive impairment or fatigue can arise regardless of the initial illness severity [7, 10–12], a considerable number of individuals might develop long-COVID symptoms, especially if the virus continues to spread rapidly. These health issues could especially affect women and unvaccinated individuals, as research suggests a higher risk of long-COVID for women [7, 13, 14] and those without a COVID-19 vaccination [15]. Among various other risk factors, also a heightened body mass index [16] and a higher age [17] might increase the risk of developing long-COVID.

In general, the most common long-COVID symptoms include fatigue, chest pain, dyspnea, and cough [18], but also cognitive symptoms such as memory problems and brain fog are reported frequently [11]. As those symptoms may persist for months, the outbreak of the coronavirus disease has led to significant changes in the occupational [19] and personal lives of those affected. Individuals may need to consider reducing their working hours or are completely incapable of work [11, 20]. Others might be affected by psychological challenges, such as an increased level of depression, anxiety, anhedonia, or stress [21–23]. In addition, changes in peoples' sex life were observed [7], such as a high prevalence of erectile dysfunction [24]. Finally, many also experience cognitive/mental limitations, such as global cognitive dysfunction [20], brain fog [25], attention disorders [22, 26] or memory problems [27].

Despite extensive examination of the diverse domains affected by individuals suffering from long-COVID, detailed information about the variety of symptoms and negative impact on work-life (e.g., changes in a person's profession), private-life (e.g., stress, mood, need for assistance, and sex life), and cognition is scarce [11, 28].

Hence, there is an urgent need to investigate this complex medical condition and raise awareness regarding the ongoing effects of the COVID-19 pandemic. The current study aims at (a) describing the disease course, duration, and self-reported severity of participants' acute COVID-19 infection, (b) characterizing the frequency and burden of acute and ongoing symptoms, (c) analyzing the impact of those symptoms on a variety of domains, including work life, financial losses, drug/medication intake, stress, mood, breathing, and sexuality, (d) investigating differences between vaccinated/unvaccinated individuals as well as between male and female respondents, (e) and analyzing the relationship between selected risk factors (e.g., BMI) and long-COVID symptoms.

Materials and methods

Participants and recruitment

This study represents a cross-sectional online survey available from March 29th to May 3rd, 2022. All questions were presented in German. The study was approved by the ethics committee of the Medical University of Graz (34–166 ex 21/22). Informed consent was obtained by accepting an online data privacy statement, and participants were informed about the objective and duration of the study. All responses were anonymous and participants were free to withdraw from the study at any time, without providing reasons and without any negative consequences. Participants were recruited through social media advertisements, press releases, and information folders distributed in rehabilitation clinics. The online platform "LimeSurvey" was used to collect the data. ML, BM, GP and MK are specially trained in generating (online) questionnaires. Before and during the generation of the questionnaire, authors interviewed long-COVID patients, experts working with COVID patients (such as general doctors, neurologists, and nurse specialists), family members and the founder of a support group for long-COVID. Based on this information, we created the questionnaire used in this study and gave it to three long-COVID patients who evaluated it regarding its comprehensibility and goal-directedness. Afterwards, the questionnaire was adapted based on the feedback of the patients.

An a priori sample size calculation was conducted to determine the appropriate sample size for this study. The calculation was performed using the program G*Power (Version 3.1) and was based on an alpha level of 0.05, a statistical power of 0.80 and an anticipated medium effect size. The calculation indicated that a minimum of 159 individuals is required to detect the anticipated effects for all inferential statistical analyses.

The study sample comprised 416 individuals (73.9% female) between the ages of 16 and 80 years (M = 44.18, SD = 12.90) with a median active disease duration of 11–15 days (IQR: 6–10–16–20 days) and a median long-COVID disease duration of about 12 months (IQR: 2.77–17.36). As it was not mandatory to answer all questions provided, the sample size varies among questions. The majority reported being from Austria (91.1%), holding a university degree (26.3%), and reported working as an employee (70.2%). Detailed demographic information is provided in Table 1. Additionally, information regarding pre-existing health conditions was gathered and depicted in Table 2. There were no exclusion criteria in this study. However, the survey only targeted individuals with self-reported symptoms of long-COVID. Those with implausible values (e.g., year of birth "2022") were excluded from the analyses.

Procedure

The online survey assessed several domains, including demographic characteristics, pre-existing health conditions, duration of the initial COVID-19 illness, course of the disease, hospitalization rates, frequency and burden of acute ("which symptoms did you experience during the acute COVID-19 infection and how burdensome were these symptoms for you?") and ongoing/long-COVID ("what long-COVID symptoms do you experience and how burdensome are these symptoms for you?") symptoms (assessed utilizing a Likert Scale ranging from 1 to 5), the onset and relation between long-COVID symptoms, medical examinations, utilization of long-COVID therapies, changes in long-COVID symptoms, changes in breathing, stress, or mood, need for support, substance abuse, sexual alterations, financial changes and changes in the participants' occupation due to long-COVID, information about the participants'

Table 1. Demographic characteristics.

	N (total)	%	*M* ± *SD*	Range
Total *n*	416			
Age, years	317		44.18 ± 12.90	16–80
Gender	333			
Female	246	73.9		
Male	87	26.1		
Origin	338			
Austria	308	91.1		
Germany	24	7.1		
Switzerland	4	1.2		
Netherlands	1	0.3		
France	1	0.3		
Height, cm	328		171.09 ± 9.22	123–200
Weight, kg	333		76.33 ± 21.41	43.0–178.0
BMI, kg/m^2	327		25.96 ± 6.56	15.4–62.5
Education, years	164		14.55 ± 4.12	6.5–25.0
Education	335			
Lower secondary school	2	0.6		
Compulsory schooling	9	2.7		
Apprenticeship	65	19.4		
High school diploma	79	23.6		
College	24	7.2		
University degree	88	26.3		
University of applied sciences	30	9.0		
Pedagogical university	16	4.8		
Others	22	6.6		
Work	363			
Employee	255	70.2		
Student	22	6.1		
Pupils	5	1.4		
Retiree	23	6.3		
Unemployed	7	1.9		
Self-employed	29	8.0		
Other	22	6.1		

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vaccination status and administered vaccines, training opportunities, and training motivation. Data was collected using single-choice and multiple-choice questions, which could be answered on a computer, mobile phone, or tablet. Participants had the option to provide additional information to specific questions by using text fields in the survey. The online survey took approximately 10 to 15 minutes to be completed.

Statistical analysis

The data were analyzed using the statistics software SPSS (Version 29.0). We used descriptive statistics to describe the data. Chi-square or Fisher's exact tests were computed to examine the relationship between categorical variables. Non-parametric tests (e.g., Mann-Whitney-U, Kruskal-Wallis) were applied to ordinal data or skewed continuous variables. Finally, univariate comparisons for continuous variables were performed using analyses of variance

Table 2. Pre-existing health conditions.

Pre-existing conditions (n = 217)	Frequency	Percentage (%)
Specification	**151**	
Dementia	0	0
Parkinson	0	0
Epilepsy	0	0
Multiple Sclerosis	0	0
Stroke	2	1.3
Hypertension	30	19.9
Diabetes	10	6.6
Chronic obstructive pulmonary disease	4	2.7
Cardiac insufficiency	5	3.3
Cancer	6	4.0
Other*	94	62.3

*Other pre-existing conditions include, for instance, allergies, asthma, depression, gastrointestinal disorders or hypo-/hyperthyroidism

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(ANOVAs) and corresponding post-hoc tests. We computed Spearman correlation coefficients to analyze relations between not normally distributed continuous or ordinal scaled variables, otherwise Pearson correlations were performed. A significance level of α = .05 was used. Effect sizes (e.g., Cohen's d, η_p^2, φ_c, OR, r) were calculated and specified in the corresponding analyses. All research data used in this study can be accessed in the S1 File (https://doi.org/10.3886/E196861V1).

Results

Acute COVID-19 infection: Symptoms and burden

Individuals with self-reported symptoms of long-COVID and stating to have had a COVID-19 infection between February 2020 and May 2022 were included in the subsequent analyses. A graphic illustration of the infection frequency as a function of time is depicted in Fig 1. The duration of participants' acute illness was positively skewed with a median of 11–15 days (*IQR*: 6–10–16–20 days) (Fig 2). Out of 299 respondents, the majority (74.3%) reported having had a mild course of disease (n = 222), while 6.0% (n = 18) had an asymptomatic or severe (19.7%, n = 59) disease course, respectively. Detailed information is presented in Table 3. Moreover, 7.8% stated they were admitted to the hospital. Of those dependent on hospital care due to the severity of their symptoms during the acute illness (n = 23), 60.9% were treated on a COVID-19 ward, while 17.4% were admitted to an ICU or did not further specify their hospital admission (21.7%). The median length of hospitalization was 0–10 days (*IQR*: 0–10–21–30 days) and only one respondent reported a hospitalization duration exceeding one month (Table 4).

The participants experienced a median number of 23.5 different symptoms (*IQR*: 13–39 symptoms) during the acute phase of their illness. The most common initial symptoms included fatigue (93.4%), tiredness/exhaustion (84.4%), dry cough (76.2%), cognitive dysfunction (e.g., brain fog; 75.5%), poor memory (75.2%), a runny nose (73.8%), headache or headache-associated symptoms (72.5%), loss of appetite (72.5%), fever (72.2%), sweating or chills (71.9%), muscle aches (71.9%), and dyspnea (71.2%). A comprehensive list of symptoms can be found in Fig 3 and S1 Table.

The subjective burden of those symptoms during the acute and ongoing phase was assessed using a 5-point Likert Scale (*1* = very mild to *5* = very strong). Exhaustion (M = 4.13, SD =

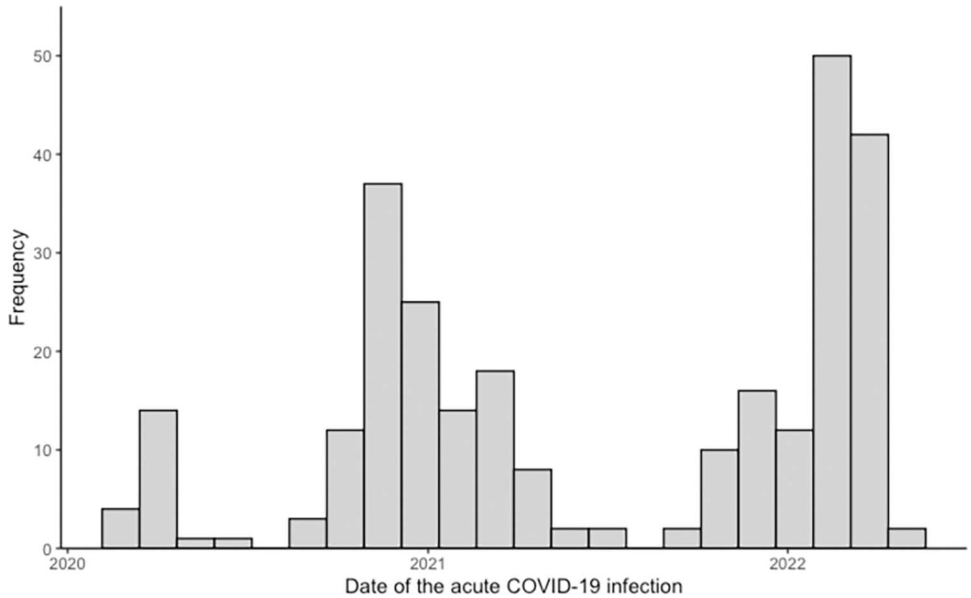

Fig 1. Infection frequency of survey respondents as a function of time.

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0.94), an altered sense of taste and smell (*M* = 3.97, *SD* = 1.31), fatigue (*M* = 3.96, *SD* = 1.02), discomfort after physical exertion (*M* = 3.82, *SD* = 1.04), headache or headache-associated symptoms (*M* = 3.76, *SD* = 1.18), and dyspnea (*M* = 3.59, *SD* = 1.22) were reported to be the most significant burdens during the acute illness (S1 Table). In general, respondents experienced a very mild (26.4%) or mild (15.4%) burden caused by their symptoms, while the majority reported a moderate (22.1%), strong (20.0%), or very strong (16.1%) burden, respectively.

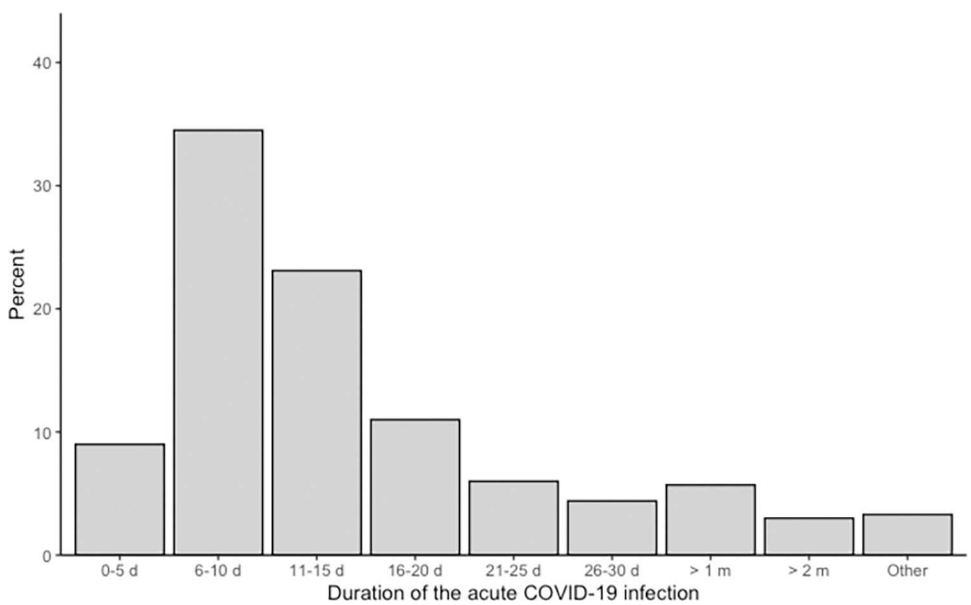

Fig 2. Duration of participants' acute COVID-19 illness. *d* = days, *m* = months.

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Table 3. Detailed information about the duration and severity of participants' acute infection.

Duration of acute infection (*n* = 299)	**Frequency**	**Percentage (%)**
0–5 days	27	9.0
6–10 days	103	34.5
11–15 days	69	23.1
16–20 days	33	11.0
21–25 days	18	6.0
26–30 days	13	4.4
> 1 month	17	5.7
> 2 months	9	3.0
Other*	10	3.3
Disease severity (*n* = 299)		
Asymptomatic	18	6.0
Mild	222	74.3
Severe	59	19.7

*Other information includes, for example, a still continuing infection

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Long-COVID: Symptoms and burden

A median number of 17.0 (*IQR*: 9–27) symptoms that persisted or were developed after the acute COVID-19 infection were reported. The most prevalent were fatigue (97.4%), exhaustion (83.8%), poor memory (82.7%), cognitive dysfunction (e.g., brain fog; 77.1%), dyspnea (70.5%), discomfort after physical exertion (63.8%), chest discomfort (62.4%), dizziness (62.0%), headache or headache-associated symptoms (59.0%), insomnia (56.1%), breathing difficulties (55.4%), and muscle aches (49.8%). Detailed information about the frequency and burden of all long-COVID symptoms is depicted in S2 Table and Fig 4.

The most significant burden was found to be associated with symptoms such as fatigue (M = 4.12, SD = 0.99), exhaustion (M = 4.03, SD = 0.96), discomfort after physical exertion (M = 3.92, SD = 0.94), sleep alterations (M = 3.44, SD = 1.16), an altered sense of taste and smell (M = 3.44, SD = 1.46), and cognitive dysfunction (e.g., brain fog; M = 3.43, SD = 1.21) (S2 Table). In general, participants experienced a very mild (18.6%), mild (19.4%), moderate (26.1%), strong (20.2%) or very strong (15.7%) burden by their long-COVID symptoms, respectively.

About half of the study participants (49.8%, n = 132/265) reported the onset of their long-COVID symptoms within the initial two weeks after the acute infection. 18.9% (n = 50) stated

Table 4. Duration of hospitalization during the acute illness.

Hospitalization (*n* = 296)	***n***	**Percentage (%)**
Yes	23	7.8
No	273	92.2
Duration of hospitalization*		
0–10 days	12	66.7
11–20 days	2	11.1
21–30 days	3	16.7
31–60 days	0	0.0
> 2 months	1	5.5

*Duration is given for those hospitalized and providing further information (n = 18)

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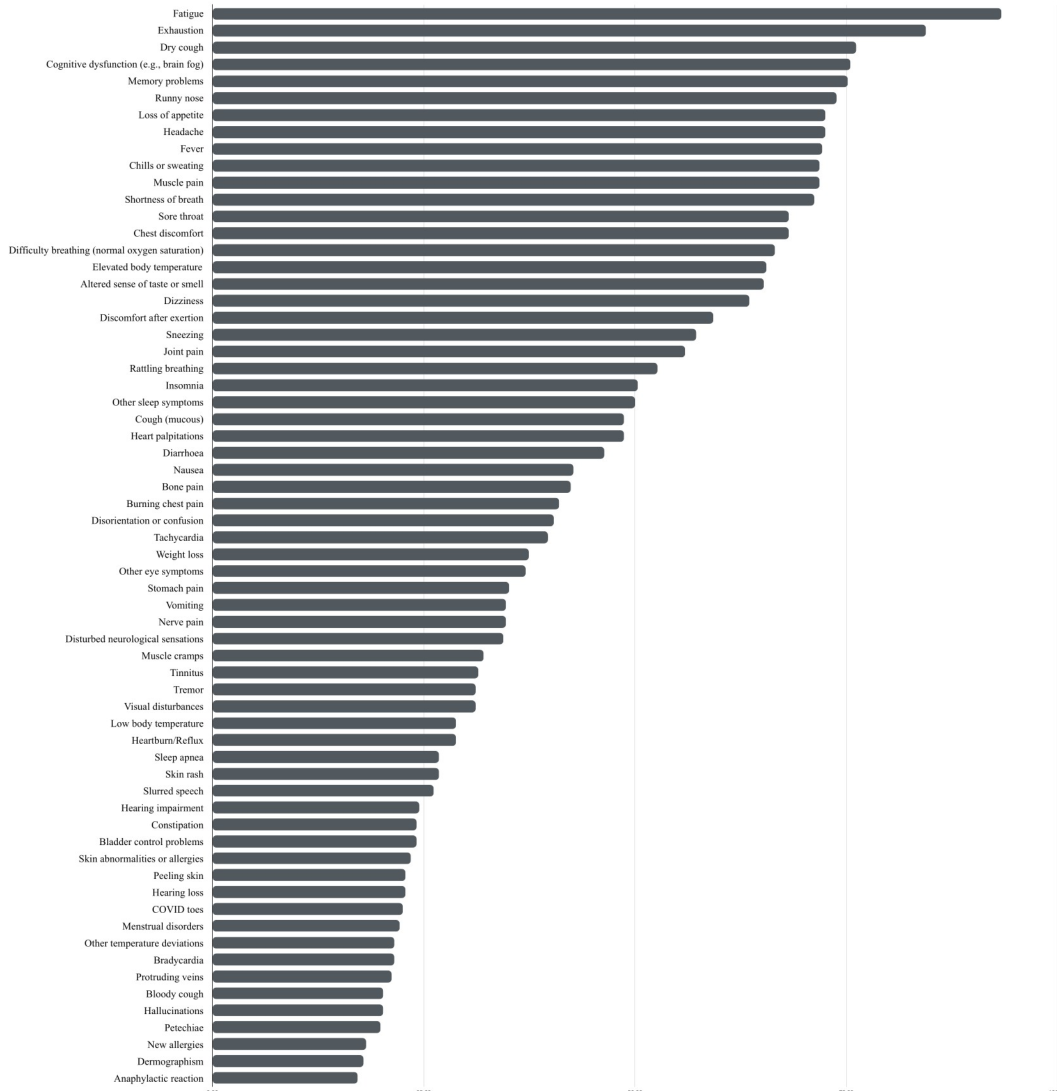

Fig 3. Percent of COVID-19 symptoms during the acute phase of the illness.

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that their symptoms emerged between the third- and fourth-week post-infection, while 15.8% (*n* = 42) of the respondents experienced the appearance of ongoing symptoms two- or three months post-infection. A further 15.5% (*n* = 41) reported ongoing symptoms immediately after their infection, after vaccination, or later than three months post-acute infection.

