Archives of Clinical Neuropsychology, 2025, **00**, 1–18
https://doi.org/10.1093/arclin/acaf064
Original Empirical Article

Profiles of Individuals With Long COVID Reporting Persistent Cognitive Complaints

Carmen Cabello Fernandez[1], Vincent Didone[1], Hichem Slama[2,3], Gilles Dupuis[4], Patrick Fery[2], Gaël Delrue[5], Alexia Lesoinne[1], Fabienne Collette[1,6,†], Sylvie Willems[1,*,†]

[1]Psychology and Cognitive Neuroscience Research Unit (PsyNCog), University of Liège, Liège, Belgium
[2]Department of Neuropsychology and Speech Therapy, Erasme Hospital, ULB, Brussels, Belgium
[3]UR2NF-Neuropsychology and Functional Neuroimaging Research Group at CRCN-Research Centre in Cognitive Neurosciences, ULB, Brussels, Belgium
[4]Department of Psychology, UQAM, Montreal, Québec, Canada
[5]Department of Neurology, CHU of Liège Sart Tilman, Liège, Belgium
[6]GIGA-CRC Human Imaging (GIGA-CRC), University of Liège, Liège, Belgium

*Corresponding author at: Psychology and Cognitive Neuroscience Research Unit (PsyNCog), University of Liège, Place des Orateurs 1, Bât. B33 (Sart Tilman, Quartier Agora), Liège 4000, Belgium. Tel.: +32-4-366-23-74. *E-mail address*: sylvie.willems@uliege.be (S. Willems).

†Fabienne Collette and Sylvie Willems contributed equally as co-last author.

ABSTRACT

Objective: A subset of COVID-19 patients continues to experience cognitive difficulties 24 months post-infection. The factors driving these symptoms are complex, and the underlying pathophysiology is unclear. This study aimed to characterize individuals with Long COVID reporting cognitive issues.

Method: One hundred twenty-three patients underwent a comprehensive neuropsychological evaluation resulting from the baseline of an RCT study (COVCOG), along with questionnaires assessing cognitive complaints, fatigue, sleep difficulties, quality of life, psychological distress, and impact on daily activities. Latent Profile Analyses on cognitive scores were conducted to investigate the presence of different patient profiles. Robust analyses of variance and Pearson's chi-square examined the profiles' effects on demographic variables and questionnaire scores.

Results: Patients had had predominantly mild to moderate infections (87.8%) and were assessed an average of 20.9 (±8.6) months post-infection. Neuropsychological assessment showed cognitive impairment in at least one domain in 72% of the patients, mainly in attention and executive functions. Over 80% reported sleep problems and fatigue, 97% concentration problems, and some 80% memory and word-finding problems. The self-report questionnaires also revealed significant complaints. Three profiles emerged (all *ps* < .001). Profiles 1 and 2 both experienced widespread cognitive issues; Profile 1 patients expressed more complaints about cognitive functioning and daily fatigue (all *ps* < .045). Patients in Profile 3 were more frequently men (all *ps* < .049) with a specific impairment of verbal long-term memory and fewer complaints.

Conclusions: The study identifies three different profiles of individuals with Long COVID, highlighting the need for comprehensive evaluations including neuropsychological, psychological, somatic, and functional aspects to implement effective, tailored interventions.
Clinicaltrials.gov: NCT05167266.

Keywords: Infectious diseases; clinical trials; everyday functioning; quality of life

INTRODUCTION

Although the global health emergency caused by the Coronavirus disease-19 (COVID-19) pandemic officially ended on May 11, 2023, the long-term effects of COVID-19 continue to represent a major public health concern (Song et al., 2024). Long COVID is the label most commonly used to describe these long-term effects (Gheorghita et al., 2024). It is defined by symptoms that begin within 3 months of an infection and persist for more than 2 months without being explained by any other diagnosis (WHO, 2021).

