Review

Improving Neuropsychological Rehabilitation for COVID-19 Patients

Guideline-Based Advances

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Abstract: Cognitive sequelae after recovery from an initial COVID-19 disease are present in a subset of affected individuals, coalescing around several important issues such as effects of age, COVID-19 disease severity, comorbidities, and other factors. Some neuropsychological symptoms appear more common among certain patient populations. Comorbidities may complicate neuropsychological assessment as well. Hence, we need a guideline-based evaluation to guide neuropsychological rehabilitation. Drawing from the recent revision of the German National Guideline for the Long- and Post-COVID Syndrome and current advances in international guidance on neuropsychological assessment, this article provides practical and scientifically informed recommendations for the neuropsychological assessment of individuals recovering from coronavirus-related diseases.

Keywords: SARS-CoV-2, post-COVID-19 syndrome, cognition, neuropsychology, rehabilitation

Optimierung der neuropsychologischen Rehabilitation bei COVID-19: Leitfadengestützte Fortschritte

Zusammenfassung: Langfristige kognitive Auswirkungen von COVID-19 betreffen insbesondere bestimmte Subgruppen von Patient_innen. Die Vulnerabilität für derartige Beeinträchtigungen scheint durch Faktoren wie Alter, Schweregrad der COVID-19-Erkrankung, mögliche Komorbiditäten und andere Faktoren beeinflusst zu werden. Bestimmte Patientengruppen scheinen besonders vulnerabel für neuropsychologische Symptome zu sein. Das Vorhandensein von Komorbiditäten kann die Durchführung neuropsychologischer Assessments zusätzlich erschweren. Eine systematische Herangehensweise erfordert daher eine leitliniengestützte Einschätzung der neuropsychologischen Rehabilitationsmöglichkeiten. Ausgehend von der aktuellen Version der deutschen Nationalen Leitlinie für das Long-/Post-COVID-Syndrom sowie unter Berücksichtigung der neuesten Entwicklungen internationaler Leitlinien werden in diesem Beitrag wissenschaftlich fundierte, praktische Empfehlungen für das neuropsychologische Assessment bei Personen mit COVID-19-assoziierten Symptomen vorgestellt.

Schlüsselwörter: SARS-CoV-2, Post-COVID-Syndrom, Kognition, Neuropsychologie, Rehabilitation

Introduction

The construct "long/post-COVID syndrome" (hereinafter jointly referred to as PCS) has garnered public attention because of neuropsychological disorders that occur after a patient recovers from an initial episode of coronavirus disease 2019 (COVID-19). The latter is a top category construct encompassing physical and psychological symptoms that arise during or after *severe acute respiratory syndrome coronavirus 2 (SARSCoV2)* infections and continue during the subsequent weeks. The observed signs of PCS reveal varying degrees of severity (Soriano et al., 2021), many directly or indirectly related to cognitive performance. The current international guidelines for diagnosing and treating PCS encompass a general, nonspecific approach (National Institute for Health and Care Excellence (NICE), 2020; World Health Organization (WHO), 2021) and refer to cognitive disturbance as an unspecific brain disorder, commonly referred to as "brain fog." These guidelines are based primarily on evaluations of data from heterogeneous sources and mostly from Western countries, including small cohort studies, long-established epidemiological studies, and health claims data.

In Germany, at publication, close to 40 million cases of COVID-19 have been documented (Robert Koch-Institut: COVID-19-Dashboard, last updated 9 February 2023). In industrialized societies, the point prevalence of PCS has been estimated to range from 7.5% to 41% in

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nonhospitalized adults and up to 37.6 % in hospitalized adults, according to a recent meta-analysis (Nittas et al., 2022). Because of the nascent state of research and the relatively diffuse diagnostic categories, there is still much uncertainty about the incidence or degree of neuropsychological impairment.

According to the WHO International Classification of Disease (ICD-10), the clinical case definition of PCS is designated as "U09.9 Post-COVID-19 Condition." This definition encompasses patients with a confirmed or probable SARS-CoV-2 infection whose symptoms begin within 3 months of the onset of COVID-19. These symptoms must persist for at least 2 months and must not be explainable by any alternative diagnosis (WHO, 2021). There is a broad international consensus with the WHO Delphi Committee representing all WHO regions regarding the most common symptoms: fatigue, shortness of breath, and cognitive dysfunction, impacting daily functioning. These may be newly emerging symptoms or persist since the initial infection and vary in intensity or disappear and relapse. The WHO suggested that this condition still requires more research and standardization but forms the first basis for a postacute definition of COVID-19-related symptoms.

Terms such as *long-COVID-19* (continuance of symptoms since the acute phase for eight weeks and more) and *post-COVID-19* (symptoms developed during or after an infection consistent with COVID-19 and persist 12 weeks after resolution of the acute phase) have been set out by the NICE Guidelines. These have also been adopted into national (e.g., German) guidelines. Other commonly used terms for PCS conditions include *COVID long haulers* initially described by affected patients (Callard & Perego, 2021) and *postacute sequelae of SARS-CoV-2* or *postacute COVID-19 syndrome, PASC)*.