Extramural examination of long-COVID symptoms

62.3% (*n* = 162/260) underwent medical examinations to clarify their symptoms. These evaluations encompassed pulmonary function tests (72.8%, *n* = 118), X-rays (53.1%, *n* = 86), neurological assessments (41.4%, *n* = 67), MRI scans (38.3%, *n* = 62), CT scans (35.2%, *n* = 57), neuropsychiatric evaluations (25.9%, *n* = 42), and other tests such as ECG (electrocardiogram) or blood tests (18.5%, *n* = 30). A long-COVID outpatient clinic was visited by 17.7% (*n* = 46/260) of all respondents. In addition, 21.9% reported having visited a specialized long-COVID

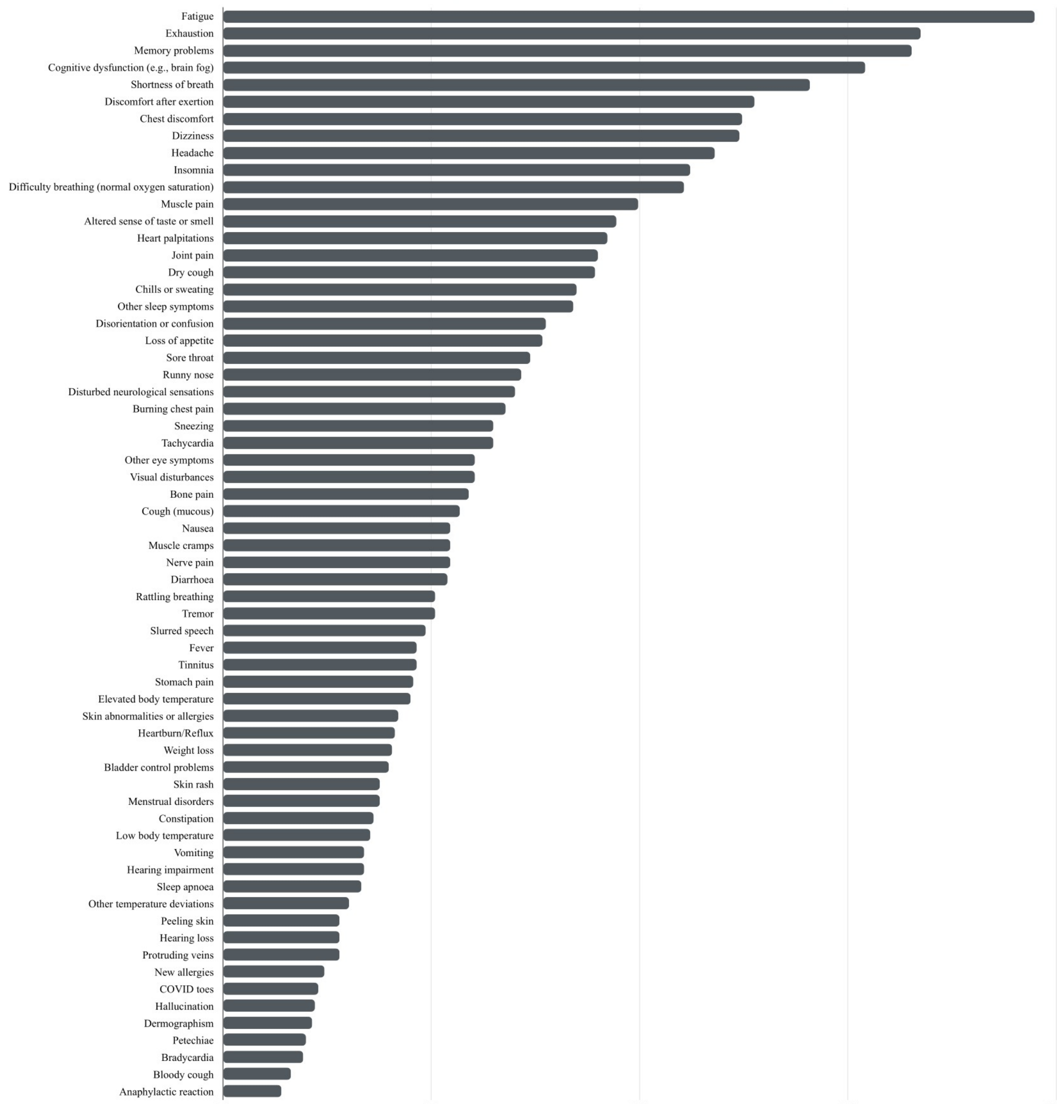

Fig 4. Percent of ongoing or newly developed symptoms (long-COVID symptoms).

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rehabilitation clinic due to their long-COVID symptoms. Numerous study respondents (n = 152) further reported connections between their symptoms, for instance, a simultaneous occurrence of anxiety and dyspnea, exhaustion and concentration difficulties, memory problems and headache or between physical exhaustion and cognitive symptoms (e.g., concentration difficulties, or trouble with finding the correct words).

Alteration of long-COVID symptoms

We further asked all participants about alterations in their long-COVID symptoms by using several multiple-response questions. The majority reported that their symptoms got worse after physical (70.2%, n = 186) or mental (52.1%, n = 138) activity, while 53.6% (n = 142) described them as fluctuating. However, some even reported an improvement in their symptoms after physical (8.3%, n = 22) or mental (4.5%, n = 12) activity. Moreover, 26.0% (n = 69)

Table 5. Alterations in long-COVID symptoms (*n* = 265).

Symptoms. . .	*n*	Percentage (%)
are getting worse after physical activity	186	70.2
are getting worse after mental activity	138	52.1
are fluctuating	142	53.6
are getting better after physical activity	22	8.3
are getting better after mental activity	12	4.5
are improving in general	69	26.0
are getting worse in general	21	7.9
are unchanged since their onset	75	28.3

Percent do not add up to 100% as multiple answers were permitted.

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experienced an overall improvement in their symptoms, while 7.9% (*n* = 21) reported a substantial deterioration of their long-COVID symptoms. A further 28.3% (*n* = 75) described their symptoms as unchanged since their onset. The findings are summarized in Table 5.

To alleviate the negative impact of long-COVID, participants reported engaging in movement (59.0%, *n* = 138), breathing (53.4%, *n* = 125), and cognitive exercises (36.8%, *n* = 86). Nonetheless, about a quarter (27.4%, *n* = 64) stated having not attempted any exercises yet, although many consider that breathing (65.4%), movement (80.4%), and cognitive exercises (72.1%) could potentially mitigate their symptoms. The participants mentioned a possible enhancement of their overall health as a crucial motivational factor for starting a training program.

Impact of long-COVID on participant's professional life

A total of 41.0% (*n* = 133 of 324 respondents) experienced work-related changes since the onset of their long-COVID symptoms. Of those, 9.0% stated to now be unable to work, 23.3% had to reduce working hours, 57.9% went on sick leave, and 25.6% reported other changes in their work routine, such as termination or the requirement for rehabilitation. The median number of work-related sick days was 16 days (*IQR*: 10–42 days). In addition, substantial financial losses were reported by 40.5% of all study participants.

Impact of long-COVID on participants' physical and mental health

Regarding breathing difficulties among the survey participants (*n* = 242), 58.7% reported having complete control over their breathing during the day, while the remaining 41.3% stated that control over their breathing is situational. A few (1.1%, *n* = 3) even require oxygen therapy at home. Further, some (23.3%) depend on help from relatives or external organizations in order to perform daily tasks such as cooking, cleaning, childcare responsibilities, or lifting heavy loads.

Additionally, nearly half of all respondents (44.6%, *n* = 116/260) reported a significant increase in substance or medication intake (e.g., alcohol, medication, drugs), and more than a third experienced noticeable changes in their sexual life (e.g., loss of libido; 38.1%, *n* = 88/231). One factor driving these changes was fatigue, as those who experienced substantial changes in their sexual life (*MR* = 130.80, *Mdn* = 5.00) experienced a higher burden of fatigue as compared to those who did not report any sexual alterations (*MR* = 99.29, *Mdn* = 4.00) (U = 4188.00, z = -3.82, $p < .001$, r = -0.26).

Finally, the impact of long-COVID extends beyond physical limitations and encompasses substantial psychological alterations as well. 87.5% (*n* = 231/264) reported a modification in their stress load capacity, as most of these individuals experienced a considerable deterioration (97.0%). Further, mood changes were reported in about 72.1% (n = 189/262). Of those, the majority (91.5%) experienced a worsening of their mood since their COVID-19 infection and the associated long-COVID symptoms.

Vaccination status

134 out of 296 individuals (45.3%) stated to have received a COVID-19 vaccine before their SARS-CoV-2 infection. However, as many study participants got infected prior to the public availability of COVID-19 vaccines in Austria, we further assessed their vaccination status after their infection (when they completed the online survey). 85.2% (n = 138/162) of those unvaccinated at the time of their infection got vaccinated after their illness, while 14.8% (n = 24) declined to receive a COVID-19 vaccine up to the point of our data collection. The most common vaccine at the first vaccination (n = 111) was Comirnaty (BioNTech Pfizer; 60.4%, n = 67), followed by Vaxzevria (AstraZeneca; 33.3%, n = 37) and Spikevax (Moderna; 6.3%, n = 7). A comparable pattern was observable for participants' second and third vaccination.

Differences between vaccinated and unvaccinated individuals

Participants who had received at least one dose of the COVID-19 vaccine at the time of their infection (n = 128) experienced a significantly shorter acute illness duration (MR = 113.72, Mdn = 6–10 days) compared to those who were not vaccinated (n = 156) prior to their infection (MR = 166.11, Mdn = 11–15 days; U = 6300.50, z = -5.52, $p < .001$, r = -.33). However, there was no difference between the groups in terms of their self-reported disease course/illness severity (n = 289, $\chi^2(2) = 3.04$, p = .219, $\varphi_c = .10$) or hospitalization rates (n = 191, $\chi^2(1) = 0.01$, p = .904, OR = 1.05, 95% CI (0.45, 2.49), $\varphi_c = .01$).

With respect to work absence, no differences in sick leave days were found between vaccinated (n = 115) and unvaccinated (n = 127) individuals (U = 6364.00, z = -1.73, p = .084, r = -.11). Furthermore, both groups (n = 257) did not differ in the frequency of needing support from family, friends, or caregivers ($\chi^2(1) = 0.50$, p = .479, OR = 1.24, 95% CI (0.69, 2.23), φ_c = .04). However, those unvaccinated at the time of their COVID-19 infection more frequently reported having visited a rehabilitation clinic than vaccinated participants ($\chi^2(1) = 36.11$, $p <$ .001, OR = 14.06, 95% CI (4.90, 40.36), $\varphi_c = .37$).

Also, the onset of long COVID symptoms (time until new symptoms emerged after the infection) was found to be significantly earlier in vaccinated (n = 99, MR = 91.85, Mdn = after 1–2 weeks) than in unvaccinated (n = 122, MR = 126.54, Mdn = after 3–4 weeks) participants (U = 4143.00, z = -4.52, $p < .001$, r = -.30). Finally, there was no significant difference between the groups regarding the number of their acute (n = 295, U = 10168.50, z = -0.85, p = .396, r = -.05) or ongoing COVID-19 symptoms (n = 265, U = 8055.50, z = -0.86, p = .388, r = -.05).

Differences between male and female respondents

We did not find any statistically significant differences between men and women in the duration of their acute COVID-19 infection (n = 284, U = 7586.50, z = -0.64, p = .521, r = -.04), self-reported disease course/illness severity (n = 289, $\chi^2(2) = 0.60$, p = .740, $\varphi_c = .05$), or hospitalization rates (n = 291, $\chi^2(1) = 3.72$, p = .054, OR = 2.30, 95% CI (0.86, 5.98), $\varphi_c = .11$). However, the hospitalization analyses indicated a possible trend towards higher hospitalization rates for men (13.0%) compared to women (6.1%).

Further, no differences in the number of sick leave days (n = 244, U = 4821.00, z = -1.72, p = .086, r = -.11), the frequency of needing support from family, friends, or caregivers ($\chi^2(1) = 1.20$, p = .273, OR = 1.47, 95% CI (0.74, 2.91), $\varphi_c = .07$), the frequency of having visited a rehabilitation clinic ($\chi^2(1) = 0.09$, $p = .767$, $OR = 0.91$, 95% CI (0.47, 1.75), $\varphi_c = .02$), or the onset of long-COVID symptoms ($n = 220$, $U = 5336.00$, $z = 1.74$, $p = .081$, $r = .12$) were observed.

Concerning the frequency of symptoms during the acute phase of the illness, no significant difference was observed between men and women as well ($U = 8247.50$, $z = -0.34$, $p = .731$, $r =$ —.02). However, in general, women ($MR = 141.39$, $Mdn = 18$ symptoms) reported significantly more ongoing COVID-19 (long-COVID) symptoms compared to men ($MR = 110.98$, $Mdn = 13$ symptoms) ($U = 5242.50$, $z = -2.83$, $p = .005$, $r = -.17$).

Possible risk factors associated with acute COVID-19 and long-COVID symptoms

Next, we were interested in possible risk factors (BMI, age, and hypertension) associated with participants' acute infection and ongoing symptoms. A higher BMI ($M = 26.19$, $SD = 6.73$) was associated with a longer duration of illness during the initial COVID-19 infection ($r_s = .13$, $p = .025$).

Further analyses confirmed that individuals with different self-reported disease courses (asymptomatic ($n = 17$), mild ($n = 210$), severe ($n = 56$)), on average, differed in their body mass index ($F(2, 280) = 5.50$, $p = .005$, $\eta_p^2 = .038$). We found significant differences between individuals with a mild ($M = 25.46$ kg/m^2, $SD = 6.55$) and severe ($M = 28.71$ kg/m^2, $SD = 7.29$) illness ($M_{diff} = 3.25$ kg/m^2, $p = .004$), while no differences to asymptomatic individuals ($M =$ 27.15 kg/m^2, $SD = 5.37$) were observable (asymptomatic vs. mild: $p = .675$; asymptomatic vs. severe: $p = .778$).

In addition, no age differences between individuals with different disease courses (asymptomatic ($n = 17$), mild ($n = 202$), or severe ($n = 57$)) were found in this data ($F(2, 273) = 1.90$, $p = .151$, $\eta_p^2 = .014$), but our analyses revealed a positive relationship between age ($M = 44.69$, $SD = 12.81$) and participants' illness duration during their acute infection ($r_s = .23$, $p < .001$). However, age was not associated with the frequency of acute COVID-19 symptoms ($r = .02$, $p = .713$) and long-COVID symptoms ($r = .03$, $p = .627$).

Among 340 participants that made a statement about their blood pressure, 8.8% ($n = 30$) suffered from hypertension. Participants with heightened blood pressure ($MR = 159.25$, Mdn = 11–15 days) did not statistically differ in the duration of their acute illness from normotensive participants at the time of completing the survey ($MR = 143.47$, Mdn = 11–15 days) ($n = 289$, $U = 4053.00$, $z = 0.98$, $p = .327$, $r = .06$). In addition, no statistically significant differences between those with and without hypertension were found regarding their self-reported illness severity (asymptomatic, mild, severe; $n = 294$, $\chi^2(2) = 5.59$, $p = .061$, $\varphi_c = .14$), the frequency of symptoms during their acute illness ($U = 3959.00$, $z = -1.35$, $p = .178$, $r = -.07$) or ongoing symptoms ($U = 4329.50$, $z = -0.63$, $p = .531$, $r = -.03$), and the time until the occurrence of long-COVID symptoms ($U = 2274.00$, $z = -1.09$, $p = .275$, $r = -.07$).

Discussion

The findings of the present online study offer valuable insight into the various domains impacted by individuals suffering from long-COVID. Symptoms such as fatigue, exhaustion, and considerable cognitive deficits (e.g., brain fog or memory problems) were predominant in both the acute and ongoing phases of their illness. This clinical presentation is consistent with other studies, indicating that long-COVID symptoms affect multiple organ systems, with cognitive dysfunction and fatigue being among the most frequent ongoing symptoms [20]. Although those symptoms were already reported in other studies [11, 20], our findings suggest that they were experienced as a significant burden for those affected, which might lead to serious mood disorders such as depression or anxiety [29]. Thus, highlighting the burden and impact of long-COVID and focusing on tailored rehabilitation opportunities represents a significant challenge for future research on this topic. We could further confirm a shorter acute illness duration and an earlier onset of long-COVID symptoms in vaccinated compared to unvaccinated individuals, as well as a higher number of long-COVID symptoms in women than in men. The key findings of the present study are summarized in the following section and compared to the current state of knowledge.

Acute COVID-19 illness

Consistent with one of the earliest studies investigating the course of a coronavirus infection [2], reporting about 81% of mild and 19% of severe/critical cases, most participants in the present study stated to have experienced a mild (74.3%), severe (19.7%) or asymptomatic (6.0%) infection. In line with Menni et al. [30], the acute illness of most individuals did not exceed about two weeks. Symptoms affecting the respiratory tract (e.g., cough, dyspnea, chest tightness) as well as fatigue/exhaustion, fever, headache, or cognitive dysfunction were present as typical signs of an acute COVID-19 infection [11, 31, 32]. Our results further suggest that both a higher body mass index and a higher age are associated with a longer-lasting illness during the acute infection. A higher BMI, on average, was further present in those with a more significant illness severity [33, 34]. In addition, diverging illness characteristics of vaccinated (45.3%) and unvaccinated (54.7%) individuals (at the time of their infection) were present, as not being vaccinated was associated with a longer-lasting acute infection. Finally, although belonging to the male sex was found to be associated with an increased risk of hospitalization in previous studies [35], no significant gender differences in hospitalization rates were present in the current study. Nonetheless, we found indications that men were hospitalized about twice as often as women (13.0% vs. 6.1%).

Long-COVID

In the majority (49.8%), ongoing or newly developed symptoms emerged already in the first two weeks post-infection. Common symptoms included fatigue, exhaustion, memory problems, cognitive dysfunction, and dyspnea. Consequently, numerous participants reported an adverse impact regarding their profession (41.0%), financial losses (40.5%), and changes in their ability to cope with stress (87.5%). Those affected encountered changes in their work life such as sick leave, loss of income, and reduced working hours or were even incapable of work which also aligns with prior literature [11, 20]. Ziauddeen et al., for instance, reported a loss of income in 37.6% of all study participants [11], comparable to a high number of 40.5% of participants in the current study.

Furthermore, long-COVID symptoms such as cognitive dysfunction or brain fog [20, 36, 37] might interfere with demands in the work and private life of those affected, as those symptoms were often described as fluctuating and deteriorating after physical or cognitive activity [11]. Consequently, reducing working hours has been a common outcome for those suffering from long-COVID [11, 20]. A gradual reintegration into the labor market as well as adjusted working hours might be advisable to prevent prolonged sick leave or early retirement.

It is concerning to note that a considerable number of participants in the current study experienced changes in their mood (72.1%), had problems with their breathing control (41.3%), were dependent on help from organizations or relatives (23.3%) or suffered from changes in their sexual life (38.1%). Alterations in the sexual life (e.g., erectile dysfunction) of patients living with long-COVID had also been reported in previous studies [24], which might lead to significant distress. Psychological distress and depressive symptoms were found to be prevalent in more than 25% of individuals three months after the acute phase of infection [38], suggesting that the risk of mood disorders such as depression or anxiety in COVID-19 survivors is high [39]. Comprehensive mental health care and clinical strategies for individuals with long-COVID are therefore needed.

Regarding the influence of COVID vaccines on the emergence of long-COVID or its symptoms, studies consistently show an association between vaccinations and reduced odds and risk of developing long-COVID [40, 41]. Consequently, ongoing research proposes that COVID-19 vaccines could offer both protective and therapeutic benefits against long-COVID [42]. Although numerous studies provided evidence that the risk of developing long-COVID is lower among vaccinated individuals than in those without a vaccination [14, 15, 43], there seems to be no difference regarding the number of long-COVID symptoms between both groups according to the results found in this study. However, with respect to gender differences, we did observe a higher number of long-COVID symptoms in women compare to men, which aligns with the findings of a previous study by Jensen et al. [44].

Despite the range of symptoms and adverse impact on various domains, most individuals did not seek help in long-COVID outpatient clinics (82.3%) or rehabilitation facilities (78.1%), which might result in a significant economic burden on the worldwide healthcare system and the well-being of those affected.