Among the difficulties frequently cited are problems affecting cognition. According to a systematic review, fatigue/weakness (28%/95%), memory (19%), and concentration (18%) problems are the most frequently reported issues, all types

Received: April 15, 2025. **Revised:** June 14, 2025. **Accepted:** June 17, 2025

of symptoms considered, at 12 months after infection or hospitalization (Han et al., 2022). In a study of hospitalized patients, at least 30% of the patients still reported symptoms related to cognition, sensorimotor function, and mental fatigue that affected their everyday life 24 months post-infection, even when improvements were observed (Wahlgren et al., 2023). The same observation was made in patients who were not hospitalized at the time of infection (Fernandez-de-las-Peñas et al., 2024). The complaints observed were not just subjective: objective cognitive tests showed that Long COVID participants performed less well than non-COVID participants, even more than a year after the infection (Bland et al., 2024).

Although subjective cognitive complaints and objective performance deficits are observed in individuals with Long COVID, the correlation between the two is inconsistent. In some cases, a correlation is observed (García-Sánchez et al., 2022), whereas in others, these two measures are not associated (Bland et al., 2024; Gouraud et al., 2021). In addition, Schild and colleagues (2023) observed that more patients reported subjective cognitive complaints than impairments backed up by cognitive assessment. Several explanations have been proposed for this discrepancy. First, a high level of cognitive functioning before the disease may allow some patients to remain within the normal range on objective tasks despite a real decline expressed via subjective measures. Another possible explanation is that neuropsychological tests may lack the sensitivity to detect milder cognitive difficulties, even when they have a genuine impact on daily life. Alternatively, other health problems or psychiatric considerations may affect the importance of cognitive complaints. For example, in a 6-month follow-up study, Pihlaja and colleagues (2023) observed an association between subjective cognitive complaints and depressive and PTSD symptoms, whereas cognitive performance was only weakly correlated with scores on the self-report questionnaire. Furthermore, 12 months after infection, fatigue and stress may also explain a significant proportion of cognitive complaints (Bland et al., 2024). These results suggest that a complex interplay of factors with different etiologies may explain cognitive complaints and cognitive difficulties in Long COVID and that their influence may evolve over time. Indeed, while the pathogenesis of Long COVID is still under discussion, the scientific community agrees that there is a combined effect of multiple pathological mechanisms including direct viral infection of the central nervous system (CNS) (Politi et al., 2020), hypoxia (Dondaine et al., 2022), hyperinflammation (Najjar et al., 2020), vascular lesions (Wu et al., 2024), mitochondrial dysfunction (Molnar et al., 2024), neuropsychiatric comorbidities (Poletti et al., 2022), and dysfunction of the autonomic nervous system (Dani et al., 2021) (for reviews, see Diar Bakerly et al., 2024; Castanares-Zapatero et al., 2022).

In that context, three main hypotheses have been proposed to explain cognitive difficulties and complaints related to Long COVID: (a) a direct effect of the virus on neuronal activity; (b) maladaptive neuroinflammatory response; and (c) influence of a neuropsychiatric condition. From the moment COVID-19 appeared, it was suggested that the virus might enter the brain via the olfactory pathway (Politi et al., 2020), which would explain neurological symptoms such as altered smell and taste perception. Once in the olfactory bulb, the virus can reach the hypothalamus and the cortex by trans-synaptic traffic (Veleri, 2022). However, in some individuals, SARS-CoV-2 viruses have been detected in regions with no direct connection to the olfactory mucosa, such as the cerebellum, which suggests that alternative mechanisms or routes of viral entry into the CNS may exist (Meinhardt et al., 2021). It has also been proposed that fatigue and neurocognitive dysfunction are the result of a maladaptive inflammatory response, triggering high levels of cytokine production (interleukins and tumor necrosis factor (TNF)) (Schultheiß et al., 2022). This "cytokine storm" disrupts normal vascular function (e.g., increased permeability, hypercoagulability, or impaired blood flow) and can weaken defenses against the SARS-CoV-2 virus in multiple organs such as the CNS (Veleri, 2022). On the other hand, a cognitive impairment accompanied by CNS inflammation might result either from the inflammation itself or from another underlying pathophysiology that causes both issues (Diar Bakerly et al., 2024). The causal link is still uncertain. Finally, a neuropsychiatric hypothesis regarding the origin of the cognitive impairment is also under discussion. Higher amounts of circulating biomarkers of inflammation are observed in mood disorders and could underlie the pathogenetic mechanisms for depressive psychopathology, among other psychiatric disorders (Gibney & Drexhage, 2013; Poletti et al., 2021). Depression, in turn, also affects neurocognitive performance (McDermott & Ebmeier, 2009). In Long COVID, there is indeed a proven presence of anxio-depressive symptomatology that affects cognitive performance (Poletti et al., 2022) and could therefore explain the post-COVID problems. However, scores on depression and anxiety questionnaires do not systematically correlate with cognitive performance, which could suggest that the cognitive disorder observed in individuals with Long COVID is not exclusively secondary to the psychological aspects (Delgado-Alonso et al., 2022).