The National Institute for Health Research (NIHR) has indicated that PCS may not be a singular condition but a collection of various syndromes and disorders. Examples include post-intensive care syndrome (Biehl & Sese, 2020), post-viral fatigue syndrome (Calabria et al., 2022), organ-related disorders (e.g., sensory, respiratory, cardiovascular), and psychiatric and psychosomatic conditions. All of these entities may have characteristics, symptoms, and diagnostic criteria that overlap with the current definition of PCS (Allendes et al., 2022; Dehghani et al., 2022; Jonigk et al., 2022; Zawilska & Kuczyńska, 2022). Consequently, PCS is not a distinct and easily recognizable clinical entity. Therefore, the assessment, classification, and treatment of neuropsychological dysfunction in the context of PCS require further refinement.

Recent research findings and recommendations are available, and this article aims to explore these aspects in detail. Specifically, this article presents pertinent information regarding the direct and indirect biological and psychological effects of SARS-CoV-2 infection on cognition and an overview of known trajectories of cognitive impairment. Additionally, factors that are adverse to cognition, such as older age, disease severity, and specific comorbidities, are described. Finally, we derive assessment and rehabilitation recommendations for neuropsychologists based on the most recent information from national and international guidelines that offer specific information tailored to cognitive symptoms within PCS.

Direct and Indirect Effects of a SARS-CoV-2 Infection

Biological Mechanisms

Numerous potential pathomechanisms have been implicated in PCS: these may include the continued presence of viral RNA and proteins and the persistence of inflammatory reactions in important organs, such as the lungs, heart, brain, or vascular system (Bussani et al., 2023) causing thrombosis, micro or macrovascular changes, and, possibly even long-term damage to many kinds of tissue (Jonigk et al., 2022). Moreover, systemic alterations involving metabolism and immune changes, such as hyperinflammation or autoimmune reactions, may be permanent. In those with severe courses of COVID-19, who experience organ and respiratory dysfunction, persistent COVID-19 symptoms have been associated with dysregulated autoimmunity and immunodeficiency (Garmendia et al., 2022; Sotzny et al., 2022). Alterations in immune function have been observed in various other viral infections, including Epstein-Barr, Ebola, SARS-CoV-1, and MERS. Anomalies in the activation of immunological pathways have been linked to persistent symptoms over time (Needham et al., 2022; Proal & VanElzakker, 2021).

Systemic alterations in transmitter systems have been found, such as the renin-angiotensin-aldosterone system (RAAS) and the Hypothalamic–Pituitary–Adrenal (HPA) axis (Jensterle et al., 2022; Maranduca et al., 2022), that are essential in regulating blood pressure and in coordinating inflammatory responses of the body. Specifically, the SARS-CoV-2 virus obstructs the production of angiotensin-converting enzyme type 2 (ACE-2), part of the RAAS system, resulting in disrupted homeostasis (Méndez-García et al., 2022). Furthermore, the dysregulation of the immune system appears to play a central role in persistent changes following COVID-19, termed *Multisystem Inflammatory Syndrome in Children (MIC-S),* among pediatric populations (Chakraborty et al., 2023; P.-I. Lee & Hsueh, 2023).

Some authors (de Melo et al., 2021; Käufer et al., 2022; Schwabenland et al., 2021) have hypothesized that sustained neurocognitive impairments after SARS-CoV-2 infection could be related to these mechanisms, as the latter may have repercussions on cognition or neuropathy. Peripheral inflammatory cytokines may cross the blood-brain barrier and modulate central nervous system (CNS) inflammatory processes resulting in impaired cognitive functioning in animal models (Lee et al., 2009; Marsland et al., 2015; Zuliani et al., 2007). In humans, abnormally high levels of the C-reactive protein and interleukin-6 have been associated with a decrease in specific cognitive abilities (e.g., spatial reasoning, short-term memory, verbal ability, learning, memory, and executive function) as well as with brain morphological changes in grey and white matter volumes, and hippocampus and cortical surface areas (Marsland et al., 2015).

Long-term neurological disorders associated with PCS may involve encephalopathy, cerebral dysregulation, and ischemic stroke (Hingorani et al., 2022). There may be direct viral damage to the CNS via the binding of the SARS-CoV-2 virus to specific receptors that allow them to pass the blood-brain barrier (Heneka et al., 2020). However, direct invasion into the brain or spinal column is not the most salient mechanism of long-term COVID-19-related changes (Gerhard et al., 2022; Kanberg et al., 2021).

Given the extensive range of pathomechanisms involved and the need for clarity in the context of PCS, novel research initiatives have emerged, such as the transdisciplinary international consortium NeuroCOV (https://www.neurocov.eu/) and the RECOVER Initiative (Researching COVID to Enhance Recovery) in the United States (Reese et al., 2023; Zhang et al., 2023). They are strategically studying the various phenotypes of PCS and specific mechanisms over time, utilizing multiple approaches such as epidemiology, molecular biology, machine learning, and social science.