Limitations

The current study used a convenience non-probability sampling approach, whereby subjects were chosen not randomly from the population but rather based on their geographical proximity and availability at a given time. In addition, the majority were female and reported a high educational status. Nonetheless, studies have demonstrated that long-COVID occurs more frequently in women, which makes it reasonable for a higher representation of women in long-COVID studies [45]. Given that this study was conducted online, it might not have been accessible to all individuals living with long-COVID in the population. Consequently, the generalization of our results to the total population is limited.

Due to economic reasons, the length of the survey was as short as possible in order to recruit a large number of participants with a little drop-out rate of unanswered questions. Therefore, some parameters (e.g., the Post-COVID-19 functional status [46]) were not collected and should be included in future studies as they might add valuable information to this research topic. In addition, the current study may be affected by two possible sources of bias: Firstly, participants may have had difficulty correctly recalling their symptoms, burden, or the length of their acute illness, especially if their initial infection occurred several months before completing the online survey. In addition, individuals with more severe symptoms might have been more likely to participate in a long-COVID online survey, again compromising the generalizability of the results.

Also, despite enquiring the duration of the acute disease, and the timepoint of the first long-COVID symptoms, we cannot guarantee that all participants meet the current definition of long-COVID with persistence of symptoms being present for at least four weeks following the acute infection. Finally, this study did not provide guidelines for categorizing individuals into “asymptomatic”, “mild”, and”severe” disease courses. Therefore, participants could indicate a severe disease course, for instance, regardless of whether they were hospitalized or not.

Implications for future research

Future studies should raise awareness concerning the effects of COVID-19 tailored rehabilitation possibilities. However, as general treatment for patients is scarce or unavailable [7], multidisciplinary teams need to specialize in rehabilitating the various symptoms associated with this condition. As fatigue (ongoing and constant exhaustion in mental and physical aspects that does not improve with resting/sleeping) and exhaustion (short-term lack of energy that improves after taking a rest), for instance, emerged among the most prevalent symptoms reported, future research should focus on validating the use of techniques such as psychoeducation [47], energy management [47], training based on cognitive-behavioral-therapy [48, 49], mindfulness [50] or relaxation exercises [51] in ameliorating fatigue in patients suffering from long-COVID. In addition, cognitive deficits like memory problems, trouble finding the correct words, and planning-oriented thinking [52, 53] are common long-COVID symptoms and require tailored cognitive rehabilitation programs. Future research on long-COVID should also examine the implications and consequences due to insufficient, incomplete, or discontinued treatment in the acute phase, since a variety of consequences might be associated with it.

Conclusion

Long-COVID represents a highly heterogeneous disease, encompassing a variety of symptoms such as fatigue, cognitive dysfunction, or dyspnea. The impact of this prolonged illness is not yet fully understood, as symptoms can affect multiple domains, including an individuals' professional and personal life. Multidisciplinary teams and treatments are needed to develop individually tailored rehabilitation approaches, enabling individuals to ameliorate their symptoms and better cope with the substantial burden of long-COVID in the future.

Supporting information

S1 Table. Frequency of acute symptoms and subjective burden (n = 302). *a* Multiple modes exist, the smallest value is shown.
(PDF)

S2 Table. Frequency of ongoing symptoms and subjective burden (n = 271). *a* Multiple modes exist, the smallest value is shown.
(PDF)

S1 File. Research data. Koini, Marisa. Characteristics and burden of acute COVID-19 and long-COVID. Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], 2024-01-06. https://doi.org/10.3886/E196861V1.
(XLSX)

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Research Report

Functional connectivity changes in long-Covid patients with and without cognitive impairment

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ABSTRACT

Long-Covid is associated with cognitive deficits in memory, attention, or executive function. However, the associated cerebral structural and functional changes are insufficiently studied to date. We investigated 39 long-Covid patients with ($n = 16$) and without ($n = 23$) cognitive impairment. Impairment was defined by a pronounced deficit (−1.5 SD) in at least one cognitive domain including memory, attention, executive function, and verbal fluency. All participants underwent structural and functional resting-state magnetic resonance imaging (MRI). We assessed differences in resting-state networks (within and between networks) between both groups as well as structural differences in total gray matter and subcortical volumes. Both groups did not differ in demographic or disease-related characteristics. Patients with cognitive deficits showed higher functional connectivity (FC) between the default mode network (DMN) and parts of the posterior supramarginal gyrus, angular gyrus and posterior-occipital part of the middle temporal gyrus, compared to those cognitively unimpaired. In addition, inter-network analyses indicated a stronger connectivity between the visual and ventral stream network in those with cognitive impairment. We found no volumetric differences between the two groups. Our results indicate that altered FC with the DMN as well as a stronger connectivity between the visual and ventral stream network in cognitively impaired long-Covid patients are associated with worse cognitive performance and therefore suggests a maladaptive functional change.

1. Introduction

Although there is no unified definition for long-Covid (Munblit et al., 2022), the World Health Organization (WHO) defines long-Covid as “the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation” (WHO, 2022). The global prevalence of long-Covid (also known as Post-Covid-19 condition, PCC) was estimated to be around 10–20% of individuals who were ever

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infected with SARS-CoV-2 (Altmann, Whettlock, Liu, Arachchillage, & Boyton, 2023; Ballering, van Zon, Olde Hartman, Rosmalen, & Lifelines Corona Research, 2022; Davis, McCorkell, Vogel, & Topol, 2023; WHO, 2022). Additionally, studies indicate that approximately 18–22% of individuals ever infected with Covid-19 specifically suffer from various cognitive symptoms as part of their condition (Ceban et al., 2022; Han, Zheng, Daines, & Sheikh, 2022). However, due to the loose definition of long-Covid (Regunath, Goldstein, & Guntur, 2023), estimating the prevalence of this complex condition is challenging, resulting in varying estimates across populations [e.g., higher prevalence in women compared to men and for unvaccinated compared to vaccinated individuals (Hastie et al., 2023)]. These symptoms include, but are not limited to, brain fog (Graham et al., 2021; Jennings, Monaghan, Xue, Duggan, & Romero-Ortuno, 2022; Lanz-Luces et al., 2022; Leitner, Pötz, et al., 2024; McWhirter et al., 2023), concentration difficulties (Byambasuren, Stehlik, Clark, Alcorn, & Glasziou, 2023; Fleischer et al., 2022; Kim, Bae, Chang, & Kim, 2023; Ruzicka et al., 2024; Seessle et al., 2022; Wong et al., 2023; Ziauddeen et al., 2022), attention disorders (Cipolli et al., 2023; Crivelli et al., 2022; Graham et al., 2021; Guillen et al., 2024; Hadad et al., 2022; Herrera et al., 2023; Kozik et al., 2023; Krishnan, Miller, Reiter, & Bonner-Jackson, 2022; Lauria et al., 2023; Lopez-Leon et al., 2021; Martin et al., 2024; Nicotra et al., 2023), executive dysfunction (Ariza et al., 2022; Cipolli et al., 2023; Dacosta-Aguayo et al., 2024; Godoy-Gonzalez et al., 2023; Hadad et al., 2022; Hampshire et al., 2024; Herrera et al., 2023; Kozik et al., 2023; Krishnan et al., 2022; Nicotra et al., 2023), and memory problems (Ariza et al., 2022; Byambasuren et al., 2023; Chen et al., 2022; Cipolli et al., 2023; Dacosta-Aguayo et al., 2024; Fleischer et al., 2022; Godoy-Gonzalez et al., 2023; Hampshire et al., 2024; Kim et al., 2023; Kozik et al., 2023; Laskovski, Felcar, Fillis, & Trelha, 2023; Lauria et al., 2023; Leitner, Pötz, et al., 2024; Martin et al., 2024; Nicotra et al., 2023; Ruzicka et al., 2024; Scardua-Silva et al., 2024; Ziauddeen et al., 2022), often lasting for several months or even years (Herrera et al., 2023). In addition, several risk factors have been identified such as female sex (Cohen & van der Meulen Rodgers, 2023; Fernandez-de-Las-Penas et al., 2022; Largent et al., 2023; Nalbandian, Desai, & Wan, 2023; Subramanian et al., 2022; Sudre et al., 2021; Sylvester et al., 2022; Tan et al., 2024; Tene, Bergroth, Eisenberg, David, & Chodick, 2023; Thompson et al., 2022; Tsampasian et al., 2023; Vanichkachorn et al., 2021), older age (Abdelrahman, Abd-Elrahman, & Bakheet, 2021; Bonfim et al., 2024; Largent et al., 2023; Sudre et al., 2021; Tene et al., 2023; Thompson et al., 2022; Tsampasian et al., 2023), smoking (Barthelemy et al., 2022; Subramanian et al., 2022; Tene et al., 2023; Tsampasian et al., 2023), pre-existing comorbidities (Subramanian et al., 2022; Tsampasian et al., 2023), and an elevated body mass index (Subramanian et al., 2022; Sudre et al., 2021; Thompson et al., 2022; Tsampasian et al., 2023). Until today, the exact cause of the development of long-Covid remains unclear (Liu, Gu, Li, Zhang, & Xu, 2023). However, the large number of neurological and cognitive symptoms led to an increasing number of studies that focused on structural and functional alterations within the brain.

Studies on post-acute Covid-19 patients reported decreased gray matter (GM) volumes or shape differences in olfactory-related regions (Campabadal et al., 2023), the left thalamus (Heine et al., 2023; Jin, Cui, Xu, Ren, & Zhang, 2024), putamen (Heine et al., 2023), pallidum (Heine et al., 2023), parahippocampal gyrus (Douaud et al., 2022), orbitofrontal cortex (Douaud et al., 2022), and cerebellar areas (Diez-Cirarda et al., 2023). One study also reported a greater age-dependent increase in WMH (white matter hyperintensity) volumes in hospitalized long-Covid patients compared to a healthy control group (Atik et al., 2025).

In addition to structural imaging, resting-state functional magnetic resonance imaging (rs-fMRI) could serve as a functional marker for diseases (Bijsterbosch, Smith, & Beckmann, 2017; Tanashyan, Kuznetsova, Morozova, Annushkin, & Raskurazhev, 2024). These markers might be used for the early detection of diseases, disease progression or to indicate treatment response (Bijsterbosch et al., 2017), therefore helping us to better understand the development and progression of the long-Covid disease and its association with cognitive impairment. The current literature on functional connectivity (FC) changes in long-Covid patients reports various findings, including hypo-connectivity between the left and right parahippocampal areas, as well as between bilateral orbitofrontal and cerebellar areas (Diez-Cirarda et al., 2023), FC alterations in the right pallidum and left putamen (Zhao et al., 2024) or lower temporal and subcortical FC in long-Covid patients compared to controls (Churchill et al., 2023). In one of our previous studies, we further found decreased FC from the thalamus to mainly motor areas in fatigued long-Covid patients compared to long-Covid patients without fatigue (Leitner, Opriessnig, et al., 2024).

Finally, a variety of studies reported alterations in large resting-state network connectivity following a Covid-19 infection and in long-Covid (Muccioli et al., 2023; Nasir, Yahya, & Manan, 2024; Paolini et al., 2023). These network alterations include, for instance, the salience network (Carreras-Vidal et al., 2025; Paolini et al., 2023), the dorsal attention network (Liu et al., 2025; Paolini et al., 2023; Voruz et al., 2023), the default mode network (Carreras-Vidal et al., 2025; Madden et al., 2025; Paolini et al., 2023; Trufanov et al., 2025; Voruz et al., 2023), the executive control network (Carreras-Vidal et al., 2025), and the sensorimotor network (Voruz et al., 2023). In one recently published study, the authors found an increased inter- and intra-network functional connectivity of cognitively relevant networks, including the DMN, compared to healthy controls (Carreras-Vidal et al., 2025). However, both hyper- and hypo-connectivity between resting-state networks and between parts of those networks have been reported in a recently published systematic review (Nasir et al., 2024).

Most importantly, the brain alterations reported in the literature are associated with cognitive dysfunction in long-Covid patients (Diez-Cirarda et al., 2023; Heine et al., 2023; Muccioli et al., 2023; Paolini et al., 2023; Serrano del Pueblo et al., 2024; Voruz et al., 2023). Impaired short-term memory has been linked to volume loss in subcortical brain structures (Heine et al., 2023), while altered connectivity of WM regions has been associated with impairments of episodic memory, attention, verbal fluency and overall cognitive function (Serrano del Pueblo et al., 2024). In addition, functional connectivity changes were found to be associated with learning and recall performance (Diez-Cirarda et al., 2023), as well as memory and executive functions (Voruz et al., 2023). The most recent studies on long-Covid and cognition also indicate that patients with long-Covid show increased FC between the caudate and the left precentral gyrus, with these alterations negatively related to the severity of cognitive impairment (Troll et al., 2025). These studies also provide evidence that the DMN plays an important role in the cognitive abilities of long-Covid patients. Samanci and colleagues (Samanci et al., 2025) found an increased DMN and visual network connectivity in patients with neurocognitive deficits (brain fog) compared to healthy controls, while others found a positive correlation between DMN connectivity and cognitive performance in non-hospitalized patients with long-Covid (Madden et al., 2025).

In this study, we aim to explore resting-state networks and the volume of subcortical brain structures in long-Covid patients and their association with cognition. We hypothesize that long-Covid patients with impaired cognition differ from those with intact cognition in their resting-state functional connectivity within and between different brain networks such as the default-mode network, and networks related to cognition, including the fronto-parietal network or the salience network. As previous literature reported both increases (Esposito et al., 2022; Niroumand Sarvandani et al., 2023; Zhang, Chung, Wong, Hung, & Mak, 2022) and decreases (Churchill et al., 2023; Diez-Cirarda et al., 2023) in FC among patients with long-Covid, we aim to test our hypotheses in both directions to avoid missing any relevant alterations. Therefore, all statistical tests were conducted two-sided. Additionally, we explore the association between cognition and the shape and volume of subcortical brain structures.

2. Methods

2.1. *Participants and recruitment*

Forty-two long-Covid patients participated in the study conducted as part of the “Cogni Reha project” between October 10th 2022 and February 2nd 2023. This study was carried out by the Medical University of Graz to validate a tablet-based training program aimed at alleviating cognitive and psychological problems in patients suffering from long-Covid. All participants from this umbrella study were included for this MRI study as well. We defined the following inclusion criteria before the commencement of the study: a) ongoing or newly developed symptoms 3 months after a positive Covid-19 infection, b) with these symptoms lasting for at least 2 months with no other explanation (WHO, 2022), c) symptoms leading to a new health impairment (self-report), or d) deterioration of a pre-existing disease (self-report), e) none of the following pre-existing diseases: dementia, multiple sclerosis, Parkinson’s disease, stroke, and f) no current participation in any other pharmacological or psychological training study aimed at improving cognitive or psychological complaints. As part of the study, all participants had a comprehensive neuropsychological assessment and both a structural and functional magnetic resonance imaging (MRI) scan on the same day. Three individuals were excluded from the study because they were either unable to undergo the MRI (e.g., metal fragments in the eye) or voluntarily withdrew from the study (e.g., claustrophobia, refusal). Hence, the final sample was composed of 39 individuals (months since disease onset: $M = 18.08$, $SD = 10.42$). The majority were female (84.6%), aged between 36 and 71 years ($M = 49.97$, $SD = 8.63$), and had a university degree (30.8%; years of education: $M = 14.06$, $SD = 3.10$). 20 individuals (51.3%) reported that they were vaccinated before their Covid-19 infection (Table 1). Self-reports of brain fog (87.2%), memory problems (87.2%) and fatigue (38.5%) emerged as the most prevalent symptoms in our final sample.

2.2. *Assessments*

To evaluate the participants' attentional performance/processing speed, the ‘Digit Span Forward’ and the ‘Digit Span Backward’ subtests from the German version of the Neuropsychological Assessment Battery [NAB (Petermann, Jäncke, & Waldmann, 2013)] as well as the Trail Making Test A [TMT-A (Reitan, 1958)] were used. The ‘Planning’ and ‘Categories’ subtests of the NAB (Petermann et al., 2013) and the Trail Making Test B [TMT-B (Arbuthnott & Frank, 2000)] were used to assess executive functions of patients. Memory performance was evaluated using the ‘Word List Learning’ subtests of the NAB (Petermann et al., 2013). To assess word fluency, we used the Regensburger Word Fluency Test [RWT (Aschenbrenner, Tucha, & Lange, 2001)], focusing on formal-lexical and semantic word fluency (subtests “S-words” and “animals”). Finally, we used the Montreal Cognitive Assessment (MoCA) as a cognitive screening test to detect global cognitive deficits (Nasreddine et al., 2005).

We further assessed a variety of psychological domains, including subjective cognitive complaints [German translation of the Le Questionnaire de Plainte Cognitive (Thomas-Antérion, Ribas, Honore-masson, Million, & Laurent, 2004)], anxiety [Hospital Anxiety and Depression Scale (Herrmann-Lingen, Buss, & Snaith, 2018)], depression [Hospital Anxiety and Depression Scale (Herrmann-Lingen et al., 2018), General Depression Scale (Hautzinger, Bailer, Hofmeister, & Keller, 2012)], fatigue [German version of the Fatigue Impact Scale (Häuser, Almouhtasseb, Muthny, & Grandt, 2003)] as well as grip strength using a hand strength measurement instrument (Preston, n.d.).

2.3. *Group formation*

We allocated patients into two groups (cognition impaired versus unimpaired) using general population-based diagnostic cut-offs [T-scores (T) and percentile ranks (PR)] in the domains attention, executive function, memory, and word fluency. We defined patients with cognitive deficits ($n = 16$) when they scored significantly below the population norm ($T < 35$, $PR < 10$) as defined in the manuals of the assessments in at least ≥1 cognitive domain, as this approach aligns with various previous studies in different populations (Klinkhammer et al., 2025; Ruck et al., 2025; Virgilio et al., 2025). Hence, long-Covid patients who performed worse than 1.5 standard deviations below the mean of individuals in the healthy population, respectively, in one or more of the

Table 1 – Group differences in demographic and disease-related characteristics.

	Total ($n = 39$)		Cognition not impaired ($n = 23$)		Cognition impaired ($n = 16$)		Significance
	M	*SD*	*M*	*SD*	*M*	*SD*	
Age [years]	49.97	8.63	50.13	8.34	49.75	9.31	$t(37) = .13$, $p = .894$
BMI [kg/m^2]	28.11	5.19	28.01	4.72	28.26	5.94	$t(37) = -.15$, $p = .883$
Education [years]	14.06	3.10	14.48	3.15	13.47	3.03	$t(37) = 1.00$, $p = .324$
	Mdn		*Mdn*	*MR*	*Mdn*	*MR*	
Disease duration [m]	20.27		10.71	19.04	21.74	21.38	$U = 206.00$, $p = .530$
Acute infection [d]	1 [6–10 days]		1	18.61	1.50	22.00	$U = 216.00$, $p = .346$
Functional status	2		0	18.48	2	22.19	$U = 219.00$, $p = .260$
Symptom count [acute][a]	8		7	17.41	10	23.72	$U = 124.50$, $p = .090$
Symptom count [post][b]	5		5	18.04	5	22.81	$U = 139.00$, $p = .207$
			n	%	*n*	%	
Sex [male/female]	6/33		4/19	17/83	2/14	12/88	Fisher's test: $p > .999$
Vaccination[c] [no/yes]	19/20		10/13	43/57	9/7	56/44	$\chi^2(1) = .62$, $p = .433$
Hospitalization [no/yes]	37/2		22/1	96/4	15/1	94/6	Fisher's test: $p > .999$
Pre-existing condition [no/yes]	15/24		10/13	43/57	5/11	31/69	$\chi^2(1) = .60$, $p = .440$
Alcohol intake [no/yes][d]	20/19		9/14	39/61	11/5	69/31	$\chi^2(1) = 3.31$, $p = .069$

Note.
[a] Symptom count reported with regards to the acute Covid-19 illness.
[b] Number of symptoms reported with respect to long-Covid.
[c] Vaccination before infection.
[d] Only individuals who never drink alcohol were classified as “no”. m. = months. d. = days. *M* = mean, *SD* = standard deviation, *Mdn* = Median, *MR* = Mean rank. Significance tests compare patients with and without assessed cognitive impairment.

evaluated domains, were classified as “cognitively impaired” for the purpose of this study. Those who performed $T \geq 35$ and $PR \geq 10$ compared to a healthy norm were classified as “cognitively unimpaired”. This decision was made because, given the relatively small sample size, it is only possible to identify relatively large effects by forming extreme groups. Overall (including patients showing impairments in more than one domain), 15.4% of all individuals exhibited impairments in attention/processing speed ($n = 6$) or executive functions ($n = 6$), 7.7% had a memory impairment ($n = 3$), and 20.5% showed impairments in word fluency ($n = 8$). Finally, as we previously conducted a study with this cohort (Leitner, Opriessnig, et al., 2024), we want to highlight that this publication provides novel and also non-overlapping insights, which we ensured by a) investigating different research questions, b) applying distinct statistical analyses and neuroimaging methods, c) comparing different subgroups, and d) reporting entirely new findings that were not part of the previous publication. Individuals with and without cognitive impairment do not significantly differ in their self-reported fatigue [$\chi 2(1) = 3.63$, $p = .057$] or in their fatigue scores obtained from a fatigue questionnaire (Table 2). These results highlight that the present study offers novel insights beyond those reported in our previous work.