Cognitive difficulties may therefore result from the interaction of multiple factors, and it is therefore highly probable that different patient profiles exist. In a prospective cohort study of 1,837 patients hospitalized for COVID-19, two different associations of acute blood biomarker profiles and cognitive outcomes obtained with a global measure of cognition at 6 and 12 months later were found: high fibrinogen protein levels in comparison to C-reactive protein (CRP) levels were associated with objective and subjective cognitive deficits, while raised D-dimer protein levels relative to CRP levels were associated with subjective but not objective cognitive deficits (Taquet et al., 2023). These results suggest the existence of at least two types of individuals with Long COVID as early as the acute phase. The presence of distinct profiles was also observed with a more detailed assessment of cognitive functions. For example, a comparison between patients with and without anosognosia for memory dysfunction (and anosmia) 6–9 months post-infection showed that the anosognosic group was characterized by greater memory impairments; fewer self-reported psychiatric symptoms of depression, anxiety, and stress; better self-reported quality of life; and decreased functional connectivity between brain regions, which could affect a range of cognitive and motor processes (Voruz et al., 2022). Studies suggest that there is a link between cytokines (more specifically TNFα) released during the acute phase of infection and anosognosia for memory deficits, probably related to changes in functional hippocampal, temporal pole, accumbens nucleus, amygdala, and cerebellum functional

connectivity (Nuber-Champier et al., 2023, 2024). Finally, while improved performance 1-year post-infection was observed in most patients, some of them had neuropsychological deficits that persisted or even increased, which also suggests that several different recovery trajectories exist (Voruz et al., 2024).

In summary, cognitive complaints and cognitive impairments are observed over the long term after COVID-19 but their correlations are not consistent across studies. The literature also seems to reveal the existence of different patient profiles for cognitive performance, but these studies did not discuss whether complaints are associated with cognitive impairments in a profile-specific way. Identifying different patient profiles based on a complete phenotyping including both subjective and objective measures of cognitive functioning is crucial for the development of specific rehabilitation programs designed to facilitate recovery in individuals with Long COVID. In this context, the research questions in this study were:

(1) Are there different patient profiles based on their cognitive performances?
(2) Is each profile associated with differing amounts and types of cognitive complaints?
(3) Is each profile associated with different specific difficulties in daily life (i.e., self-evaluated fatigue, sleep difficulties, quality of life, psychological distress, and work and activity impairment)?

To explore these questions, 123 patients were assessed at more than 20 months post-infection with a battery of cognitive tests covering memory, attention, executive function and language domains, quality of life, psychological distress, and discomfort with work and activities. A semi-structured interview also targeted complaints associated with Long COVID.

MATERIALS AND METHODS

General Procedure and Ethics

The data included results from the baseline neuropsychological assessment of 123 patients enrolled in the COV-COG multicenter randomized clinical trial (Clinicaltrials.gov: NCT05167266) conducted in Belgium. The protocol was published prior to data collection (Willems et al., 2023). Patient's enrollment and visits took place between March 2022 and August 2023. The study was approved by the Hospital-Faculty Ethics Committee of CHU-Liège (Belgium) under the reference number: 2021/432. All of the participants gave written informed consent.

Each participant underwent two evaluation sessions (90 min each) including a clinical interview, a neuropsychological assessment, and an assessment of psychological and somatic symptoms using a variety of questionnaires. Cognitive assessment was carried out by neuropsychologists, and normative data for the French-speaking population were used. Participants completed all questionnaires through Castor Electronic Data Capture (https://www.castoredc.com/) except for the Quality of Life Systematic Inventory (completed at http://qualitedevie.lepsyq.ca/fr).