Psychological Factors

Cognitive performance decrements cannot be explained based only on biological mechanisms; many psychological factors must also be considered. Because a diagnosis of PCS cannot be determined by a laboratory test, assessing the current symptoms and their temporal associations with a SARS-CoV-2 infection is the first essential step. Important factors precipitating PCS may comprise several levels encompassing contextual, person-centered, disease-related, and situational determinants, as Figure 1 shows. The variety and range of symptoms complicate this process. In the affected individual, neuropsychological experts evaluate the complex relationships among *premorbid cognitive ability* (mental engagement, intelligence, education, and cognitive reserve), *personality traits,* and *psychiatric burden* (stress, depression, anxiety, posttraumatic stress disorder, etc.). Such an assessment must consider the complex interplay among neurocognitive, affective, personal, and situational factors and their combined effects on the individual's current functioning.

The psychological aspects of PCS may include increased anxiety, depression, stress, and sleep disturbances (Badinlou et al., 2022; Damiano et al., 2022; Premraj et al., 2022). In some individuals, PCS may lead to feelings of isolation, hopelessness, or even trauma. Other nonpsychiatric symptoms, such as fatigue, hair loss, breathing problems, and sleep disturbance (Lopez-Leon et al., 2021), may secondarily cause psychological burdens among affected individuals. PCS may also affect motivation, a core symptom of fatigue and one of the most frequently reported symptoms of PCS (Peper & Schott, 2021; Premraj et al., 2022). Psychological processes of coping behavior may induce specific patterns of cerebral activity resulting in a response pattern overlapping or interacting with PCS. It is crucial to recognize that the psychological impact of PCS can be intensified by uncertainty and unpredictability related to the pandemic and the illness as well as by a general lack of comprehension and acknowledgment of its consequences by society. As a result, numerous pandemic-related factors, in addition to COVID-19 disease, can adversely affect an individual's quality of life, physical well-being, mental aptitude, social surroundings, interpersonal relationships, and financial situation.

The results of neurological diagnostic procedures are essential in linking self-reported changes to neuropsychological alterations. Various neurological dysfunctions such as stroke, impairment of motor coordination, sensory changes, general pain, headache, vision changes, and loss of taste and smell are all pertinent in the context of neuropsychological assessment (Zawilska & Kuczyńska, 2022). Nevertheless, changes in neuropsychological functions are not solely associated with virus-induced alterations in brain structure and function. Slight damage to noneloquent brain regions may present as nuanced deficits in psychophysiological activation, automatic regulation of emotional reactions, contextual learning processes, executive dysfunction, and others.

Complaints about concentration and memory problems, commonly referred to as "brain fog," ought to be the initial signs for referral to a neuropsychological evaluation. Empirical data from past viral pandemics and the current COVID-19 outbreak reveal that subtle, "invisible" changes in an individual's experiences and behaviors may manifest in otherwise asymptomatic patients (Peper & Schott, 2021). Presently proposed protocols are consistently challenged by the possibility of inconspicuous functional disorders eluding the expert's scrutiny. The primary internationally recommended screening protocols may not fully capture some subclinical impairments. Therefore, assessing the presentation of patients' conditions involves considering the available resources and information flows required for seeking medical treatment and complying with legal norms for compensation (cf. Box 1). These inevitably have ramifications on neuropsychological assessments. The absence of documentation of initial SARS-CoV-2 infection or acute brain dysfunction during the initial COVID-19 disease does not definitively rule out long-term cognitive impairments associated with the disease. However, current statutes in Germany require such documentation for cases of compensation.

Pandemic Effects vs. Effects of the SARS-CoV-2 Virus

Complaint rates following SARS-CoV-2 infections are potentially conflated with those related to other diseases; symptoms (Moniuszko-Malinowska et al., 2022), insomnia (Scarpelli et al., 2022), and biomarkers of stress (e.g., serum cortisol levels; Šik Novak et al., 2022) exist in otherwise "healthy" populations. Undoubtedly, the COVID-19 pandemic has far-reaching and profound effects on individuals, families, and society. It is noteworthy that recruiting healthy controls during the pandemic was a rare occurrence in cognitive studies of COVID-19.

Widmann et al. (2023) recruited healthy participants during the first year of the pandemic as part of a larger German COVID-19 Cohort study (Covimmune-Clin), before the widespread availability of vaccines. The study included men and women of middle age (*M, SD*: 47.4, 13.2 years) with no history of psychiatric, neurological, or other illnesses, no concerns about their cognitive health, and negative antibody tests. The control group showed higher rates of remarkably poor scores (< –1.5 *SD*) on several attention and language tasks compared to historical norms. Although one cannot entirely rule out self-selection biases, it is essential to consider that these findings may result from general pandemic effects.

Socioeconomic deprivation and declining quality of life in the general population during the pandemic are important contextual factors (Beese et al., 2022). Understanding these effects is essential when interpreting cognitive outcomes, since they are known to have downstream effects on psychological and cognitive health.