2.4. Brain MRI data acquisition

MRI was performed on a 3-T scanner (Prisma, Siemens Healthcare, Erlangen, Germany) using a 20-channel head coil. High-resolution structural 3D images were acquired using a T1-weighted sequence with .8 mm isotropic resolution (TI = 1100 msec, TR = 2560 msec, TE = 4.1 msec, 224 slices). Resting-state functional magnetic resonance imaging (rs-fMRI) data were acquired with a single-shot echo planar imaging sequence with $3 \times 3 \times 3$ mm resolution (TR = 3000 msec; TE = 30 msec; 150 volumes, field of view read = 192 mm, matrix = 64×64, 36 slices, slice thickness = 3 mm, acquisition time = 7.5 min). For rs-fMRI, participants were asked to close their eyes. For the identification of white matter hyperintensities, a 3D T2-weighted FLAIR sequence (TR = 5000 msec, TE = 393 msec, TI = 1800 msec, number of slices = 176, slice thickness = 1 mm, in-plane resolution = 1 mm $\times$ 1 mm $\times$ 1 mm) was used.

2.5. Analysis of structural MRI data

We used the FMRIB Software Library (FSL Version 6.0.7.11, Oxford, UK) for the analysis of structural MRI data (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004; Woolrich et al., 2009). FSL FAST (FMRIB's Automated Segmentation Tool) was used to segment each individual's high-resolution T1-weighted brain image into different tissue types [cerebrospinal fluid (CSF), white matter (WM), gray matter (GM)], while also correcting for spatial intensity variations (Zhang, Brady, & Smith, 2001). Subsequently, the individual total GM volume in cm^3 was calculated. Next, we used FSL FIRST [FSL's tool for automatic segmentation of subcortical structures (Patenaude, Smith, Kennedy, & Jenkinson, 2011)] to segment subcortical brain structures (i.e., nucleus accumbens, amygdala, caudate nucleus, hippocampus, globus pallidus, putamen, and thalamus) in both hemispheres (i.e., left and right) and calculated the volumes of the different subcortical structures. The quality of the automated segmentation was assessed visually for all participants, and no major segmentation errors were observed. More information on FIRST can be found in the publication of Patenaude

Table 2 – Differences in cognition, psychological questionnaires and grip strength between individuals with and without cognitive impairment.

Domain	Subtest	Cognition not impaired ($n = 23$)		Cognition impaired ($n = 16$)		*U*	*p*
		Mdn	MR	Mdn	MR		
Global cognition	MoCA	29.00	24.46	28.00	13.59	81.50	**.002**
Attention/Processing speed	Digit span forward	9.00	23.67	6.50	14.72	99.50	**.015**
	Digit span backward	6.00	25.00	3.50	12.81	69.00	**<.001**
	TMT-A (time)	29.83	18.02	33.41	22.84	229.50	.194
Executive function	Planning	10.00	23.80	7.00	14.53	96.50	**.006**
	Categories	32.00	25.02	22.50	12.78	68.50	**<.001**
	TMT-B (time)	57.00	14.91	76.65	27.31	301.00	**<.001**
Memory	Immediate recall (list A)	31.00	24.65	27.00	13.31	77.00	**.002**
	Immediate recall (list B)	7.00	23.54	5.00	14.91	102.50	**.018**
	Short-delayed recall	11.00	21.80	10.50	17.41	142.50	.219
	Long-delayed recall	11.00	21.37	11.00	18.03	152.50	.345
Word fluency	Formal-lexical (S-words)	26.00	24.33	18.00	13.78	84.50	**.004**
	Semantic (animals)	43.00	24.98	34.50	12.84	69.50	**.001**
Subjective cognitive complaints	QPC	6.00	20.28	6.00	19.59	117.50	.850
Anxiety & depression	HADS-A	5.00	19.37	6.00	20.91	198.50	.675
	HADS-D	6.00	21.43	4.00	17.94	151.00	.344
	ADS-L	16.00	19.37	17.50	20.91	198.50	.678
Fatigue	Total	78.00	19.83	73.50	17.91	150.50	.592
	Cognitive	21.50	19.55	22.50	19.44	175.00	.976
	Physical	19.00	19.76	20.50	20.34	189.50	.875
	Psychosocial	32.00	20.39	29.50	18.28	156.50	.564
Grip strength [kg]	Left hand	27.15	19.30	27.20	21.00	200.00	.648
	Right hand	28.10	19.15	30.23s	21.22	203.50	.578

Note. Significant results are highlighted in bold. *ADS* = Allgemeine Depressionsskala (General Depression Scale), *HADS* = Hospital Anxiety and Depression Scale, *Mdn* = Median, *MoCA* = Montreal Cognitive Assessment, *MR* = Mean Rank, *QPC* = Le Questionnaire de Plainte Cognitive (German translation), *TMT* = Trail-Making-Test.

(Patenaude et al., 2011). In a next step, we used these segmentations to create deformable surface meshes of the structures of interest using vertex analysis implemented in FIRST, allowing us to investigate how a structure may differ in shape between two groups. Finally, white matter hyperintensities (WMH) were assessed and graded (grade 0–3) by a single blinded rater (SS) using the Fazekas score (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987).

2.6. Analysis of resting state fMRI data

2.6.1. Within-network differences

We used the FMRIB's Software Library (FSL Version 6.0.7.11, Oxford, UK) for fMRI data pre-processing and analyses. The images were first reoriented in order to match the orientation of the standard template images (MNI152) and cropped to remove the neck and lower head. Subsequently, brain extraction was performed (Smith, 2002). To start the pre-processing steps, motion correction (MCFLIRT), temporal filtering (high-pass filter cut-off .01 Hz), and spatial smoothing using a Gaussian kernel of full width and half-maximum (FWHM) of 5 mm was applied with the Melodic (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) GUI. The functional images were then boundary-based registered (BBR) to the individual high-resolution T1-weighted images.

Subsequently, we ran single-subject independent component analyses (ICA) with automatic dimensionality estimation and variance-normalized time courses. The resulting components were then hand-classified into "good" components (i.e., signal) and "bad" components (i.e., noise) by evaluating their spatial maps, time courses and power spectra in 20 out of 39 individuals. The flowchart, presented by Griffanti and colleagues (Griffanti et al., 2017) was used to standardize the classification algorithm. Ambiguous components were classified together with a second, independent researcher (MK). Subsequently, we used FSL FIX (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014) as an automated classification algorithm that uses the hand-labelled training data to train a multi-level classifier and to classify the components in the remaining 19 individuals. Finally, all noise components were automatically regressed out of the data in order to obtain clean (denoised) functional data using a non-aggressive approach. The cleaned functional data were further registered into standard MNI152 space.

We used MELODIC to decompose the cleaned rs-fMRI data into 20 components (Beckmann & Smith, 2004). We correlated our networks with those provided by Smith and colleagues in order to ensure consistency (Smith et al., 2009). The set of spatial maps from the group-average analysis was used to generate subject-specific versions of the spatial maps, and associated time series, using dual regression (Beckmann, Mackay, Filippini, & Smith, 2009; Filippini et al., 2009). First, for each subject, the group-average set of spatial maps is regressed (as spatial regressors in a multiple regression) into the subject's 4D space-time dataset. This results in a set of subject-specific time series, one per group-level spatial map. Next, those time series are regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map. We then tested for group differences using FSL's randomise permutation-testing tool (Beckmann, Mackay, Filippini, & Smith, 2009; Filippini et al., 2009). An independent samples *t*-test design within the General linear model (GLM) framework was used, controlling for age, education and gender. We demeaned all covariates before entering them into the GLM model. Randomized voxelwise nonparametric permutation testing (5000 permutations) was used as a method for estimating and thresholding the *p*-value. Results were corrected for multiple comparisons across space using a threshold free cluster enhancement (TFCE). The resulting files (all corrected for multiple comparisons) were subsequently inspected for significance ($p_{corr.} < .05$). Brain region labeling was conducted using the Harvard–Oxford Atlas. Only clusters with more than 30 voxels were considered relevant. In a last step, we extracted functional connectivity values from the area of difference between both groups. We therefore created a binary mask out of the largest cluster of significance from the between-group comparison and used this mask to extract functional connectivity values (values represent Z-statistics, normalized by the within-subject noise).

2.6.2. Between-network differences

FSLNets (Version .8.5) was used to perform network modelling from fMRI time series data. We defined the resting-state networks identified by the group-ICA performed earlier as our nodes and extracted the individual time series from these nodes by running a dual regression to obtain the stage 1 outputs for each component (i.e., subject-specific component time series for each group component). We inspected all subjects' time series data, examined their power spectra and removed components' (nodes') time series that corresponded to artefacts. An aggressive cleaning approach was used and the good components (i.e., signal) were used for further analyses. In a next step, a network matrix was calculated for each subject [full correlation and partial correlation (regularization parameter: .1 to obtain a less noisy estimate)]. To obtain a mean network matrix across all subjects, the simple average of network matrices across all subjects and a one-sample *t*-test (at each edge) were calculated. Finally, we tested whether the network matrices (the regularized partial network matrices were used as the input matrix) differed between patients with and without cognitive impairment by performing a two-sample *t*-test. The design was created with the GLM GUI. We used randomise from within fslipython (IPython Version 8.24.0, Python Version 3.11.8) with 5000 permutations for each contrast.

2.7. Statistical analysis

Statistical analyses were carried out using SPSS (Version 29) and graphical illustrations were created using RStudio. Since the sample size (specifically per group) is relatively small, we carefully checked the data for normal distribution. Non-normally distributed variables were analyzed using non-parametric statistical methods (e.g., Mann–Whitney *U* test), while normally distributed variables were analyzed using parametric methods (e.g., *t*-test). Chi-square tests were used to analyze group differences in categorical variables. Fisher's exact test was used as an alternative when the expected frequencies in more than 20% of the cells in the contingency table were less than 5.

2.8. Ethical approval

The present study received approval from the ethics committee of the Medical University of Graz (34-206 ex 21/22). Study recruitment was carried out through advertisements in newspapers and social networks, managed by the company "Probando GmbH". All eligible patients provided written informed consent for data recording and agreed to the study procedures. All data were pseudonymized (assignment of a subject code) and only the authors of the manuscript have access to the subject code. Hence, no identification of individual participants is possible for others. Participants had the right to withdraw from the study at any time without providing reasons, and without any disadvantage to them. In general, patients did not receive compensation for participating in the study; however, their travel expenses to and from the study site (Medical University of Graz) were reimbursed.

2.9. Data availability

Data that support the findings of this study are available under: doi: 10.17632/k3r47sp27r.3 (Leitner, 2025).

3. Results

3.1. Differences in neuropsychological assessments

Both groups (cognitively impaired versus unimpaired) did not differ in any demographic or disease-related characteristics (Table 1), nor in their self-reported symptoms of memory problems (Fisher's exact test, $p = .631$), brain fog (Fisher's exact test, $p = .631$) or fatigue [$\chi^2(1) = 3.63$, $p = .057$].

With respect to patients' cognitive performance, those categorized as having cognitive impairment ($n = 16$) and those without ($n = 23$) differed significantly in several cognitive domains, including global cognition (MoCA, $p = .002$), attention (digit span forward: $p = .015$ and backward task: $p < .001$), executive functions (planning: $p = .006$ and categories task: $p < .001$, TMT-B: $p < .001$), short-term memory (immediate recall A: $p = .002$ and B tasks: $p = .018$), and word fluency [both formal-lexical (S-words task: $p = .004$), and semantic (animals task: $p = .001$) word fluency]. However, no differences were found in long-term memory performance, psychological factors and grip strength (Table 2).

3.2. Differences in within-network resting-state functional connectivity

We identified 12 common functional resting-state networks. These networks included the 1) medial visual network, 2) a

Table 3 – Cluster size and anatomic region corresponding to the area of difference in FC.

Cluster Index	Voxels	Max 1-*p*-value (TFCE-corrected)	Max X (MNI)	Max Y (MNI)	Max Z (MNI)	Anatomic region
1	216	.995	42	−46	16	Supramarginal gyrus (posterior), angular gyrus, middle temporal gyrus (temporo-occipital part)

Note. TFCE = Threshold-Free Cluster Enhancement.

network corresponding to the occipital pole, 3) the default mode network, 4) the dorsal attention network, 5) the precuneus network, 6) the fronto-parietal right and 7) left networks, 8) the sensory-motor network, 9) the ventral stream, 10) the salience network, 11) the cerebellar network, and a 12) frontal network (Supplementary Fig. 1).

Group comparisons revealed a significant difference in functional connectivity between both groups with respect to the Default Mode Network (DMN). Patients defined as cognitively impaired had significantly higher functional connectivity between the DMN and a) the right posterior supramarginal gyrus, b) the angular gyrus and c) the right temporo-occipital part of the middle temporal gyrus. In total, this area of difference consisted of a cluster containing 216 voxels [peak: X = 24, Y = 40, Z = 44, peak MNI coordinates: (42, −46, 16), Table 3]. Fig. 1 displays the DMN within all patients (A.) as well as the area of difference between both groups (B). The DMN-specific maps for each group separately are presented in Supplementary Fig. 2. We did not observe any group differences in other resting-state networks.

In line, both groups highly differed in the connectivity values from the cluster of difference, as indicated by the large effect size [$t(37) = -7.39$, $p < .001$, $d = -2.41$]. Fig. 2 illustrates the FC values (Z-statistics) from the area of difference (AoD) for both groups, showing, on average, a positive connectivity between the AoD and the DMN in individuals with cognitive impairment, while the connectivity values within the unimpaired group are centered around zero.

Additionally, a post-hoc power analysis based on these results (FC difference between both groups, $d = -2.41$) suggests that the likelihood of detecting the observed difference with samples of this size is virtually certain (power = .99). However, it is important to note that this

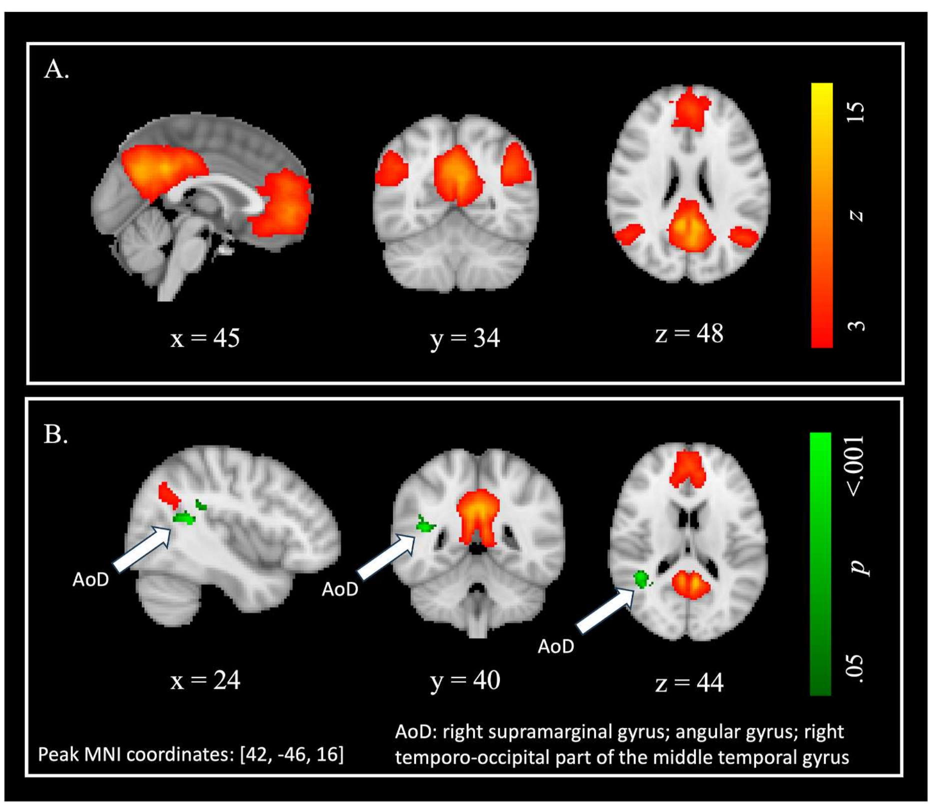

Fig. 1 – Mean functional connectivity map of the DMN (A). The group difference in functional connectivity with respect to the default mode network (DMN) is displayed in B. *Note*. The left hemisphere of the brain corresponds to the right side in this image. The DMN is shown in red-orange; the area of difference (AoD; impaired > unimpaired) is displayed in green (arrow). The AoD [peak MNI coordinates: (42, −46, 16)] indicates that long-Covid patients with cognitive deficits had higher FC between the DMN and the AoD (covering the right posterior supramarginal gyrus, the angular gyrus, and the right temporo-occipital part of the middle temporal gyrus) as compared to the unimpaired group.

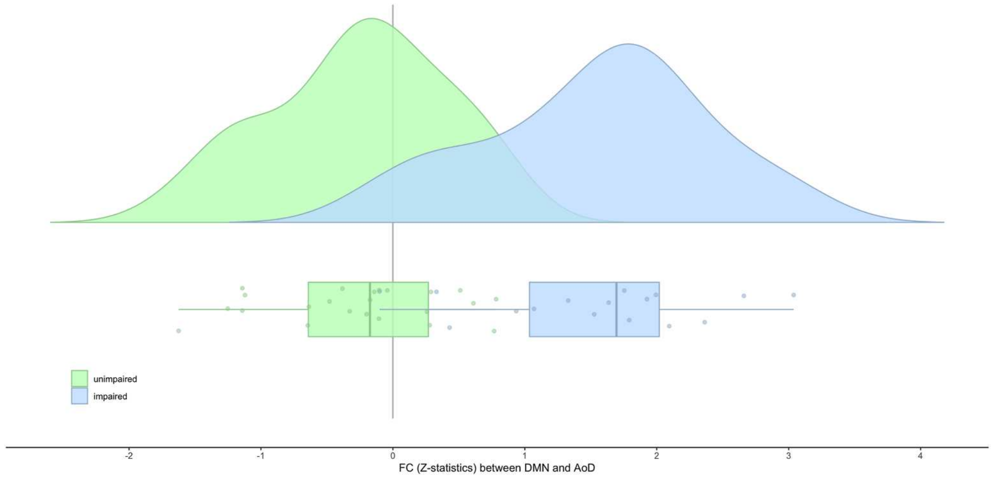

Fig. 2 – Functional connectivity between the DMN and the AoD (Z-statistics) for both groups with and without impaired cognition. *Note.* Green = unimpaired group, blue = impaired group. Violin plots illustrate the distribution of the data. Boxplots represent median, IQR, and min/max values.

effect size was calculated based on statistically significant FC differences, which may lead to an overestimation of the true effect.

3.3. Differences in between-network resting-state functional connectivity

Our between-network resting-state functional connectivity analyses revealed a significant difference in patients with and without cognitive impairment with respect to two networks: the visual network [occipital pole (Smith et al., 2009)] and the ventral stream network (Veer et al., 2010) (Supplement Fig. 1). The mean z-transformed edge strength across all groups was +2.02, indicating a positive association between both networks overall. However, patients assigned to the cognitively impaired group showed, on average, higher edge strength between these networks compared to those without cognitive impairment, indicating a stronger functional association in cognitively impaired long-Covid patients [$t(37) = 3.51$, $p_{corr} = .037$].

3.4. Structural brain measures

We found no significant differences in total grey matter volume nor in any of the subcortical brain regions examined between groups (Table 4). In addition, the vertex analyses performed for each subcortical structure yielded no significant results (all $p > .05$), indicating that structures did not differ significantly in shape between the two groups.

3.5. White matter hyperintensity (WMH) rating

Overall, 20 participants showed a Fazekas score of 1 (20 participants in deep white matter, including 5 participants with

Table 4 – Differences in total GM and subcortical volumes between patients with impaired and intact cognition.