Patients

Most patients were recruited through advertisements (more than 60%) and via their usual care pathways (more than 35%). The inclusion criteria were as follows: being aged between 18 and 70; medically stable; had had infection with SARS-CoV-2 at least 3 months before inclusion in the study confirmed by a polymerase chain reaction test (PCR test), antigen test, or by the general practitioner or specialist following the patient at the time of the infection; report sufficiently good physical condition to attend the appointments; report no major hearing or vision disorders; and expressed cognitive complaints (that place the person in the top 20% of dissatisfied functioning on the BRIEF-A or MMQ questionnaires). Participants were excluded if they had any pre-existing neurological, cognitive, or psychiatric disorders; pre-existing cognitive impairment; acute brain injury or acute encephalopathy from another aetiology than COVID-19; documented pre-existing history of psychiatric illness; open-heart cardiac surgery or cardiac arrest during the last 6 months; current hospitalization; or current revalidation care for cognitive difficulties. A structured interview was conducted to verify the World Health Organization (WHO) criteria for Long COVID and the inclusion and exclusion criteria.

Clinical Interview

At the first visit, a semi-structured interview was conducted to collect information on cognitive complaints and other problems since infection, medical treatments, premorbidities, history of COVID infection (number of infections, date, and severity), employment status, and years of education.

The criteria of the National Institutes of Health guideline (COVID-19 Treatment Guidelines Panel, n.d.) were used to characterize the severity of the acute infection, considering all individuals who tested positive for SARS-CoV-2 but had no symptoms consistent with COVID-19 as having an asymptomatic infection; those who had any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but did not have shortness of breath, dyspnea, or abnormal chest imaging, as having a mild illness; those who showed evidence of lower respiratory disease during clinical assessment or imaging and had an oxygen saturation measured by pulse oximetry (SpO2) $\geq$94% on room air at sea level, as having a moderate illness; those who had an SpO2 $<$ 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) $<$300 mm Hg, a respiratory rate $>$ 30 breaths/min, or lung infiltrates $>$50%, as having a severe illness; and those who had respiratory failure, septic shock, or multiple organ dysfunction, as having a critical illness.

Cognitive Complaints

Executive and attentional functioning complaints were assessed with the Behavior Rating Inventory of Executive Function (BRIEF-A) questionnaire that has two indices (Behavioral Regulation, BRI; Metacognition, MI) and an overall score (Global Executive Composite, GEC) (Waid-Ebbs et al., 2012). Higher scores indicate greater complaints.

Memory functioning complaints were assessed with the Multifactorial Memory Questionnaire (MMQ), which measures three

aspects: memory abilities (Satisfaction), frequency of forgetfulness in different situations (Ability), and strategies used in everyday life to cope with memory difficulties (Strategies) (Troyer & Rich, 2002). Higher scores indicate better self-reported memory functioning.

The BRIEF-A and MMQ were administered twice within a 2-week period to reduce the impact of occasional fluctuations in problems. The mean of the two scores was used for analyses. Scores below the second percentile (P2) were considered as pathological and clearly below the statistical threshold (Crawford & Garthwaite, 2005; Fery & Claes, 2025; Guilmette et al., 2020).

Psychological and Somatic Complaints

Fatigue and sleep

Fatigue level was examined with the 21-item Modified Fatigue Impact Scale (MFIS-21; Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). The MFIS-21 evaluates the impact of fatigue on physical, cognitive, and psychosocial functioning. Higher scores indicate that fatigue has a greater impact on a patient's activities. Previous studies had established that a total score of 38 can be considered a threshold for discriminating between fatigued and non-fatigued individuals (Kos et al., 2005; Téllez et al., 2005).

Sleep quality was assessed with the Pittsburgh Sleep Quality Inventory (PSQI; Buysse et al., 1989). Higher scores denote worse quality of sleep, and a global score of over 5 distinguishes between good and poor sleepers.

Psychological distress and quality of life

The Outcome Questionnaire 45 (OQ-45) (Lambert et al., 1996) was used to measure changes in psychological distress. This questionnaire has three subscales (symptom distress, interpersonal relations, and social role) and a global score. Cut-off scores of 63 (global score), 36 (symptom distress score), 15 (interpersonal relations score), and 12 (social role score) were used to identify clinically significant symptoms. Higher scores indicate greater distress.