Dynamics of Cognitive Symptoms

Among cognition studies done within the first 2 months after COVID-19 onset, reported rates of cognitive impairment vary greatly and appear to depend on the specifics of the cohort examined. This impedes reliable statements about the actual rates of cognitive impairment. While one

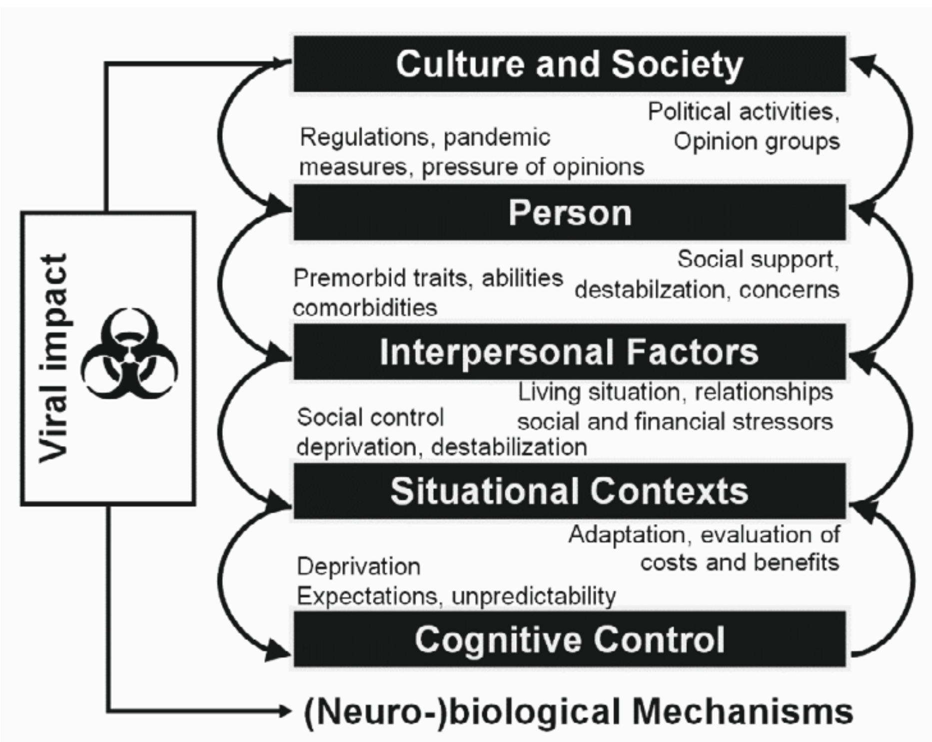

Figure 1. A simplified multilevel framework (adapted from Peper et al., 2015) describing biopsychosocial interactions potentially influencing cognitive performance in post-Covid-19 syndrome (PCS). Arrows represent top-down influences (left) that determine how lower-level processes must be adapted depending on the higher-order context; bottom-up influences (right) may explain how information at a lower level determines a higher-order context.

Assessment in the legal decision-making process in cases of occupational disability or liability related to COVID-19 infections and PCs requires the neuropsychologist to take into account not only the specific laws and local rules of jurisdiction but also pertinent general guidelines (e.g., in Germany, see Föderation Deutscher Psychologenvereinigungen, 2017; Marx & Gaidzik, 2019) as well as the specific guidance on neuropsychological expert assessment (e.g., Aschenbrenner et al., 2023, in prep.). Expert reports in the context of the German legal accident insurance system serve the recognition and compensation of occupational diseases, encompassing PCS and related neurocognitive impairment, may also take recommendations such as those of Tegenthoff et al. (2022) into account. Correspondingly, the evidence link between an insured infection event and PCS may be substantiated by (a) verification of the objective severity of the acute infectious event, (b) biomedical documentation of brain disease or consciousness disturbance during the acute phase, (c) substantiation of patient's complaints using psychological tests while also taking into account a potential negative response bias, (d) elaboration of convincing evidence that is not biased, (e) consideration of symptom improvement over time, which may be substantiated by follow-up examinations, (f) examination of alternative factors decisively producing or maintaining the symptoms, and (g) overall evaluation of plausibility in the synopsis of all evidence. However, concerning neuropsychological assessment, note that a single measure derived from a performance validation procedure is insufficient evidence for credible or valid neuropsychological test performance. On the contrary, one can convincingly evaluate the validity and credibility of findings only if the results of procedures assessing effort, response bias, and malingering by interpreting within the context of a detailed consistency and plausibility evaluation procedure in combination with additional results and contextual information. In particular, competently determining response bias needs means considering the social, cultural, and legal contexts of low effort as well (e.g., Sweet et al., 2021). It is mandatory to adhere to pertinent national guidelines for neuropsychological assessment (e.g., Aschenbrenner et al., 2023, in prep.). This generally accepted practice of comprehensive evaluations of neuropsychological deficits should not be abandoned in the assessment of COVID-19-related diseases.

Box 1. Neuropsychological assessment in the legal compensation context.

study reports no identifiable impairment after an early rehabilitation intervention (Daynes et al., 2021), one-third of patients with acute respiratory distress syndrome (ARDS) admitted to an intensive care unit showed cognitive impairment (Negrini et al., 2021), and 80 % of patients in a rehabilitation setting showed cognitive impairment (Alemanno et al., 2021). Low scores on attention, verbal fluency, and executive function measures were often reported having occurred together with an increased psychiatric burden, such as symptoms of depression and anxiety (e.g., Daynes et al., 2021; Mazza et al., 2021; Negrini et al., 2021; Poletti et al., 2022). However, these early-stage studies did not generally explicitly define the type or levels of cognitive impairment.