Brain area		Cognition not impaired ($n = 23$)		Cognition impaired ($n = 16$)		Significance	
		Mdn	*MR*	*Mdn*	*MR*	*U*	*p*
Total GM volume		535.35	19.65	541.53	20.50	176.00	.832
Nucleus accumbens	*Left*	0.475	21.04	0.489	18.50	160.00	.507
	Right	0.417	20.83	0.417	18.81	165.00	.601
Amygdala	*Left*	1.157	18.65	1.257	21.94	153.00	.388
	Right	1.325	21.22	1.229	18.25	156.00	.437
Caudate nucleus	*Left*	3.304	20.13	3.282	19.81	181.00	.944
	Right	3.380	19.35	3.463	20.94	169.00	.682
Hippocampus	*Left*	3.542	21.04	3.474	18.50	160.00	.507
	Right	3.717	19.57	3.802	20.63	174.00	.775
Globus pallidus	*Left*	1.636	20.74	1.638	18.94	167.00	.641
	Right	1.647	20.35	1.638	19.50	176.00	.832
Putamen	*Left*	4.254	20.70	4.272	19.00	168.00	.662
	Right	4.434	19.74	4.603	20.38	178.00	.877
Thalamus	*Left*	7.195	20.48	7.100	19.31	173.00	.767
	Right	7.151	21.48	6.960	17.88	150.00	.343

Note. Units: cm^3, GM = gray matter, *Mdn* = Median, *MR* = Mean rank.

periventricular WMHs). All other patients had a Fazekas score of 0. There was no significant difference [$\chi^2(1) = 1.37$, $p = .242$] with respect to the rating of WMHs in patients with noticeable cognitive impairment ($n = 10$, 62.5%) and those without ($n = 10$, 43.5%).

4. Discussion

In this study, we examined within- and between-network resting-state functional connectivity alterations and differences in subcortical brain volumes and shape between long-Covid patients with and without cognitive impairment. We observed functional connectivity changes with respect to the DMN. Long-Covid patients with cognitive impairment exhibited higher functional connectivity between the DMN and the posterior supramarginal gyrus, the angular gyrus and the temporo-occipital part of the middle temporal gyrus as compared to those without cognitive impairment. Between-network analyses showed that patients assigned to the cognitively impaired group had, on average, a higher edge strength (correlation) between the visual network (occipital pole) and the ventral stream network. In contrast, no differences in WMH ratings, or in the volumes or shapes of subcortical brain structures were found.

With respect to the DMN functional connectivity differences, our results show increased connectivity values in the cognitively impaired group. Hence, we interpret these changes in functional connectivity to be maladaptive. Additionally, other studies found that FC of the DMN, which emerged as a key network in our analyses, is associated with neurocognitive performance in different patient populations, such as patients with Parkinson's disease (Baggio et al., 2015) and in patients suffering from long-Covid (Madden et al., 2025; Samanci et al., 2025). Similar results were found in three previously conducted studies. Research on people suffering from multiple sclerosis (MS) found that an increased functional connectivity with and within the DMN was associated with cognitive impairments (Hawellek, Hipp, Lewis, Corbetta, & Engel, 2011; Meijer et al., 2017). In patients with WMH-related cognitive impairment, alterations in the functional connectivity within the DMN (e.g., increased DMN FC in the medial frontal gyrus) indicated worse cognitive performance (Chen et al., 2019). Finally, heightened intra-network FC within the DMN was observed in long-Covid patients compared to healthy controls, with this FC being correlated with general cognition (Carreras-Vidal et al., 2025). This increased DMN connectivity could be an unsuccessful attempt by the brain to compensate for cognitive deficits. Also, in general, the DMN is deactivated during cognitive tasks in order to focus on relevant processes. If DMN connectivity is increased, it could suggest a failure to efficiently suppress its activity, which may indicate impaired cognitive performance.

In the current study, the increased DMN FC was found in connection with brain areas important for phonological decisions and reading (Hartwigsen et al., 2010; Stoeckel, Gough, Watkins, & Devlin, 2009), memory retrieval, inhibition, and higher-order motor control (Farrer et al., 2008; Seghier, 2013) or language processing and semantic cognition (Xu et al., 2015). In general, hyperconnectivity was found to be a common response to neurological disruption and may be observed across different brain regions (Hillary et al., 2015). Therefore, we think that the higher connectivity with areas mainly outside of the DMN component in our sample could suggest that the normal default-mode network dynamics are disrupted in individuals with cognitive impairment. Hence, this increased connectivity of brain regions with the DMN might indicate a maladaptive process.

Although we found differences in the connectivity of brain areas with the DMN, we did not find any differences related to other networks, such as the fronto-parietal networks or the salience network (SN), as we hypothesized. It is possible that the magnitude of the deficits found in the impaired group was not large enough to detect differences in these networks, or that the effects are only small and could not be detected in this specific sample (i.e., low power). In addition, effects might have emerged when building groups based on impairments in more specific domains (e.g., comparing individuals with attention deficits to those without).

Our results regarding between network differences highlight that patients with cognitive impairment have a higher functional connectivity between the occipital pole and the ventral stream network, as compared to those without cognitive impairment. Although this has not been previously reported in the literature, this higher connectivity could again indicate maladaptive processing due to the brain's unsuccessful attempt to cope with cognitive impairment. When higher-order cognitive networks (e.g., the DMN) are not functioning properly, it might be possible that lower-level sensory systems (such as the networks described above) may become hyperactive as an attempt to compensate. The visual network and the ventral stream are both involved in the recognition of objects and perception of shapes (Bull & Zhang, 2021). One previous study reported an association between the visual network (VN) and cognition (Bergamino et al., 2024), pointing into the same direction as our study, which suggests that visual network regions might be involved in cognitive impairments such as visual attention and memory deficits (Lazarou et al., 2022). Although not investigated in this study, one preliminary study found evidence that visual perception may be impaired in Covid-19 (Coco-Martin et al., 2023). This result could therefore suggest problems with the integration of visual information with memory or other higher-order functions. However, the ventral stream network in our study is a large network, which also includes frontal areas (inferior frontal gyrus, frontal pole) and parts of the middle temporal gyrus, the superior temporal gyrus, and the temporal pole, and therefore areas that are responsible for various tasks and processes. This increased connectivity between networks could be a sign of maladaptive changes within the brain, as it was observed in the cognitively impaired group. However, possible impairments in long-Covid patients and the associated changes between the networks found in this study still need to be investigated.

We could not detect any structural differences in total GM volume or subcortical volumes of various brain structures, and did not find any group differences with respect to white matter hyperintensities, which contrasts with previous literature (Campabadal et al., 2023; Diez-Cirarda et al., 2023; Douaud et al., 2022; Heine et al., 2023; Jin et al., 2024). Díez-Cirarda and colleagues (Diez-Cirarda et al., 2023) found an association between GM volume loss and cognition, which we could not replicate in our study. Heine et al. (2023) described decreased volumes of the left thalamus, putamen, and pallidum in fatigued patients with long-Covid compared to a healthy control group. Additionally, increased cortical thickness in several brain areas was shown to be negatively associated with working memory performance in patients with long-Covid (Pacheco-Jaime et al., 2025). However, to our knowledge, most of the previously conducted studies compared post-acute Covid-19 infections or long-Covid patients to a healthy control group, which differs from the aim of this study. Moreover, we did not find a single study that directly compared long-Covid patients with and without cognitive deficits in terms of their cognitive impairments, making our study one of the first studies to conduct this direct comparison. In addition, a recently published review on the effects of Covid-19 on cognition and brain health demonstrated that cognitive symptoms might also occur in the absence of neuroimaging changes (Zhao, Toniolo, Hampshire, & Husain, 2023). It is also possible that functional changes become visible before structural changes occur, which could be an explanation for our results.

Finally, vertex analyses, assessing how structures differ in shape between the two groups, did not yield any significant differences in our sample. This partially contrasts with a study on structural brain changes in patients with post-Covid-19 fatigue, reporting shape deformations in subcortical regions such as the thalamus, pallidum, and putamen (Heine et al., 2023). However, to our knowledge, our study is the first one that investigated shape differences/deformations in long-Covid patients with and without impaired cognition.

This study has some limitations: First, the study has a relatively small sample size and the allocation into the groups 'cognitively impaired' and 'cognitively unimpaired' could be considered a somewhat arbitrary approach, as different classification methods are possible. For instance, due to the relatively small sample size, groups were not built based on deficits in a specific domain (e.g., individuals with attention deficits versus individuals without attention deficits), but rather on a broader basis (i.e., individuals with/without deficits in any cognitive domain). Focusing on a more specific domain might yield FC differences in networks that are related to specific cognitive tasks (e.g., attention) and should be investigated in future studies. However, we have tried to address this limitation by building groups according to population-based, normative data and by trying to build extreme groups to achieve higher statistical power. In addition, this study represents a cross-sectional study. However, to make causal statements, longitudinal studies should be conducted to examine the progression of long-Covid and cognitive abilities. Additionally, this study does not include a healthy control group, as the MRI data were obtained within another study focusing on improving cognition in long-Covid patients through tablet-based training, making it impossible to compare the functional changes to individuals without persistent Covid-19 symptoms. We also want to state a general limitation of resting-state paradigms, namely the fact that it is impossible to monitor what patients were thinking about during the resting-state scan, as well as if participants fell asleep or not. However, all participants were instructed to remain awake with their eyes closed and not to think about anything specific. Also, potential differences in spontaneous mental imagery are unlikely to have systematically biased the present results, especially because both groups were comparable regarding their demographic characteristics.

Future studies should include a healthy control group to establish whether the observed connectivity patterns represent deviations from normal brain function or are specifically related to cognitive impairment within the context of long-Covid. In addition, they should explore the role of structural and functional brain changes and other psychological domains, such as fatigue, depression, and anxiety. Previous research indicates that structural and diffusion imaging markers are associated with fatigue (Heine et al., 2023), depression (Khodanovich et al., 2024), anxiety, and perceived stress in these patients (Liang et al., 2023). Further investigation of these brain changes is of great importance, as long-Covid encompasses a wide range of symptoms, and understanding which brain alterations occur is important for developing future therapies.

Finally, as long-Covid is associated with various cognitive impairments across different domains, intervention studies to alleviate these symptoms are highly needed (Vakani, Ratto, Sandford-James, Antonova, & Kumari, 2023).

5. Conclusion

Cognitive deficits are among the most frequently observed symptoms of long-Covid. In this study, comparing long-Covid patients with and without objectively assessed cognitive impairments, a difference in functional connectivity between the angular gyrus, supramarginal gyrus, and middle temporal gyrus with the DMN was observed. These results lead us to assume that the changes might be maladaptive. In addition, we found stronger connectivity between the occipital pole and the ventral stream in cognitively impaired long-Covid patients. Both results might indicate a disrupted/maladaptive network dynamic/change in individuals with cognitive impairments. Importantly, the findings presented in our study are among the first highlighting functional connectivity alterations in cognitively impaired long-Covid patients and therefore provide initial evidence for future research. Future studies are needed to validate these results in order to provide a reliable resting-state marker for long-Covid cognitive impairment.

CRediT authorship contribution statement

Manuel Leitner: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Daniela Pinter:** Writing – review & editing, Validation, Methodology, Investigation. **Stefan Ropele:** Writing – review & editing, Methodology, Conceptualization. **Marisa Koini:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Research data

Data that support the findings of this study are available under: doi: 10.17632/k3r47sp27r.3.

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Declaration of competing interest

I have nothing to declare.

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Scientific transparency statement

DATA: Some raw and processed data supporting this research are publicly available, while some are subject to restrictions: https://doi.org/10.17632/k3r47sp27r.3.

CODE: All analysis code supporting this research is publicly available: https://doi.org/10.17632/k3r47sp27r.3.

MATERIALS: No study materials supporting this research are publicly available.

DESIGN: This article reports, for all studies, how the author (s) determined all sample sizes, all data exclusions, all data inclusion and exclusion criteria, and whether inclusion and exclusion criteria were established prior to data analysis.

PRE-REGISTRATION: No part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted. No part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

For full details, see the *Scientific Transparency Report* in the supplementary data to the online version of this article.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2025.07.005.

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A tablet-based intervention study to alleviate cognitive and psychological symptoms in patients with post-Covid-19 condition

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Background: Cognitive impairment and psychological complaints are among the most common consequences for patients suffering from Post-Covid-19 condition (PCC). As there are limited training options available, this study examined a longitudinal tablet-based training program addressing cognitive and psychological symptoms.

Methods: Forty individuals aged between 36 and 71 years ($M = 49.85$, $SD = 8.63$; 80% female) were randomly assigned to either an intervention group ($n = 20$) or a waitlist control group ($n = 20$). The intervention group received a three-month tablet-based training program involving cognitive exercises, relaxation techniques, and physiotherapy exercises. Additionally, both groups underwent a thorough neuropsychological assessment (attention, memory, executive functions, word fluency, subjective cognitive complaints, fatigue, depression, anxiety, and quality of life) before the training, after 3 months of training, and after 6 months in order to assess long-term effects.

Results: Pre-post comparisons revealed that individuals assigned to the intervention group ($n = 18$ after dropout), as compared to the control group ($n = 16$ after dropout), showed a reduction in subjective cognitive complaints ($p < 0.001$) as well as in depressive symptoms ($p < 0.001$). Additionally, their MoCA Memory Index Score remained stable ($p = 0.496$), while it declined significantly in the wait-list control group ($p = 0.008$). However, the training had no effect on the other domains assessed and not all training-related effects were stable over time. Finally, a higher number of post-Covid symptoms was negatively correlated with attention and memory capabilities (all $p < 0.05$), with a longer disease duration further amplifying the negative impact of post-Covid symptoms on memory performance.

Conclusion: Tablet-based training programs can help improve subjective complaints, depressive symptoms, and memory and may serve as an additional therapy option. Further studies are needed to investigate the stability of these effects.

KEYWORDS

post-Covid-19 condition, long-Covid, tablet-based intervention, cognition, subjective cognitive complaints, depressive symptoms, mental health, psychological well-being

Introduction

Since the onset of the coronavirus pandemic in March 2020, the World Health Organization (WHO) reported more than 777 million confirmed cases of Covid-19 and over 7 million deaths until December 2024 (World Health Organization [WHO], 2024). The majority of individuals infected with SARS-CoV-2 are dealing with symptoms such as fever, cough, and fatigue during their acute illness (Carfi et al., 2020; Grant et al., 2020; Ziauddeen et al., 2022), which typically lasts up to 14 days after the symptom onset (O'Mahoney et al., 2023). However, an increasing number of individuals report persistent or newly emerging symptoms after their initial infection subsided (Carfi et al., 2020; Fernández-de-Las-Peñas et al., 2021; Sykes et al., 2021; van Kessel et al., 2022). These symptoms can be grouped under the umbrella term "Long-Covid or Post-Covid-19 condition (PCC)." PCC is defined as the "continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation" (Lippi et al., 2023; World Health Organization [WHO], 2022). However, as there are several definitions used for this complex condition (Fernández-de-Las-Peñas et al., 2023), PCC remains vaguely defined and no agreement on a standardized definition has been made yet (Munblit et al., 2022). Consequently, this resulted in great heterogeneity with respect to the PCC definitions used in interventional studies (Fernández-de-Las-Peñas et al., 2022; Haslam et al., 2023). In this study, we follow the aforementioned and universally acknowledged definition of PCC (long-Covid), as suggested by the WHO (Lippi et al., 2023; World Health Organization [WHO], 2022).

The prevalence of post-Covid will remain high (Boufidou et al., 2023) and studies indicate that globally approximately 10%–20% (Altmann et al., 2023; Ballering et al., 2022; Davis et al., 2023; World Health Organization [WHO], 2022) of individuals are affected by PCC, with about 18%–22% particularly experiencing cognitive symptoms (Ceban et al., 2022; Han et al., 2022). In addition, several risk factors have been identified that include, for instance, female sex (Fernández-de-Las-Peñas et al., 2022; Hedberg et al., 2023; Tene et al., 2023), older age (Abdelrahman et al., 2021; Thompson et al., 2022; Bonfim et al., 2024), smoking (Barthélémy et al., 2022; Tene et al., 2023; Tsampasian et al., 2023), preexisting comorbidities (Subramanian et al., 2022; Tsampasian et al., 2023) and an elevated body mass index (Subramanian et al., 2022; Sudre et al., 2021; Thompson et al., 2022; Tsampasian et al., 2023). In contrast, being vaccinated prior to a SARS-CoV-2 infection was shown to reduce the risk of developing PCC (Byambasuren et al., 2023; Krishna et al., 2023; Wong et al., 2023), suggesting that vaccination might be a protective factor against the development of persistent Covid-19 symptoms.

It is important to note that persistent symptoms can occur regardless of whether individuals were hospitalized during their acute illness or not (O'Mahoney et al., 2023; Leitner et al., 2024; Nalbandian et al., 2023), that means regardless of their illness severity (Di Gennaro et al., 2023; Vanichkachorn et al., 2021). Until today, over 200 different symptoms have been identified (Davis et al., 2023), including fatigue (Scardua-Silva et al., 2024; Torrell et al., 2024; Zhang et al., 2024), cough, or loss of sense of smell/taste (Byambasuren et al., 2023). Additionally, Covid-19 infection can cause long-term effects on the cognitive function and psychological well-being of those affected (Gonzalez-Fernandez and Huang, 2023; Jaywant et al., 2024; Möller et al., 2023), which leads to impairments such as brain fog (McWhirter et al., 2023; Lanz-Luces et al., 2022; Jennings et al., 2022), concentration difficulties (Ziauddeen et al., 2022; Ruzicka et al., 2024; Kim et al., 2023), attention disorders (Cipolli et al., 2023; Kozik et al., 2023; Guillén et al., 2024), executive dysfunction (Dacosta-Aguayo et al., 2024; Hampshire et al., 2024; Godoy-González et al., 2023), memory problems (Hampshire et al., 2024; Fleischer et al., 2022; Martin et al., 2024), anxiety (Seighali et al., 2024; Wong et al., 2023; Goodman et al., 2023) or depression (Seighali et al., 2024; McLaughlin et al., 2023; Kim et al., 2023). These symptoms may last for several months or years (Herrera et al., 2023) and manifest not only as objective deficits but also as subjective cognitive complaints (Miskowiak et al., 2021), causing substantial burden for those affected.

Although both the infection rates and the incidence of PCC remain high (Di Gennaro et al., 2023), general treatment options are limited (Davis et al., 2023; Koczulla et al., 2021; Mueller et al., 2023; Veronese et al., 2022), especially concerning the treatment of cognitive deficits (Yong, 2021). Notably, one in five individuals will exhibit cognitive impairments three or more months after receiving a Covid-19 diagnosis (Ceban et al., 2022; Möller et al., 2023). A previous study by Jebrini et al. (2024) used cognitive training and group psychotherapy to increase verbal memory and visuo-spatial construction skills in patients with long-Covid (Jebrini et al., 2024). Further study protocols have been designed to improve cognitive performance in patients through either brain stimulation-assisted cognitive training (Thams et al., 2022) or Goal Management Training (Hagen et al., 2022). However, fatigue represents a major challenge, as it was reported as one of the most common long-Covid symptoms (Joli et al., 2022; Leitner et al., 2024), limiting the opportunity to take part in such rehabilitation programs. Finally, the rehabilitation progress of patients is complicated by the heterogeneous clinical picture of this disease, which highlights the need for a tailored and multidisciplinary rehabilitation approach (Nice, 2020; Krishna et al., 2023; Nurek et al., 2021).

One opportunity to address cognitive deficits involves the use of tablets and computers. Computerized cognitive training programs have been tested in various populations, including patients with diabetes (Bahar-Fuchs et al., 2020), Parkinson's disease (Gavelin et al., 2022), or stroke (Zhou et al., 2022) and can often be applied in familiar environments (e.g., one's own home). A pilot study conducted among individuals with self-reported cognitive dysfunction for more than 3 months after an infection with the coronavirus suggested that computerized cognitive training may be effective in improving cognitive impairments (Duñabeitia et al., 2023). However, the authors concluded that future studies including a control group are necessary to draw reliable conclusions. Similar results were found in a case-control

Abbreviations: ANOVA, analysis of variance; ANCOVA, analysis of covariance; ADSL, Allgemeine Depressionsskala – Langform (General Depression Scale); BL, baseline; CG, control group; CRT, cognitive remediation therapy; FIS, fatigue impact scale; FU, follow-up; HADS, hospital anxiety and depression scale; IG, intervention group; MIS, memory index score; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NAB, neuropsychological assessment battery; PCC, post-Covid-19 condition; QoL, quality of life; RWT, Regensburger word fluency test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCC, subjective cognitive complaints; TMT, trail making test; WHO, World Health Organization.