The benchmarking of PCS at 3 months (12 weeks) reflects that initial symptoms largely resolve within that period. More reliable data can be derived from a meta-analysis of studies comprising 250,000 hospitalized individuals and 850,000 nonhospitalized individuals from 22 European and non-European Anglo-Saxon countries from March 2020 to January 2022 based on the WHO's definition of the post-Covid case (European Centre for Disease Prevention and Control, 2022). This analysis estimated that in 2020 and 202 16.2% suffered from PCS (95% Uncertainty Interval, UI, 2.4–13.3%). Further, they report ongoing self-reported cognitive problems 3 months after the initial infection, after adjusting for specific premorbid conditions among an estimated 2.2% (95% UI, 0.3–7.6%) of patients with COVID-19 (European Centre for Disease Prevention and Control, 2022). Notably, this analysis examined only the prevalence of PCS in patients with symptomatic COVID-19 courses and excluded those patients who were initially asymptomatic but developed symptoms later on as well as all non-English language publications.

Looking further along the temporal line, at 12–16 weeks, estimates of cognitive outcomes continue to be heterogeneous, which also reflects the wide range of results found in health claims-based or meta-analytic research of PCS in general (European Centre for Disease Prevention and Control, 2022; Lefrancq et al., 2021; Roessler et al., 2022). Findings depended on numerous social or medical factors but, just as importantly, on the availability of follow-up examinations, cognitive instruments used, and types of reporting (health claims require official diagnoses of cognitive impairment).

To date, cognitive follow-up studies from 6 to 12 months have mostly examined hospitalized samples. About half of the studies reviewed indicated using a cognitive screening combined with more in-depth neuropsychological testing. However, more extensive cognitive testing in most of these studies revealed deficits in memory, executive function, or attention that could not be identified using a cognitive screening. A Danish study hospital-based prospective study (IMPACT-COVID) conducted a 12-month examination in a cohort of 25 patients from the first wave of COVID-19 cases (down from the initial 83 patients at baseline). Out of this sample, 14 patients (56 %) fulfilled the criterion for clinically relevant cognitive impairment based on norm values. The largest impairments were working memory, verbal learning, fluency, and psychomotor speed. A meta-analysis of PCS at different follow-up periods indicated that the heterogeneity index I^2 across all time intervals was still too high to discern the prevalence of cognitive impairments reliably (Alkodaymi et al., 2022).

Despite growing numbers of studies beyond 12 months post-COVID-19, there is still much uncertainty about long-term trajectories and precipitating factors. Neuropsychology, as both a practical and applied profession, is well suited to assist in identifying and treating cognitive disorders among patients. Neuropsychologists are also attuned to the difficult issues of COVID-19 causality and the cycle of cause and effect across symptoms. Hence, a meaningful neuropsychological assessment may greatly assist in both understanding PCS as well as helping to direct individual treatment pathways (cf. Hasting et al., 2023).

Possible Risk Factors for PCS

An important task of neuropsychological assessment is the identification of subgroups of recovered individuals with long-term sequelae (Han et al., 2022; Sanchez-Ramirez et al., 2021). This section describes a variety of such subgroups at risk.

Age

An analysis of electronic health records in a network of countries from the East and West (TriNetX Analytics Network) evaluated 2-year risk trajectories after COVID-19 compared to other respiratory infections (Taquet et al., 2022). They derived a propensity score of 1.36 for the cognitive deficit at 6 months, which persisted 2 years after the initial SARS-CoV-2 infection (as did the risk of dementia, epilepsy, and seizures). The risk of long-term cognitive deficit was greater among older adults (1.41) than younger adults (1.35) and even greater among children (1.22).

Taquet et al. (2022) suggested that the incidence of COVID-19-related cognitive deficits among children was 3.92 %, though this did not differ from other respiratory infections (5.04 %). Recent observations show that even younger individuals, who may not show obvious symptoms of illness, may exhibit a range of subtle emotional, motivational, and cognitive impairments that may escape the clinical impression of the diagnostician. New German-language studies show that younger cohorts appear more likely to have more subtle cognitive problems in complex attention and language than memory (Schild et al., 2022; Widmann et al., 2023). In comparison, few reports have addressed adolescents or children with long-term cognitive deficits (Colvin et al., 2022; Della Corte et al., 2022; Ludvigsson, 2020; Zimmermann et al., 2021). A recent systematic review of 22 studies from 12 European or Anglo-Saxon countries found the pooled risk differences between those with a SARS-CoV-2 infection and negative controls for cognitive difficulties was 3 % (95 %, CI 1.4; Behnood et al., 2022); this specific comparison contained five studies and the heterogeneity index I^2 was 33.02 %, suggesting that results were relatively homogeneous. By contrast, other symptoms, such as cough or abdominal pain, were more reliable than comparisons of headache, fatigue, or myalgia, whose heterogeneity indexes indicated poor reliability. No increased cough or abdominal pain risk was found compared to controls in these analyses (Behnood et al., 2022).

However, among adults, the incidence of COVID-19-related cognitive deficit over 2 years was found to be 6.39 % compared to 5.5 % for other respiratory infections. For older patients, the incidence of COVID-19-related cognitive deficit was 15.44 % compared to 12.31 % for other respiratory infections. The rates of dementia in older patients after COVID-19 were also higher (4.46 %) compared to 3.34 % for other respiratory illnesses). Importantly, the hazard ratios for cognitive deficits and dementia did not differ for patients diagnosed with COVID-19 after the emergence of the alpha, delta, or omicron variants of COVID-19 (Taquet et al., 2022). Older patients are likely more vulnerable to memory problems or physical impairments.

Etiopathology

The prevalence of PCS has been linked to the severity of acute SARS-CoV-2 infection, although the exact correlation is still under investigation (Peper & Müller, 2021; Peper & Schott, 2021). Research has shown that even patients with initially asymptomatic or mild COVID-19 courses can experience PCS. In the low-prevalence range, 13.3 % of test-positive study participants experience symptoms lasting ≥28 days, 4.5 % ≥8 weeks, and 2.3 % ≥12 weeks (Schott & Peper, 2021). The prevalence of PCS is greatest among hospitalized patients, particularly those in the intensive care unit (ICU), where they are at risk of developing cognitive disorders (Voruz et al., 2022). Patients with intensive care stays, long-term or chronic hospitalizations, or long bed-ridden convalescence may also experience

PCS. However, the impairments in these cases could be because of their particular experiences rather than the after-effects of the disease directly.

We also frequently hear of symptoms such as fatigue, difficulty concentrating, shortness of breath, and impaired physical and mental performance. In many patients, a spontaneous or significant reduction of symptoms may occur during the course of the disease. Current data from Great Britain show that the probability of developing PCS after infection with the Omicron variant is only about half as high as after infection with the Delta variant (4.5% vs. 10.8%; Pilotto et al., 2021).

Reduced motivation is one of the core symptoms of fatigue after COVID-19, but the underlying mechanisms are not well understood and may be multifaceted (Peper & Schott, 2021; Premraj et al., 2022). Motivational dysregulation and changes in the dopaminergic reward system may play a role in the postacute recovery phase from COVID-19. The level of effort exerted is also critical, as the willingness to exert effort may decrease after a viral disease. Motivation and effort may both be affected by changes in the activity or resilience of certain brain systems. So far, research on the relationship between a SARS-CoV-2 infection and motivation is limited. For the most part, research has targeted behavioral adaption relating to the pandemic restrictions that led to motivation change (Dresp-Langley & Hutt, 2022; Kumaresan et al., 2022). This limited scope is somewhat surprising as a meta-analysis found reduced motivation to be one of the core symptoms of fatigue occurring most frequently after a SARS-CoV-2 infection (Premraj et al., 2022). Currently, the underlying mechanisms of fatigue syndrome are not well understood. A growing consensus is that the mechanisms are multifaceted, including, among other factors, inflammatory processes, maladaptive behavioral changes, treatment processes, and biological mechanisms associated with age and sex (Peper & Schott, 2021).

Comorbidities and Genetic Predispositions

The development of PCS has been linked to various patient populations and pre-existing conditions. Patients with prior histories of multiple sclerosis, cancer, vascular or pulmonological conditions, chronic fatigue syndrome, and psychiatric burden may have an increased risk of developing PCS. Comorbidities related to the COVID-19 course, such as fatigue, headache/pain, sleep disorders, breathing problems, cardiac complications, and psychiatric burdens, can complicate the neuropsychological assessment of PCS (Lier et al., 2022). Moreover, genetic predisposition is an additional factor linked to an increased risk of PCS. The presence of the alleles APOE 3 and 4 is believed to raise the risk of cognitive problems and PCS, which is known to raise the risk of the development of Alzheimer's disease (Monsell et al., 2015). Therefore, it is important to consider both patient history and genetic predispositions when assessing the risk of PCS.

Neuropsychological Assessment and Treatment Implications

Assessment

The newly revised German National Guidelines for Post-COVID-19 Syndrome (Koczulla et al., 2022) now include a chapter dedicated to neuropsychology, with guidance for a two-step approach to diagnostic work and the inclusion of scales for fatigue, anxiety, depression, sleep, and PTSD.

Various assessment tools have been used in the literature to screen for cognitive impairment in recovered COVID-19 patients, including the MoCA (Montreal Cognitive Assessment, Mini-Mental Status Examination (MMSE), Frontal Assessment Battery (FAB), and the Brief Repeatable Battery of Neuropsychological Tests (BRB-NT), all of which are also available in Germany (Evans et al., 2021; Ferrucci et al., 2021; Frontera et al., 2022; Rass et al., 2021). However, it is becoming increasingly apparent that cognitive screenings that can encapsulate the often-milder cognitive disorders among younger cohorts are lacking.

Neuropsychological assessment should determine the type and cause of limited performance and rule out other potential causes of cognitive difficulties requiring further testing. Even patients with asymptomatic or mild courses of COVID-19 may have significant cognitive deficits that negatively affect their daily functioning.

The standard of clinical assessment for a long time was multimodal analysis using the triple response measurement (TRM) concept (Seidenstücker & Baumann, 1987). For COVID-19 research, assessment should include complaints and perceived resilience (questionnaire data), altered behavioral activity (test scores, sleep, etc.), but also psychophysiological impairments (autonomic, immunological, etc.). The question of "invisible" impairments or "hidden" features in PCS motivates the field of neuropsychology to account for the complexity of mental functioning (Cysique et al., 2021; Peper & Schott, 2021).