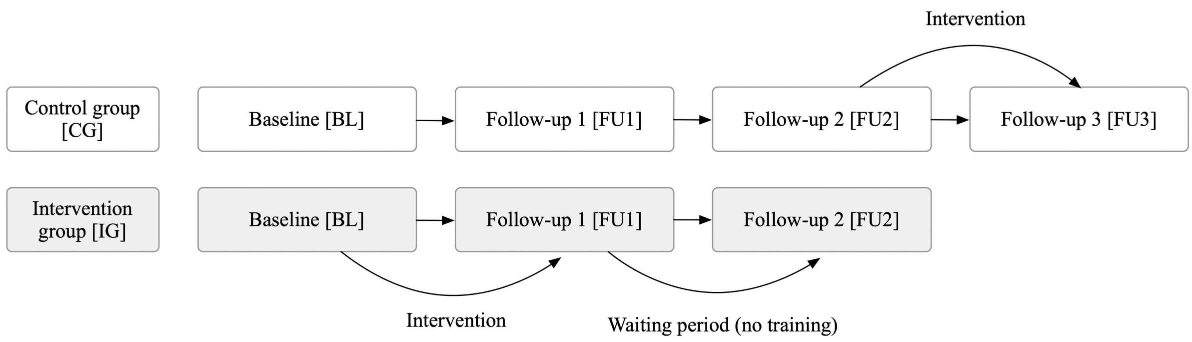

FIGURE 1
Study procedure to evaluate the effect of a three-month tablet-based intervention in patients with post-Covid-19 condition. Thorough neuropsychological assessments were conducted at each time point (BL, FU1, FU2, FU3), i.e., every 3 months. A waiting period was included to assess the stability of long-term effects.

study among seventy-three Covid-19 survivors with cognitive impairment (Palladini et al., 2023). The authors of the study used a cognitive remediation therapy (CRT) which showed positive results on cognitive functioning. These results support CRT as an effective treatment option targeting cognitive impairments in patients suffering from PCC (Palladini et al., 2023).

In general, only a small number of therapeutic intervention options are available for the treatment of cognitive and mental deficits in patients with long-Covid (Davis et al., 2023; Koczulla et al., 2021; Mueller et al., 2023; Veronese et al., 2022). Therefore, this study aims to improve these symptoms by using a three-month tablet-based training program that includes a variety of cognitive exercises (e.g., to train attention, memory and executive functions) as well as relaxation and physiotherapy exercises (see "Tablet-based intervention" in the Methods section). These trainings offer the advantage of being conducted from home (i.e., location independent) and allow individuals to practice at their own pace (self-paced). In addition, long travel times, which could be challenging for some patients, can be eliminated.

> **Primary hypotheses:** We hypothesize that participating in our training program alleviates cognitive symptoms associated with PCC in various domains, such as memory, attention, or executive functions. In addition, we hypothesize that the intervention will reduce subjective cognitive complaints and psychological symptoms, including fatigue and negative emotions such as anxiety and depression, as well as improve the quality of life of those affected by PCC. **Exploratory analyses:** In exploratory analyses, we further investigate the association between post-Covid symptom count and cognition, and the impact of disease duration on this correlation.

Materials and methods

Recruitment, participants and procedure

The recruitment was carried out by the company "Probando GmbH," which recruited patients through newspaper articles and online posts. Forty-two patients with self-reported symptoms of PCC (i.e., persistent symptoms or newly emerged symptoms after the resolution of an acute Covid-19 infection) were invited to undergo a comprehensive neuropsychological assessment as well as structural and functional MRI at the Medical University of Graz, Austria between October 2022 and November 2023. Inclusion criteria were (a) ongoing or newly developed symptoms 3 months after a positive Covid-19 infection, (b) with these symptoms lasting for at least 2 months with no other explanation (World Health Organization [WHO], 2022), and (c) symptoms leading to either a new health impairment (self-report) or deterioration of a pre-existing disease (self-report), and (d) none of the following pre-existing diseases: dementia, multiple sclerosis, Parkinson's disease, stroke, and (e) no participation on any other pharmacological or psychological training study aiming to improve cognitive or psychological complaints. Due to significant impairment (high Post-COVID-19 functional status (Klok et al., 2020) combined with high levels of fatigue), two individuals were excluded from further study participation although initially meeting inclusion criteria (after extensive discussion, these individuals were deemed unable to adequately complete the training over the 3-month duration). The remaining 40 participants were randomly (block randomization, block size = 6) assigned to either an intervention (n = 20) or a wait-list control group (n = 20) by MK after completing a baseline (BL) testing. The person who conducted the cognitive assessment (ML) was blinded to the subjects' group allocation (intervention group vs. control group). However, due to the study design, blinding of the participants was not possible. Therefore, participants knew whether they were receiving the intervention or not. Individuals assigned to the intervention group received a free tablet-based training program and had three on-site neuropsychological examinations with 3 months between each examination period to assess both a post-training effect [BL to follow up 1 (FU1)] as well as the stability of this effect (FU1 to FU2). Those who were assigned to the control group received no training or treatment as usual (since no validated treatment existed at the time the study was conducted) for the first three assessments (BL-FU1-FU2) but they received the same training after a six-month waiting period in order to assess their post-training effect (FU2-FU3) as well (Figure 1). Finally, in exploratory analyses, both groups were combined to assess pre-post effects in a larger sample.

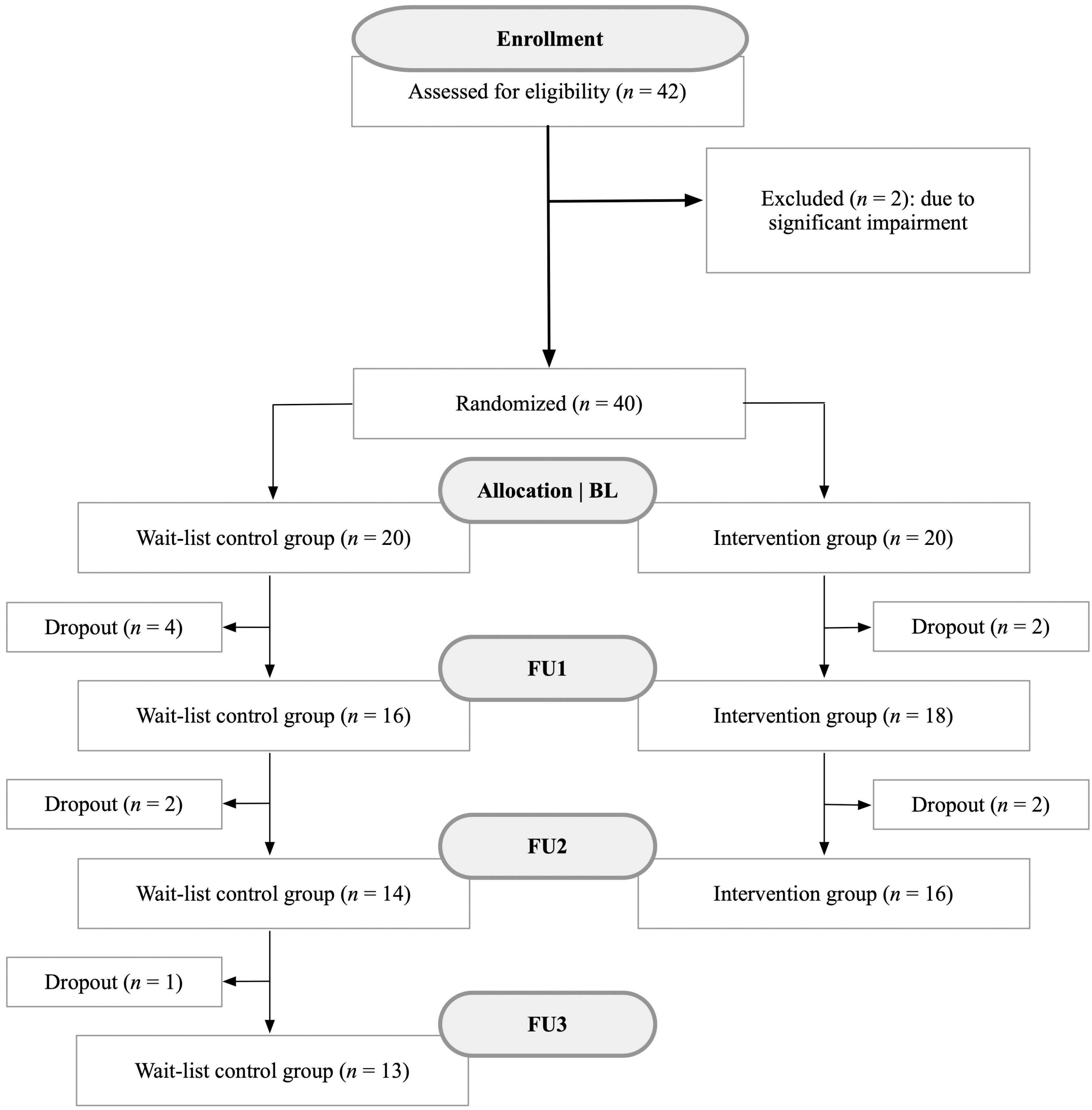

FIGURE 2
Flow chart illustrating the recruitment process of patients with post-Covid-19 condition and associated dropouts between October 2022 and November 2023. This study utilized a longitudinal design to observe changes over time. Reasons for dropouts included, for instance, loss of motivation in the training program or rejection of any further thorough neuropsychological assessments.

Due to the longitudinal study design, there were occasional dropouts during the examination period (Figure 2). All dropouts occurred due to patients who terminated their participation in the study. Participants who ceased participation did not differ from those who continued the study in sex, fatigue, or cognition ($p > 0.05$). At each time point, a comprehensive neuropsychological test battery (see assessments section) was administered along with questionnaires to assess cognition and psychological parameters such as depression or anxiety. We additionally gathered data on symptoms during the acute Covid-19 illness as well as still persistent symptoms at each visit. Participants were explicitly asked to provide only symptoms that have not occurred prior to the illness (e.g., if they had memory problems before their Covid-19 infection, they were asked to not report them as a consequence of the infection). The entire study procedure took about 2 h at each assessment.

Assessment

We collected information on the following variables: age, sex, highest level of education completed, marital status, height, weight, date of Covid-19 diagnosis, duration of acute infection, vaccination status, initial symptoms, current symptoms, hospitalization, functional status [Post-COVID-19 Functional status scale (Klok et al., 2020)], pre-existing conditions, as well as psychiatric disorders. In addition, we administered a comprehensive neuropsychological assessment battery and questionnaires on fatigue, depression, anxiety, subjective cognitive complaints and quality of life to all participants. The following domains were assessed:

Global cognitive impairment

We used the Montreal Cognitive Assessment (MoCA) as a cognitive screening test, aiming to detect global cognitive deficits (Nasreddine et al., 2005). Higher scores indicate better cognitive performance. The memory index score (MIS) was used to assess memory performance in a simple memory task (recollection of five previously read words).

Attention

To assess the attentional performance of participants, the subtests “Digit Span Forward” and “Digit Span Backward” from the German version of the Neuropsychological Assessment Battery (NAB) were used. Higher values indicate better attentional performance (Petermann et al., 2013). Additionally, the Trail Making Test A (TMT-A) was used to measure attention. A shorter processing time indicates better attentional performance (Reitan, 1958).

Executive function

The subtests “Planning” and “Categories” from the NAB were utilized to assess executive functions of patients. Higher scores represent a better performance in executive tasks (Petermann et al., 2013). Additionally, the Trail Making Test B (TMT-B) can be utilized as a tool for assessing executive functions (Arbuthnott and Frank, 2000). A shorter processing time reflects better executive functions.

Memory

For the assessment of memory performance, the subtest “Word List Learning” of the NAB was administered. Participants are required to remember as many words as possible out of a word list (12 words). Higher scores indicate a better memory performance (Petermann et al., 2013).

Word fluency

We used the Regensburger Word Fluency Test (RWT) to assess formal-lexical and semantic word fluency. In this task, individuals are required to verbally generate as many words as possible either starting with a specific letter (formal-lexical) or belonging to a particular category (semantic) within 2 min. Higher scores correspond to better performance in word fluency (Aschenbrenner et al., 2001).

Subjective cognitive complaints

To assess subjective cognitive complaints (SCC), a translated version of the Questionnaire de Plainte Cognitive (Thomas-Antérion et al., 2004) was utilized. This questionnaire had already been translated into English (Markova et al., 2017) and was further translated (and back-translated) into German by independent translators. Participants are asked to respond with “Yes” or “No” and indicate whether they have perceived any changes in themselves in the last 6 months (e.g., “Have you experienced any memory change during the last 6 months?”). The maximum score is 10 points. A score of 3 or higher is considered clinically significant (Thomas-Antérion et al., 2004).

Fatigue

The German version of the Fatigue Impact Scale (FIS-D) was used to assess fatigue (Häuser et al., 2003). It consists of 40 questions, answered on a 5-point scale from “never” (0) to “very often” (4). A higher total score corresponds to a higher level of fatigue.

Depression and anxiety

The extent of depression was assessed using two questionnaires, namely the General Depression Scale in its 20-item long form (Hautzinger et al., 2012) and the German version of the Hospital Anxiety and Depression Scale (Herrmann-Lingen et al., 2018). The General Depression Scale (ADS, Allgemeine Depressionsskala) is a self-assessment tool used to evaluate the impact of depressive symptoms experienced in the past week. While completing the HADS, patients need to report the extent of anxiety and depressive symptoms experienced in the past week. Higher scores indicate a higher level of depression and/or anxiety.

Quality of life

The German version of the WHOQoL-BREF (World Health Organization Quality of Life) in its short form (26 items) was used to assess patients’ quality of life (Angermeyer et al., 2000) during the past 2 weeks. The subscales for physical and psychological well-being were used for analyses.

Tablet-based intervention

The program was developed by DigitAAL Life GmbH, a company that designed cognitive training programs for different populations, such as patients with Alzheimer’s disease and those with long-Covid/post-Covid-19 condition. Before the patients were provided with the tablet and the installed training, each patient received individual on-site instruction, during which all participants became familiar with the technology and the exercises. Using the tablet required no specific technical knowledge. The intervention combined relaxation exercises [Jacobson muscle relaxation (Jacobson, 1938)], physiotherapy exercises and cognitive training. As the training was conducted asynchronously and from home, we were able to offer a location-independent training program, allowing patients to train as often as they wanted and at flexible times. The cognitive part included tasks such as remembering and recalling sequences (visual memory; e.g., remembering a sequence of fields and then clicking them in the same order), attention/reaction time exercises (e.g., participants had to click on the screen as fast as possible whenever they saw a number appear anywhere on it, in order to train their sustained attention), calculation tasks (e.g., solving mathematical calculation tasks), exercises to train executive functions (e.g., exercises with inhibition tasks), as well as playful activities such as the game “memory” or quiz tasks (to train short- and long-term memory). In addition, relaxation exercises, such as progressive muscle relaxation (PMR) according to Jacobson, were integrated into the training, and simple physiotherapy exercises were performed. These included, for example, exercises with balls or resistance bands, in which patients had to carry out physical exercises simultaneously with cognitive tasks. Both the physiotherapy and relaxation exercises were delivered to the patients via videos, in which they were instructed to follow the exercises. In PMR, for instance, patients learned to tense and then release the muscles in different areas of their body, which is known to foster relaxation. It was recommended to train at least three times a week for at least 30 min each session, with more frequent training being encouraged. Additionally, various difficulty levels were implemented to adapt the tasks to the cognitive abilities of the participants. Patients were contacted by phone every 2 weeks to ensure they continued training and to receive feedback. They could contact the study authors at any time if problems occurred.

Sample size calculation

Prior to the commencement of the study, a power analysis with G*Power was conducted to calculate the required sample size for the study design (Faul et al., 2007). Two meta-analyses investigating the effects of computerized cognitive training programs on cognitive impairment (Hu et al., 2021; Hill et al., 2017), as well as a study examining personalized computerized training for cognitive dysfunction after Covid-19 (Duñabeitia et al., 2023), found at least medium-sized effects with respect to cognitive outcomes. As the primary focus of our study was to compare both groups (CG, IG) across three time points (BL, FU1, FU2), a power analysis for a 2 × 3 analysis of variance (ANOVA) was performed. 28 individuals (14 per group) are needed to detect a medium-sized effect ($\eta_p^2 = 0.06$) with 80% power (1- β) at a significance level of $\alpha = 0.05$. Due to potential dropouts, we exceeded the calculated minimum sample size with a total of $n = 40$ individuals ($n = 20$ per group).

Statistical analysis

Statistical analyses were performed with SPSS (Version 29.0). The figures were created using RStudio (R version 4.2.2). For all variables, normality was checked by using Shapiro-Wilk tests as well as histograms and Q-Q-plots. To examine the effect of the tablet-training on the improvement in cognitive and psychological symptoms, 2 × 3 analyses of variance were conducted. Hence, group (levels: control group, intervention group) represented the between-subjects factor and time (levels: BL, FU1, FU2) was the within-subjects factor. To statistically control for potential confounders such as age, sex, and education, these were included as covariates in the analyses, if the assumptions were met (1. homogeneity of regression slopes, 2. no group differences in the covariates). If an assumption was violated, the covariate was dropped from the model. Since the interaction effects of the individual 2 × 3 analyses may not be significant, even though a difference from baseline to follow-up 1 in the intervention group (compared to the control group) might be present, additional 2 × 2 analyses of variance (with covariates) were calculated. This could especially be the case if the effect (e.g., improvement in cognition in the intervention group from baseline to follow-up 1) declines until the next visit (follow-up 2), or when the control group shows spontaneous improvement between the time points. Significant interaction effects were further examined using *post hoc* tests to assess whether the groups differed at specific time points and whether changes were observable within each group.

The assumption of homogeneous variances between the groups was tested by using Levene's tests for the respective outcome variable at each time-point. To test whether the observed covariance matrices of the respective dependent variables are equal across groups, the Box's M test was used. Mauchly's test of sphericity was used to assess the assumption of sphericity in the 2 × 3 analyses. In case of a violation of sphericity, Greenhouse-Geisser correction was applied. Bonferroni correction was applied to all *p*-values.

In further exploratory analyses, individuals from the waitlist control group, after completing the training as well, were merged with the original intervention group to form a combined intervention group (including all individuals who successfully completed the training), and pre-post comparisons were then conducted (pre values for intervention group: baseline; pre values for control group: follow-up 2; post values for intervention group: follow-up 1; post values for control group: follow-up 3). Hence, we performed a pre-post comparison of all individuals who eventually received the training. This approach was chosen to increase statistical power. Paired *t*-tests for each outcome were calculated for this purpose. To avoid bias in the results (e.g., significant reduction in pre-post comparison due to familiarity with the test material or spontaneous improvements), results were only interpreted if there were no familiarity effects or spontaneous changes in the original control group. Therefore, and due to the small sample size when considering only the original control group, Friedman tests were performed for the data of the control group. Finally, significant *t*-tests were interpreted only if the original control group did not exhibit a significant change over time. This approach helped us rule out spontaneous symptom improvements or familiarity effects as explanations for the significant changes in the paired *t*-tests.

For correlation analyses (e.g., analyzing the relationship between the number of post-Covid symptoms and cognition), Pearson correlation coefficients (controlled for age, sex, and education) were computed. In addition, we examined whether patients' disease duration moderated the association between post-Covid symptom count and cognition. Therefore, we performed moderation analyses by using the PROCESS SPSS Makro [Version 4.1, (Hayes, 2022)] which is available online[1]. To enhance the interpretation of main effects, variables that define the product term/interaction term (i.e., the predictor and moderator) were mean centered prior to the analyses. Additionally, moderation analyses were controlled for age, sex, and education. To counteract an alpha error inflation due to heteroscedasticity, robust standard errors of type HC3 (Davidson-MacKinnon) were used. Significant results were plotted for three specific values of the moderator (−1 *SD*, *M*, + 1 *SD*).

Finally, to assess the prevalence of cognitive impairments and psychological symptoms, we used the criteria outlined in the specific test manuals. Values more than one standard deviation below the mean ($T < 40$) and percentile ranks below 16 were considered indicative of impairment.