In their recent study, Schild et al. (2023) highlighted the challenges encountered in assessing cognitive deficits in patients with PCS necessitating a comprehensive and individualized analysis of both subjective complaints and objective impairment as well as their discrepancies. However, some sequelae of intensive care treatment may still escape these testing approaches, and certain persistent problems cannot be detected without psychophysiological methods. This suggests encouraging the use of additional neuropsychophysiological methods in specific patient groups.

New international guidance for PCS by a special interest group of the International Neuropsychology Society suggests using self-report questionnaires adapted from the Patient Assessment of Own Functioning Inventory (PAOFI) as part of a general diagnostic work-up. These questionnaires include items regarding intellectual, psychological, and general health as well as a disability scale, with the English language version being made freely available (Cysique et al., 2021). However, a German language version does not yet exist. This questionnaire includes a 10-item Memory Scale, a 10-item Language and Communication Scale, two items regarding the use of hands, four items pertaining to perception, and nine items addressing higher-level cognitive functions based on a 6-point Likert scale. Alternative self-report instruments, such as the Cognitive Failures Questionnaire (CFQ) or other patient-based subjective perceptions of cognitive function, such as the A-B Neuropsychological Assessment Schedule (AB-NAS), have been recommended. For a comprehensive overview of possible approaches and tools used in neuropsychological procedures, see Peper and Schott (2021). The psychiatric and somatic aspects of neuropsychological rehabilitation should be considered, including appropriate psychological burden and validation scales. Forensic examinations have also been conducted in cases of occupational disability. Still, any assessment in the legal context requires the neuropsychologist to take specific national guidelines into account (e.g., Aschenbrenner et al., 2023, in prep).

Textbox 1 describes the current guideline on assessing legal cases of occupational disability or liability related to COVID-19 disease and PCS. It refers specifically to the documentation of acute brain dysfunction during acute COVID-19. Ongoing and future studies of the long-term effects of COVID-19 disease are expected to reveal whether and to what extent cognitive impairment may occur because of mechanisms other than acute brain dysfunction during COVID-19.

Overall, a multilevel assessment concept considers both directly observable and indirectly detectable characteristics (e.g., Wilhelm & Fahrenberg, 2018). Therefore, the question of how to design assessment strategies to optimize detecting subtle behavioral and autonomic changes is central to the field. In addition, demographic and medical inventories, including smell and taste questionnaires and computerized testing systems, have been recommended. Furthermore, this international guidance for PCS suggests assessing psychosocial and general health for depression, anxiety, fatigue, PTSD, daily activities, and substance abuse.

Limits to Attentional Capacity

Based on empirical research, approximately 25 % to 30 % of patients may continue to exhibit abnormal attention performance 6–12 months following COVID-19 infection, regardless of the severity of the illness. The Chapter and Supplement on the neuropsychological assessment of PCS in the German Guideline offer practical advice for addressing issues of limited sustained attention or high levels of fatigue in patients (Koczulla et al., 2022). Examinations may need to be shorter, distributed over multiple sessions, or include pauses to accommodate these issues. Employing a short attentional task at the beginning and end of a cognitive assessment testing session could yield information about cognitive fatigue. Neurocognitive results because of fatigue are in and of themselves a finding, which may be interpreted as such.

Interpretation of Results

Despite completing a more extensive neuropsychological assessment, some patients report the inability to handle prolonged attention-demanding tasks in their daily lives. Neuropsychological assessment does not involve the same level of sustained attention required for tasks that stretch over an extended period. Compared to single-cognitive domain tasks in assessment, real-life situations often involve multiple cognitive functions and may require the ability to shift between different kinds of tasks and stimuli. Therefore, planning ability or sustained attention tasks may have higher ecological validity. Further, when interpreting neurocognitive findings, it is important to integrate results from the cognitive assessment, particularly complex attention, as well as those results from standardized evaluations of fatigue or postexertional malaise (Mirfazeli et al., 2022), from self-reports of daily functioning, as listed in the German National Guideline (Koczulla et al., 2022).

Rehabilitation

Current treatment for cognitive deficits is based on symptom management rather than targeting a specific etiology. In rehabilitation, neuropsychological constructs provide important causal starting points for setting treatment goals. Numerous rehabilitation guidelines exist regarding neuropsychological intervention: For optimized rehabilitation in the neuropsychological domain, important starting points arise from the recommendations of the International Neuropsychological Society (INS)-Task Force (Cysique et al., 2021) as well as from national guidelines (Koczulla et al., 2022) and those issued by German-speaking neuropsychologists (GNP, www.gnp.de). Maurer-Karattup and Rost (2023) emphasize the important role of neuropsychology in the early clinical treatment phase of patients with a critical illness. Hasting et al. (2023) propose a compelling interdisciplinary treatment approach for the postacute phase which also warrants further development.