1 www.processmacro.org

Ethical considerations

This study received approval from the ethics committee of the Medical University of Graz (34-206 ex 21/22). Study recruitment was carried out through advertisements in newspapers and social networks, managed by the company "Probando GmbH." All eligible patients provided written informed consent for data recording and agreed to the study procedures. All data were pseudonymized (assignment of a subject code) and only the authors of the manuscript have access to the subject code. Hence, no identification of individual participants is possible for others. Participants had the right to withdraw from the study at any time without providing reasons, and without any disadvantage to them. In general, patients did not receive compensation for participating in the study; however, their travel expenses to and from the study site (Medical University of Graz) were reimbursed.

Results

The final sample consisted of 40 eligible individuals (80.0% female) aged between 36 and 71 years (M = 49.85, SD = 8.63). The majority held a university degree (27.5%), completed a general higher secondary school (17.5%) or middle school without a high school diploma (15.0%). All patients met the diagnosis criteria for PCC (Lippi et al., 2023; World Health Organization [WHO], 2022). A detailed description of participants' demographic and disease-related characteristics at baseline is provided in Table 1. No significant differences between the control and intervention group were observable at baseline. An overview of symptoms during the acute illness phase and at the different visits is provided in Supplementary Table 1. In addition, the frequency of cognitive and mental impairments for all participants at baseline as assessed by means of the test manuals' norm scores is presented in Figure 3.

Training evaluation

In the 2 × 3 ANCOVAs, we observed a significant group x time interaction only for the digit span forward task of the Neuropsychological Assessment Battery (NAB). We therefore performed Bonferroni-corrected follow-up analyses, showing that the groups differed already at baseline (p = 0.016), but not at FU1 (p = 0.757) and FU2 (p = 0.272). Therefore, there was neither a significant improvement in the IG from BL to FU1 (p = 0.345) nor from FU1 to FU2 (p = 1.000), nor in the CG (BL-FU1: p = 0.593, FU1 to FU2: p = 0.313). The results of all analyses are presented in Supplementary Table 2.

As a non-significant interaction effect may occur in the 2 × 3 analyses even if differences between groups from baseline to follow-up 1 are observable, we subsequently calculated 2 × 2 ANCOVAs. These analyses yielded significant group x time interaction effects in the following tests: digit span forward task (p = 0.032), MoCA memory index score (p = 0.017), subjective cognitive complaints (p = 0.022), and depression (ADS-L; p = 0.025). No significant effects (i.e., no significant differences in the slopes of the groups from BL to FU1) were observed for the other domains tested ($p > 0.05$). The results are summarized in Table 2.

Regarding the digit span forward task, both groups did differ significantly at baseline ($M_{CG.adj}$ = 8.50, SE_{CG} = 0.44, $M_{IG.adj}$ = 6.94, SE_{IG} = 0.41; p = 0.015), but not at FU1 ($M_{CG.adj}$ = 7.77, SE_{CG} = 0.42, $M_{IG.adj}$ = 7.65, SE_{IG} = 0.40; p = 0.847). However, neither the CG (p = 0.121) nor the IG (p = 0.113) significantly increased their ability in the task.

There was no significant difference between the CG and the IG in terms of their MoCA memory index score at baseline ($M_{CG.adj}$ = 14.06, SE_{CG} = 0.44, $M_{IG.adj}$ = 12.84, SE_{IG} = 0.41; p = 0.053) and FU1 ($M_{CG.adj}$ = 12.63, SE_{CG} = 0.50, $M_{IG.adj}$ = 13.16, SE_{IG} = 0.47; p = 0.451). However, while the MoCA

TABLE 1 Baseline demographic and clinical characteristics of post-Covid-19 patients assigned to the control group (CG) and intervention group (IG).

Parameter	Total (n = 40)		CG (n = 20)		IG (n = 20)		Difference
	M	*SD*	*M*	*SD*	*M*	*SD*	
Age [years]	49.85	8.63	50.15	9.64	49.55	7.73	M_{diff} = 0.60, p = 0.829
Height [cm]	167.65	7.49	167.50	7.82	167.80	7.35	M_{diff} = −0.30, p = 0.901
Weight [kg]	79.54	15.05	80.06	13.71	79.02	16.62	M_{diff} = 1.04, p = 0.830
BMI [kg/m^2]	28.29	5.09	28.61	5.06	27.98	5.24	M_{diff} = 0.63, p = 0.701
	Mdn		*Mdn*	*MR*	*Mdn*	*MR*	
Education [years]	13.25		13.25	19.08	13.50	21.93	U = 228.50, p = 0.436
Disease duration [m]	20.60		22.74	22.43	15.61	18.58	U = 161.50, p = 0.298
Duration acute infection	1 [6–10 days]		1	18.93	1.50	22.08	U = 168.50, p = 0.379
Functional status	2		2	23.65	0	17.35	U = 137.00, p = 0.052
	Count	*%*	*Count*	*%*	*Count*	*%*	
Sex [female]	32	80.0	16	80.0	16	80.0	χ(df = 1) = 0.00, p = 1.000
Vaccination[a] [yes]	20	50.0	10	50.0	10	50.0	χ(df = 1) = 0.00, p = 1.000
Hospitalization [yes]	2	5.0	0	0.0	2	10.0	Fisher's exact test: p = *0.487*
Pre-existing condition [yes]	24	60.0	15	75.0	9	45.0	χ(df = 1) = 3.75, p = 0.053

[a]Vaccination before infection. Significance tests compare the control group (CG) against the intervention group (IG). m, months; M, mean; SD, standard deviation; Mdn, median; MR, mean rank.

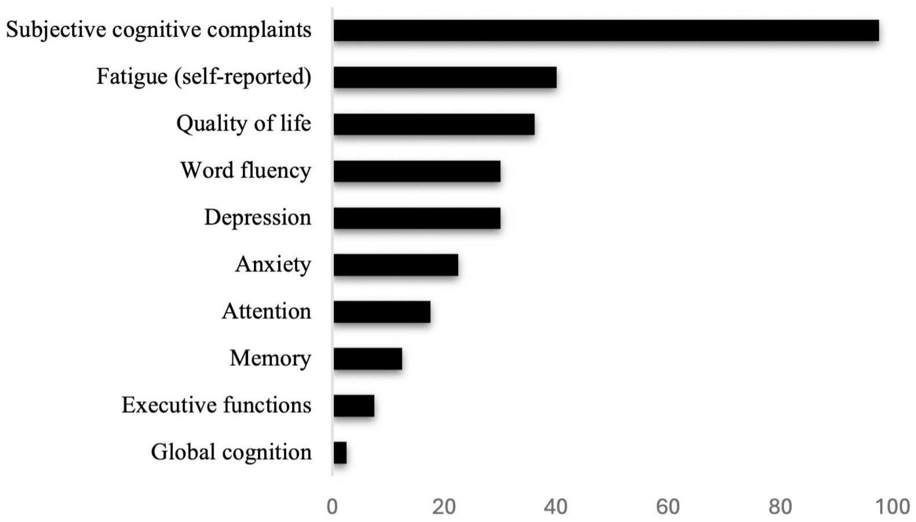

FIGURE 3
Percent of cognitive and psychological impairments of post-Covid-19 patients at baseline, evaluated according to the criteria outlined in the respective manuals or self-report (fatigue).

TABLE 2 Results of the 2 × 2 ANCOVAs. Presented is the significance of the group (2 levels: control group, intervention group) × time (2 levels: BL, FU1) interaction effect to evaluate the efficacy of a three-month tablet-based training program for post-Covid-19 patients.

Domain	Subtest	*n*	*F*	df	Error df	*p*	η_p^2
Attention	Digit span forward[a]	34	5.10	1	29	**0.032**	0.150
	Digit span backward[b]	34	0.00	1	30	0.970	0.000
	TMT-A[c]	34	0.12	1	30	0.731	0.004
Executive function	Planning[b]	34	3.74	1	30	0.062	0.111
	Categories[a]	34	2.12	1	29	0.156	0.068
	TMT-B[d]	34	0.10	1	30	0.758	0.003
Memory	Immediate recall (A)[a]	34	0.19	1	29	0.669	0.006
	Immediate recall (B)[a]	34	2.93	1	29	0.098	0.092
	Short-delayed recall[a]	34	0.24	1	29	0.630	0.008
	Long-delayed recall[a]	34	0.02	1	29	0.890	0.001
Word fluency	Formal-lexical[a]	34	0.71	1	29	0.406	0.024
	Semantic[a]	34	2.05	1	29	0.163	0.066
Global cognition	MoCA[a]	34	2.16	1	29	0.153	0.069
	MoCA Memory Index[a]	34	6.40	1	29	**0.017**	0.181
Subjective cognitive complaints	FSKB [QPC][a]	34	5.83	1	29	**0.022**	0.167
Fatigue	FISD total[a]	31	0.06	1	26	0.810	0.002
Depression	ADSL[b]	34	5.57	1	30	**0.025**	0.157
	HADS-D[b]	34	0.98	1	30	0.331	0.031
Anxiety	HADS-A[a]	34	1.07	1	29	0.311	0.035
Quality of life	WHOQoL-Physical[a]	34	1.65	1	29	0.209	0.054
	WHOQoL-Psychological[b]	34	0.14	1	30	0.710	0.005

[a]all covariates included as assumptions were met, [b]education excluded as a covariate, [c]sex excluded as a covariate, [d]age excluded as a covariate. Bonferroni correction was applied to all follow-up analyses. Significant results are highlighted in bold.

memory index score in the control group declined significantly over the three-month period (p = 0.008), the values in the intervention group remained, on average, stable (p = 0.496) (Figure 4A).

Looking at changes in subjective cognitive complaints, both groups did not differ at baseline ($M_{CG.adj}$ = 6.07, SE_{CG} = 0.46, $M_{IG.adj}$ = 6.22, SE_{IG} = 0.44; p = 0.811) or at FU1 ($M_{CG.adj}$ = 5.54, SE_{CG} = 0.69, $M_{IG.adj}$ = 3.69, SE_{IG} = 0.65; p = 0.065).

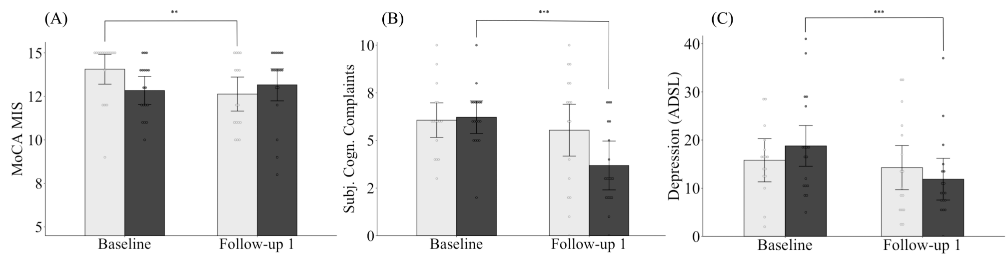

FIGURE 4
Changes in MoCA memory index score **(A)**, subjective cognitive complaints **(B)** and depression **(C)** for both the intervention and control group from baseline to follow-up 1. Light gray bars, control group; dark gray bars, intervention group. MoCA MIS, Montreal Cognitive Assessment Memory Index Score, ADSL, Allgemeine Depressionsskala (General Depression Scale). Means are adjusted for covariates (age, sex, and/or years of education). Error bars represent 95% confidence intervals (CI). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Nevertheless, while subjective cognitive complaints in the control group remained unchanged on average ($p = 0.387$), a significant improvement was observed in individuals assigned to the intervention group ($p < 0.001$) (Figure 4B).

Finally, we found no group differences in depressive symptoms between the groups, neither at baseline ($M_{CG.adj} = 16.02$, $SE_{CG} = 2.33$, $M_{IG.adj} = 18.59$, $SE_{IG} = 2.19$; $p = 0.431$) nor FU1 ($M_{CG.adj} = 14.34$, $SE_{CG} = 2.40$, $M_{IG.adj} = 11.81$, $SE_{IG} = 2.26$; $p = 0.452$). However, while the intervention group was able to reduce their depressive symptoms from baseline to FU1 ($p < 0.001$), the depressive symptoms for the control group, on average, remained unchanged between the assessment time points ($p = 0.328$) (Figure 4C).

After all individuals who completed the training were merged to form a combined intervention group ($n = 31$), exploratory pre-post comparisons were conducted (pre values for intervention group: baseline; pre values for control group: follow-up 2; post values for intervention group: follow-up 1; post values for control group: follow-up 3), and the results are presented in Table 3.

We found significant improvements in the digit span forward and digit span backward tasks, the TMT-A and TMT-B tasks, the categories task, the immediate recall of list B, subjective cognitive complaints, fatigue, depression, anxiety and quality of life (physical and psychological domain) after the training compared to before the training (Table 3). However, as discussed later, it cannot be ruled out that significant pre-post changes may have also occurred due

TABLE 3 Results of the pre-post comparisons in all patients before and after completing the three-month tablet-based training.

Domain	Subtest	*t*	df	*p*	*d*	*M* ± *SD* (BL)	*M* ± *SD* (FU)
Attention	Digit span forward	−3.22	30	**0.003**	−0.58	7.19 ± 1.66	8.26 ± 1.86
	Digit span backward	−3.00	30	**0.005**	−0.54	5.06 ± 1.93	6.26 ± 2.34
	TMT-A [time]	3.56	30	**0.001**	0.64	31.75 ± 10.55	26.15 ± 10.26
Executive function	Planning	−1.22	30	0.230	−0.22	8.42 ± 2.64	9.13 ± 2.16
	Categories	−6.64	30	**<0.001**	−1.19	30.00 ± 8.99	38.71 ± 9.92
	TMT-B [time]	4.07	30	**<0.001**	0.73	63.25 ± 18.12	52.71 ± 17.20
Memory	Immediate recall (A)	1.23	30	0.229	0.22	29.69 ± 4.21	28.90 ± 4.42
	Immediate recall (B)	−2.98	30	**0.006**	−0.54	6.03 ± 2.04	7.42 ± 2.05
	Short-delayed recall	1.25	30	0.057	0.36	10.52 ± 1.96	9.90 ± 2.14
	Long-delayed recall	0.68	30	0.502	0.12	10.42 ± 2.26	10.16 ± 2.15
Word fluency	Formal-lexical	1.16	30	0.257	0.21	22.13 ± 1.22	20.13 ± 1.43
	Semantic	−1.56	30	0.130	−0.28	30.26 ± 11.26	34.45 ± 7.69
Global cognition	MoCA	−1.48	30	0.150	−0.27	28.26 ± 1.55	28.74 ± 1.24
	MoCA memory index	−1.68	30	0.103	−0.30	12.97 ± 1.74	13.58 ± 1.88
SCC	FSKB [QPC]	4.61	30	**<0.001**	0.83	5.42 ± 2.23	3.55 ± 2.34
Fatigue	FISD total	2.61	27	**0.015**	0.49	67.96 ± 29.40	56.29 ± 31.98
Depression	ADSL	7.69	30	**0.001**	0.63	16.81 ± 9.90	11.94 ± 8.91
	HADS-D	2.39	30	**0.024**	0.43	5.71 ± 4.74	4.19 ± 3.35
Anxiety	HADS-A	2.47	30	**0.020**	0.44	4.90 ± 3.28	4.00 ± 2.92
Quality of life	WHOQoL-Physical	−2.94	30	**0.006**	−0.53	24.84 ± 5.51	26.84 ± 5.44
	WHOQoL-Psychological	−2.77	30	**0.010**	−0.50	22.65 ± 3.56	23.71 ± 3.84

SCC, Subjective cognitive complaints. Significant results (pre-post changes) are highlighted in bold.

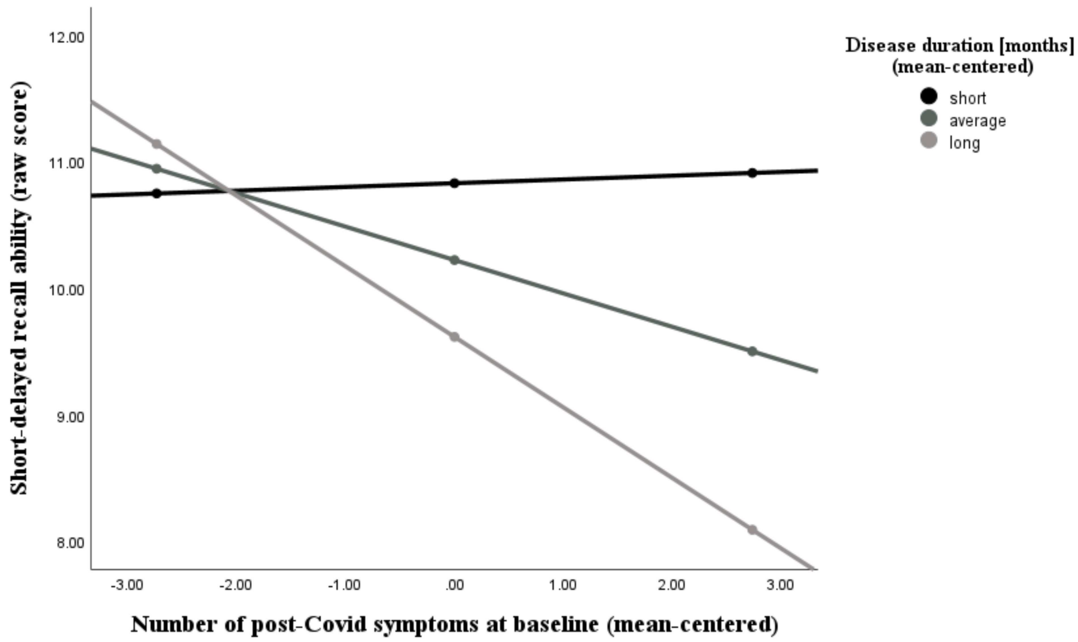

FIGURE 5
Moderating effect of post-Covid-19 disease duration on the association between the number of reported post-Covid symptoms and short-delayed recall ability. All variables that define the product term (i.e., predictor, moderator) were mean-centered. For individuals with a disease duration (months) one standard deviation below the mean (M = 18.26, SD = 10.31) in this sample (−1 SD below the mean; 7.95 months), no significant association between the number of post-Covid symptoms (BL) and their short-delayed recall ability was observed (b = 0.03, SE(HC3) = 0.16, t = 0.18, p = *0.855*). However, for those with an average disease duration, there was a significant negative correlation between symptom count and their short-term memory (b = −0.26, SE(HC3) = 0.10, t = −2.66, p = *0.012*). This negative effect is further intensified in individuals with a longer disease duration (+ 1 SD above the mean; 28.57 months) (b = −0.56, SE(HC3) = 0.08, t = −6.74, $p < 0.001$). Analyses are adjusted for age, sex, and education.

to training effects (increased familiarity with the test material) or temporal improvement (symptom improvement over time on its own). Therefore, we performed a plausibility check and examined the course of the mean values of the original control group in all significant domains (from baseline to follow-up 2) in order to check if training effects or temporal improvement occurred without a training provided. Friedman tests were used to assess whether there were changes in the respective domains and subtests that occurred in a group without training (e.g., training/familiarity effects, or improvements over time in the control group).

After doing so, we can confirm reliable effects for the subtests Digit Span Backward (attention; p = 0.178), TMT-A (attention; p = 0.607), TMT-B (executive functions; p = 0.135), immediate recall wordlist B (memory; p = 0.390), FSKB [QPC] (subjective cognitive complaints; p = 0.083), FISD (fatigue; p = 0.052), ADSL (depression; p = 0.635), HADS-A (anxiety; p = 0.174) and WHOQoL quality of life (physical: p = 0.383, psychological: p = 0.794). As can be seen from the p-values, there were only negligible and non-significant changes between the time points (BL-FU1-FU2) in these domains in the original control group, suggesting that significant results from the paired t-tests in these domains (Table 3) can likely be attributed to a real intervention-related effect. As familiarity effects can never be ruled out with certainty, these results should be interpreted with caution, as discussed later. In addition, significant changes in the original control group, even without a training, where observed in the other domains (digit span forward: p = 0.030, categories: p = 0.002, HADS-D depression: p = 0.018).

Association between symptom count and cognition

Furthermore, we were interested in exploring the correlation between the number of acute symptoms (symptoms reported during the initial Covid-19 illness) and cognition. We also investigated the same relationship for the number of persistent symptoms (post-Covid symptoms) reported by patients at baseline. The number of symptoms experienced during the initial Covid-19 infection was significantly positively correlated with the time needed to complete the NAB planning task (r = 0.43, p = 0.010), and negatively correlated with the immediate recall (A) score (r = −0.34, p = 0.038), the short-delayed recall (A) score (r = −0.34, p = 0.037), and the MoCA total score (r = −0.40, p = 0.015), while controlling for age, sex, and education.

Additionally, we found that the number of post-Covid symptoms at baseline was significantly associated with the NAB digit span forward task (r = −0.44, p = 0.006), the immediate recall (A) score (r = −0.46, p = 0.004), the short-delayed recall (A) score (r = −0.46, p = 0.005), and the long-delayed recall (A) score (r = −0.39, p = 0.017), while controlling for age, sex, and education. The latter two abilities (short- and long-delayed recall) were further moderated by participants' disease duration, as can be seen in Figures 5, 6 and Tables 4, 5. With increases in disease duration, the negative association between the number of post-Covid symptoms and patients' short delayed-recall ability increases (gets even more negative), which indicates that a longer disease

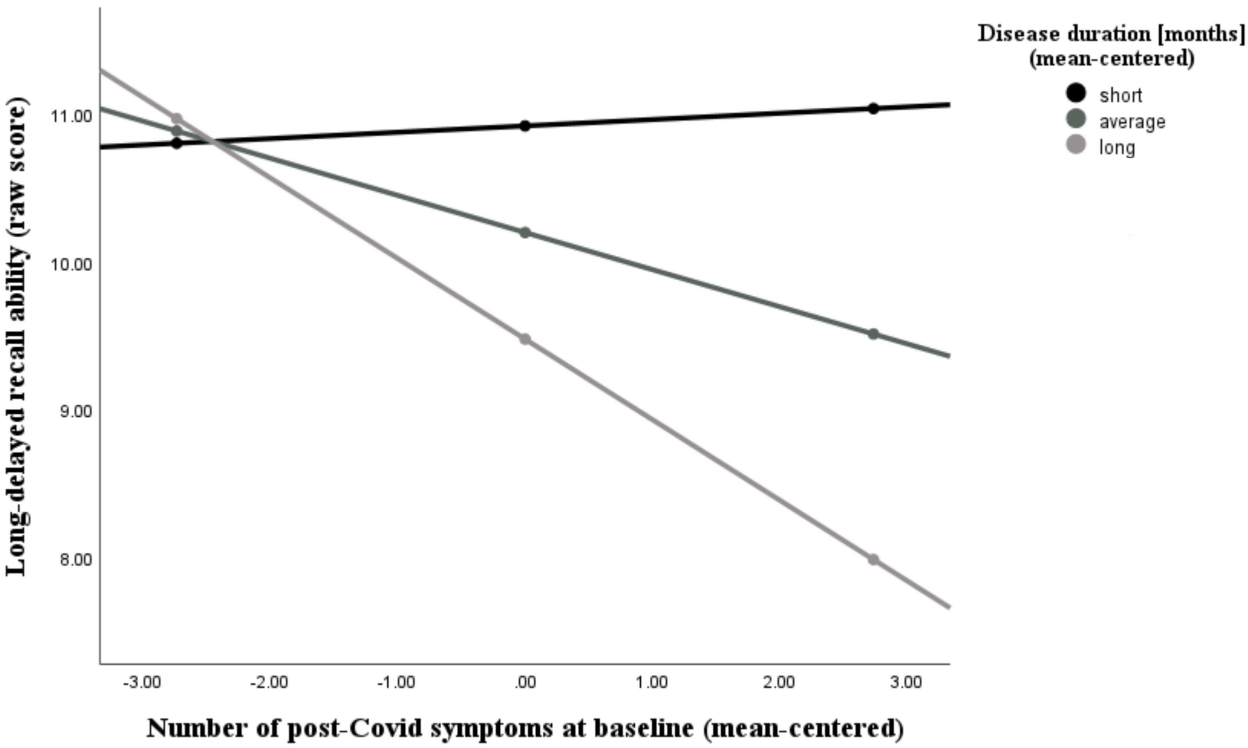

FIGURE 6
Moderating effect of post-Covid-19 disease duration on the association between the number of reported post-Covid symptoms and long-delayed recall ability. All variables that define the product term (i.e., predictor, moderator) were mean-centered. For individuals with a disease duration (months) one standard deviation below the mean (M = 18.26, SD = 10.31) in this sample (−1 SD below the mean; 7.95 months), no significant association between the number of post-Covid symptoms (BL) and their long-delayed recall ability was observed (b = 0.04, SE(HC3) = 0.18, t = 0.24, p = 0.812). Also, for those with an average disease duration, there was a visible, but non-significant correlation between symptom count and long-term memory (b = −0.25, SE(HC3) = 0.12, t = −2.04, p = 0.050). This negative effect is further intensified and statistically significant in individuals with a longer disease duration (+ 1 SD above the mean; 28.57 months) (b = −0.55, SE(HC3) = 0.13, t = −4.35, p < 0.001). Analyses are adjusted for age, sex, and education.

TABLE 4 Moderating effect of post-Covid-19 disease duration on the association between post-Covid symptom count and short-delayed recall ability in patients suffering from post-Covid-19 condition.

	Coefficient (*b*)	SE (HC3)	*t*	*p*	LLCI	ULCI
Constant	8.09	2.43	3.33	0.002	3.15	13.02
Ongoing symptom count	−0.26	0.10	−2.66	0.012	−0.47	−0.06
Disease duration [months]	−0.06	0.03	−1.93	0.062	−0.12	0.003
Interaction [P × M]	−0.03	0.01	−3.62	0.001	−0.04	−0.01

To enhance the interpretability of main effects, all terms that define the interaction (i.e., predictor [P] and moderator [M]) were mean centered. Analyses are adjusted for age, sex, and education. In addition, robust standard errors of type HC3 (Davidson-MacKinnon) were used. Model: R^2 = 0.47, $F(6, 33)$ = 12.76, $p < 0.001$; Interaction (symptoms x disease duration): b = −0.03 (SE = 0.01), t = −3.62, p = 0.001.

TABLE 5 Moderating effect of post-Covid-19 disease duration on the association between post-Covid symptom count and long-delayed recall ability in patients suffering from post-Covid-19 condition.

	Coefficient (*b*)	SE (HC3)	*t*	*p*	LLCI	ULCI
Constant	6.66	3.21	2.08	0.046	0.13	13.19
Ongoing symptom count	−0.25	0.12	−2.04	0.050	−0.50	−0.001
Disease duration [months]	−0.07	0.03	−2.11	0.042	−0.14	−0.003
Interaction [P × M]	−0.03	0.01	−3.16	0.003	−0.05	−0.01

To enhance the interpretability of main effects, all terms that define the interaction (i.e., predictor [P] and moderator [M]) were mean centered. Analyses are adjusted for age, sex, and education. In addition, robust standard errors of type HC3 (Davidson-MacKinnon) were used. Model: R^2 = 0.41, $F(6, 33)$ = 5.28, $p < 0.001$; Interaction (symptoms x disease duration): b = −0.03 (SE = 0.01), t = −3.16, p = 0.003.

duration worsens the impact of post-Covid symptoms on memory. Equivalently, this applies to the long-delayed recall ability.

There was no significant association between disease duration and post-Covid symptom count ($r = -0.12$, $p = 0.486$), as well as between disease duration and cognition (all *p-values* > 0.05), after controlling for age, sex, and education.

Finally, subjective cognitive complaints (FSKB [QPC] score) at baseline were not correlated with any cognitive or psychological domain assessed in this study (all p-values > 0.05; correlations with cognitive variables were adjusted for age, sex, and education).

Discussion

Post-Covid-19 condition (PCC) represents a debilitating illness for affected individuals, characterized by a variety of physical, psychological, and cognitive symptoms (Li et al., 2023; Bonfim et al., 2024; Möller et al., 2023). However, there is still no gold standard for treating these symptoms (Mueller et al., 2023), and only a few studies have tested the efficacy of tailored and multidisciplinary training programs. To overcome the lack of interventional studies and to follow the advice of a previous review, suggesting digital interventions for patients with PCC to better manage their symptoms (Rinn et al., 2023), this study investigated (1) the efficacy of a three-month tablet-based training program, aiming to improve cognitive and mental symptoms, (2) the frequency of persistent symptoms of Covid-19 as well as the incidence of cognitive and mental deficits, and (3) the association between post-Covid symptoms and disease duration with cognition.

Efficacy of a three-month tablet-based training program

Our findings revealed significant improvements in the intervention group compared to the control group regarding subjective cognitive complaints and depression. Furthermore, we observed that the MoCA Memory Index Score (MIS) did not deteriorate in the intervention as compared to the control group, suggesting a potential preservation of cognitive functions. These results suggest that the training had positive effects on the mental and emotional well-being of our patients. This aligns with positive effects of previous training studies in other populations, such as patients with Parkinson's disease (Gavelin et al., 2022), or stroke (Zhou et al., 2022). We believe that the combination of relaxation exercises, which are known to be beneficial to improve mental health (e.g., depression) (Jia et al., 2020) and the cognitive training led to a decrease in subjective cognitive complaints of patients, which subsequently might have resulted in a decrease of depressive symptoms. As a result of cognitive training (especially memory exercises of the training), patients in the intervention group, as compared to those in the wait-list control group, showed no decline in the MoCA memory index score. As we know from previous literature that symptoms are fluctuating over time (Ziauddeen et al., 2022), being part of the intervention group might have counteracted a fluctuation in memory performance. However, in the relatively small sample of this study, our training did not yield significant improvements in other domains such as attention or executive functions, suggesting that the training may have limitations in targeting these specific cognitive domains or that the intervention duration was insufficient to yield measurable changes. This might have been due to small, but possibly meaningful effects which were not detectable. Additionally, the training intensity (i.e., the number of session participants completed per week) might have been insufficient. Another reason might be task specificity, meaning that the cognitive exercises may have focused more on memory and subjective complaints and less on executive functioning and other domains. Moreover, the absence of long-term effects indicates the necessity for more intensified interventions to achieve sustainable effects. Therefore, future research should explore strategies to prolong the effects of such interventions. Additionally, the training program needs to be adjusted in order to also induce improvements in other domains (e.g., executive functions, attention, or fatigue). For example, planning tasks could be incorporated, in which patients plan a daily schedule or a shopping list, or tasks that specifically target the subdomains of attention (e.g., divided attention, selective attention, sustained attention). Notably, we also found no effects with respect to fatigue, although fatigue represents one of the most common symptoms in PCC (Leitner et al., 2024). This negative finding highlights the need for future studies to develop interventions targeting fatigue. In addition, the impact of significant training effects on patients' daily functionality could be further assessed through quantitative (e.g., questionnaires on activities of daily living) and qualitative interviews (e.g., focus groups) in future studies, which provide an extension to quantitative research findings. Finally, no negative side-effects were reported by patients.

Although the training had a significant effect on the domains mentioned above, it is further essential to note that participants in the intervention group either showed a decline in performance again after stopping the training (FU1 - FU2), or the control group improved from FU1 to FU2 even without training. This would suggest that effects achieved through the training are not stable and further, longer training periods are needed, or that training leads to quicker improvement in specific domains, but these improvements also occur spontaneously over time. A spontaneous improvement of post-Covid symptoms over time was also reported by previous studies (Derksen et al., 2023; Jason et al., 2021; Oliveira et al., 2022), although not necessarily for neurocognitive symptoms (Jason et al., 2021). Tröscher et al. (2024), for instance, reported that around three-quarters of patients showed an improvement of symptoms after approximately 18 months (Tröscher et al., 2024). This gives hope to patients currently suffering from lingering Covid-19 symptoms. Nonetheless, as persistent symptoms following a SARS-CoV-2 infection can be significantly debilitating and lead to limitations in the work and private life of those affected (Leitner et al., 2024; Walker et al., 2023; Ziauddeen et al., 2022), training options that lead to a faster improvement of symptoms are essential, especially since not all patients seem to recover spontaneously. A faster improvement of symptoms might help individuals in times of uncertainty regain their quality of life, reduce the risk of anxiety and depression, and allow them to return to work earlier.

After all individuals, including those in the waitlist control group, completed the tablet training, we merged both groups to form a combined intervention group. This allowed us to increase statistical power (the likelihood of detecting even small effects if they exist) by enlarging the sample size for further exploratory analyses. We found significant improvements in attention (3/3 tests), executive functions (2/3 tests), memory (1/4 tests), subjective cognitive complaints (1/1 test), fatigue (1/1 test), depression (2/2 tests), anxiety (1/1 test), and quality of life (2/2 tests). Although these results are remarkable, we cannot definitively rule out a practice/training effect. Therefore, we subsequently examined only those domains in which the original control group (before combining the groups) did not show any improvements during the period in which they did not receive training (BL - FU2). We found a significant improvement in some tests of the aforementioned domains, as the initial control group (before combining the groups) did not show any improvements (indicating that practice/familiarity effects or spontaneous improvements are unlikely). However, it is important to note that these findings are preliminary and should be validated in larger studies to definitively rule out familiarity effects or spontaneous improvement of symptoms over time. Additionally, seasonal variations and effects such as regression to the mean could not be controlled in this scenario.

As cognitive deficits might even persist for more than 2 years post-infection (Cheetham et al., 2023), and roughly 1 in 5 might not be able to work at all due to their symptoms (Walker et al., 2023), effective tabled-based interventions need to be incorporated into the treatment plan of patients with PCC (Derksen et al., 2023). Trainings should take specific care for patients that are suffering from severe fatigue, as physical or psychological exhaustion is reached easily, which might lead to negative consequences. In addition, future studies should investigate cognitive and mental training in larger samples in order to substantiate the effectiveness of such programs and address the issue of how long training sessions should last to achieve sustainable effects.

Frequency of cognitive and mental deficits

In our study, individuals suffering from post-Covid reported a variety of different symptoms, including cognition-related symptoms such as memory problems (85.0%) or brain fog (87.5%), as well as symptoms such as fatigue (40.0%) and muscle pain (27.5%). At baseline, almost all individuals reported subjective cognitive complaints (97.5%). However, this might be attributed to a sampling bias, as recruitment for the study specifically focused on individuals with cognitive and mental deficits in the context of post-Covid. In addition, although we asked patients explicitly to provide only symptoms that have not occurred already prior to the illness, we cannot rule out that some symptoms occurred due to cognitive decline which is commonly observed in the aging population. Furthermore, we found attention deficits in 17.5% of all participants, memory problems in 12.5%, as well as a high rate of psychological symptoms including depression (up to 30.0%), anxiety (22.5%), or reduced quality of life across various domains (up to 36.1%). These results are in line with a number of previously published studies, indicating a high amount of cognitive (Cheetham et al., 2023; Lauria et al., 2023), psychological (Goodman et al., 2023) and physical symptoms (Byambasuren et al., 2023) in PCC. Although the number of patients with subjective cognitive complaints was substantial, these perceived deficits were interestingly not correlated with cognition as assessed during comprehensive neuropsychological testing. Findings like these are not unusual, as previous research indicated that subjective cognitive complaints are not necessarily associated with actual cognitive deficits in different populations such as those with bipolar disorders (Svendsen et al., 2012) or traumatic brain injury (French et al., 2014). Also, in a recently published study on patients with PCC, a high number of patients reported memory and concentration problems but showed no difference in cognition compared to healthy controls (Chang et al., 2023). This might suggest that some individuals may have difficulties in accurately assessing their cognitive abilities, although these complaints are representing a significant burden for those affected. Finally, and in line with Hasting et al. (2023), although there was a high prevalence of deficits in specific domains, severe cognitive impairment was relatively rare in our study sample. The absent of severe cognitive impairment was particularly visible when focusing on global screening instruments such as the MoCA (Hasting et al., 2023).

Association between acute/post-Covid symptoms and disease duration with cognition

Finally, we could validate that PCC is associated with objectively measurable cognitive deficits (Cheetham et al., 2023; Hampshire et al., 2024; Houben and Bonnechère, 2022). The number of symptoms experienced during a patients' acute Covid-19 illness was negatively associated with the performance in tests assessing executive functions, memory, and general cognition (MoCA) at the baseline assessment. This result is significant, as it illustrates that the number of acute symptoms correlates with cognitive performance in these domains, even though the acute infection occurred months ago. A similar result emerged when focusing on persistent (post-Covid) symptoms. The number of post-Covid symptoms at baseline was associated with a decrease in attention and memory abilities. The relationship between the amount of post-Covid symptoms with short and long-delayed recall abilities was further amplified by patients' disease duration. For individuals with a relatively short duration of post-Covid illness, there was no correlation between symptom count and memory performance (i.e., regardless of how many or few symptoms were present, there was no effect on performance in memory tests). In contrast, for individuals with a relatively long duration of post-Covid illness, a higher number of post-Covid symptoms led to poorer short- and long-term memory performance. These results are a first indicator which suggests that training may be most beneficial when offered early in the course of the illness, as the impact of symptoms appears to become more prominent over time. However, it is important to note that further research is needed to confirm the optimal timing for long-Covid interventions.

In addition, post-Covid disease duration was not associated with post-Covid symptom count. This contrasts previous studies, suggesting that most symptoms show a decreasing prevalence over time (i.e., with increasing disease duration) (Derksen et al., 2023; Tran et al., 2022). However, it is likely that symptoms are fluctuating or relapsing over time (Ziauddeen et al., 2022) and that the prevalence (increase or decrease of symptoms over time) depends on the type of symptoms (Tran et al., 2022).

Limitations

Despite numerous strengths of the study, such as comprehensive neuropsychological testing and the longitudinal study design, it is important to note some limitations as well. The impact of tablet-based interventions may mainly consist of smaller effects, which can only be detected in larger samples (hence requiring greater statistical power). The relatively small sample size per group [as the study design focused on medium to large effects (see power analysis)] could account for some non-significant effects that might be detected in studies with a larger sample size. Future studies should consider using more conservative effect size assumptions and recruiting larger samples to improve the generalizability of their findings. We also suggest an exact recording of how often and for how long participants perform the exercises to obtain a clearer picture of retention and adherence. Another point to consider is that while we found more effects after merging both groups into a single intervention group, we cannot rule out the possibility that these effects arose due to familiarity with the test material or spontaneous remission over time. Also, seasonal variations and phenomena such as regression to the mean could not be controlled in these exploratory analyses. These results should therefore not be overinterpreted. Therefore, future studies should focus on a similar training design with a larger sample size to examine smaller but meaningful effects that can be achieved through tablet-based interventions. In this regard, we recommend that future studies also consider differences in depressive symptoms between groups (as they can affect cognition) and include an active control group in their study design. This active control group should receive an alternative intervention that is comparable in effort and duration but does not include the active component of the main intervention (e.g., exercises to improve cognitive functioning). This approach could significantly improve the generalizability of the results. For recruitment, we recommend ensuring that all age groups, races, and genders have equal opportunities to participate in future studies. Another general limitation of tablet-based interventions, as conducted in this study, is the fact that the patients could not be blinded to the treatment and therefore knew whether they belonged to the intervention or control group. We also want to acknowledge that this study was only registered retrospectively and not prospectively, which we encourage future studies to do. A final limitation of the study concerns the transferability of the effects into the daily life, as it remains unknown whether the training also improved participants' everyday functioning.

Conclusion

Our study suggests that home- and tablet-based cognitive and mental training may be partially effective in improving specific symptoms associated with Post-Covid-19 condition (PCC). Participants in the intervention group showed a significant reduction in subjective cognitive complaints and depressive symptoms compared to a control group. Additionally, their MoCA Memory Index Score remained stable, while it declined significantly over time in the wait-list control group. From a clinical perspective, such interventions could provide a valuable and flexible option to support cognitive and psychological recovery in patients suffering from PCC. Finally, we found preliminary evidence that the negative association between the number of post-Covid symptoms and participants' memory performance becomes more pronounced with increased disease duration. This is a first indicator which suggests that training should be provided early in the course of the illness. Future studies with larger sample sizes should include an active control group and focus more on the transferability of effects into patients' daily lives. Overall, our findings suggest that tablet-based training programs could be considered an additional add-on therapy to improve cognition and mental health in patients suffering from post-Covid-19 symptoms.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics committee of the Medical University of Graz, Graz, Austria. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ML: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. LP: Conceptualization, Methodology, Validation, Writing – review & editing. ML-G: Conceptualization, Data curation, Resources, Writing – review & editing. MF: Conceptualization, Funding acquisition, Project administration, Resources, Writing – review & editing. MK: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

LP was employed by Joanneum Research. ML-G was employed by Probando GmbH. MF was employed by digitAAL Life GmbH and was therefore involved in the development of the tablet-based training used in this study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2025.1582742/full#supplementary-material

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