Recovered individuals could presumably be better classified and assigned to different treatment schedules if the subtle and clinically unobservable alterations were considered to a greater degree. We proposed a preliminary classification that considers neuropsychological disorders to achieve this objective and might include the following categories: (a) individuals with a history of verified COVID-19-related neurobiological alterations associated with cognitive dysfunction; (b) individuals with probable neurobiological involvement and verified cognitive dysfunction; (c) individuals with a verified SARS-CoV-2 infection and no detectable neurobiological involvement and subjectively experienced impairments; (d) individuals without a history of SARS-CoV-2 infection who subjectively experience impairment. Thus, to predict somatic, cognitive, and emotional sequelae, we need to specifically scrutinize the relevant combinations of biomedical findings, neuropsychological outcomes, and subjective complaints. While approaches to predicting and preventing critical courses following COVID-19-associated disease are still pending, there are some promising suggestions of approaches for other cerebral diseases (e.g., traumatic brain injury; Caplain et al., 2017). We need new disease models that consider both psychosocial influences and neurobiological mechanisms. Instead of validating questionable descriptive syndromes, we should identify the neurobiological, neuropsychological, and psychosocial dimensions of COVID-19-associated disorders during their development. The Research Domain Criteria Framework (RDoC; National Institute of Mental Health 17 May 2022) might help guide such an assessment, at least in the field of research. It recommends considering self-report and behavior in the context of multiple levels of information to better capture the basic dimensions of impaired mental functioning. These dimensions stem from basic psychobiological systems. We might better understand the nature of disorders in light of the brain systems involved. Although RDoC implies moving away from the symptom orientation of diagnostic categories, it does not intend to replace the traditional category systems of the ICD or ICF. Rather, it suggests a stronger foundation based on the neurobiological substrate and related neuropsychological functioning.

Perspectives

We need an efficient allocation of neuropsychological healthcare resources because of the increasing burden of PCS and its impact on cognitive functioning in affected patients. The efficient allocation of healthcare resources is important to ensure patients receive timely and appropriate care, and to minimize the strain on the healthcare system. A recent approach to achieving this goal is outlined in a practice guidance paper (Considine et al., 2023) and is presently in its pilot phase in multiple clinical settings in the United States (personal communication, Considine, 19 March 2023). The attending physician or care-extension provider uses a series of cognition, health behavior, and health-related quality-of-life screening measures at first contact with the patients. In that treatment framework, an initial appointment with a neuropsychologist is arranged after clinically managing all other factors that could cause neurological disorders, such as sleep problems, psychological stress, pain, and fatigue, and after determining that further neuropsychological assessment is necessary.

The different contributions of neuropsychology are essential depending on the stage. During hospitalization, acute care, or ICU stays – and after recovery from disease – identifying patients at risk is worthwhile for several reasons: This may help determine the extent of cognitive impairment and provide early interventions to prevent long-term consequences. However, restrictions may result from the fact that the mental impact of PCS may not become apparent until after recovery. In brief, it is crucial to allocate healthcare resources efficiently to tackle the cognitive effects of PCS and ensure that patients get suitable care. The initial step should involve a comprehensive intake interview that assesses potential sources of cognitive disorders, such as pre-existing conditions, comorbidities, known genetic predispositions, and any relevant factors like sleep disturbance, pain, fatigue, and emotional health.

The future of neuropsychological evaluation and rehabilitation of PCS looks promising with the integration of technology in app-based assessments and self-tracking. For example, the English-language app “Visible” (https://www.makevisible.com) and the German-language app “Neotiv GmbH App” now being employed in a citizen-science initiative of the German Centre for Neurodegenerative Diseases (www.exploring-memory.org) help individuals track their cognitive health and generate new datasets for exploration of long-term outcomes. These apps not only allow for more convenient and accessible assessments but also incorporate a citizen-science aspect while embracing the advancements in e-health and telehealth. The potential for yearly cognitive health checks is presently being considered to monitor and address any changes in cognitive functioning post-Covid-19 infection. Additionally, the RDOC framework may be expanded to provide a comprehensive evaluation of individuals affected by PCS.

Conclusions

COVID-19-associated diseases are frequently associated with subtle impairments and complaints that are difficult to validate and that place high demands on all experts and disciplines involved. Meta-analyses of these impairments are still rare, and the quality of available results is not always satisfactory. Current results suggest long-term psychological impairments such as reduced resilience, increased fatigability, attention deficits, and memory problems can occur in patients with initially severe COVID-19 disease but also with initially asymptomatic, mild, or moderate courses.

There is agreement that subjective impairments should be taken seriously, and that changes in experience and behavior not apparent to the clinician should be examined, evaluated, and documented. Within the framework of PCS research, neuropsychological assessment can contribute to the detection of concealed functional impairment. It also promotes the elaboration of new classification models and instruments to support decision-making with the aim of early detection of unfavorable disease courses and to identify the most successful or ineffective treatment options. For this purpose, we must adapt assessment strategies depending on the rehabilitation phase, research question, and the affected individual's resilience, age, and performance limitations.

Previous descriptive classification systems may have the disadvantage of failing to represent and explain the specific mechanisms leading to different PCS disorders. Identifying causally relevant developmental pathways to PCS based on psychological, social, and neurocognitive mechanisms, for example, along the lines of the well-known RDoC recommendations, shows great promise. This information presents an opportunity to develop screening tools to accurately predict and prevent adverse disease outcomes, enhance diagnostic processes, and design more appropriate rehabilitation programs for COVID-19-associated disorders. We hope these findings can inform the development of strategies to mitigate the impact of the COVID-19 disease on global public health.

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