The status of quality of life was assessed with the Quality of Life Systematic Inventory (QLSI; Duquette et al., 1994). Participants self-rated their current situation and their desired situation for 34 life domains. The global score corresponds to the mean of the gaps between current and desired situations for all domains. The score was then compared with a normative population of 580 healthy individuals (mean: 3.78; standard deviation [*SD*]: 4.03). Higher scores indicate poorer quality of life. According to the authors, global scores at the 75th percentile and above should be considered problematic (scores >5.56).

Work and activity

Impairments and reduction in work and activities due to persistent Long COVID symptoms were assessed with the Work Productivity and Activity Impairment (WPAI) instrument (Reilly et al., 1993). Work Productivity and Activity Impairment outcomes are expressed as percentages, with higher values indicating greater impairment and less productivity.

Neuropsychological Assessment

An extensive battery of tests was administered (see Table 1) to assess verbal and visuo-spatial episodic memory, selective attention, divided attention, and executive functioning (measures of inhibition, flexibility, working memory, phonetic, and semantic fluency). An estimation of processing speed and attentional fluctuation was obtained from the medians and standard deviation scores in the attentional and executive tasks, respectively, with scores <P2 considered as pathological (Crawford & Garthwaite, 2005; Fery & Claes, 2025; Guilmette et al., 2020).

Global cognitive performance was measured with the Montreal Cognitive Assessment (MoCA), with a global score below 26 considered as pathological (Nasreddine et al., 2005).

Statistical Analysis

Data analyses consisted of (a) descriptive analysis, (b) exploratory factor analysis to reduce the large number of relevant measures from cognitive assessment, (c) latent profile analysis on the outcomes of the cognitive assessment, (d) robust analysis of variance and Pearson's chi-square tests to examine patient profiles, and (e) Pearson correlation coefficients between subjective and objective measures of cognitive difficulties.

Given the large number of relevant measures from the cognitive assessment, a pre-processing step consisted of reducing the number of variables to enter in the analyses. First, indices based on the Inverse Efficiency Score (IES; Vandierendonck, 2018) were calculated for the computerized tasks assessing selective visual and auditory attention, divided attention, flexibility, and updating processes. This score integrates speed (mean reaction time, RT) and accuracy (proportion of errors, PE) in a single variable as defined by the formula: $IES = RT/(1 - PE)$. Next, bivariate correlations were conducted on the whole data set to identify pairs of scores with correlations greater than 0.8; one member of each pair was removed from further analysis, based on clinical relevance. Exploratory Factor Analyses (EFAs) were then performed as the final step to reduce the number of variables to enter in the statistical analyses of interest. The appropriateness of the data for EFA was checked using the Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy (overall KMO values ≥ 0.70 are desired) and Bartlett's test of sphericity. Cognitive scores were expressed as *Z*-scores calculated by comparison with matched (age, educational level) normative data, and those that saturated together were grouped into factors according to associations generally found in the literature. Variables that did not saturate with factors were retained as single variables.

The statistical analyses of interest were performed on the factors and single variables that emerged from the EFA. Latent Profile Analyses (LPAs) were carried out to determine whether patient profiles existed based on their cognitive performances. A list of the variables included in EFAs and LPAs can be found in Supplemental Table 1. Latent Profile Analysis is a categorical latent variable modeling approach (Collins & Lanza, 2009) that focuses on identifying latent subpopulations within a population based on a certain set of variables (Collins & Lanza, 2009; Howard & Hoffman, 2018; Spurk et al., 2020). The final choice of the number of relevant profiles was made on the basis of not only theoretical assumptions but also several fit indices

Table 1. Domains and functions measured through the neuropsychological assessment with tests and indices selected to cover the main cognitive domains

Domains	Functions	Test	Indices selected
Memory	Episodic verbal	Word-list of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998)	Immediate and delayed recall scores
	Episodic visuospatial	Brief Visuospatial Memory Test (BVMT-Revised) (Benedict et al., 1996)	Immediate and delayed recall scores
Attention	Selective attention	Test of Attentional Performance (TAP) (Zimmermann & Fimm, 2004); D2 Test of Attention–Revised (D2-R) (Brickenkamp et al., 2015)	Response time and accuracy
	Divided attention	TAP (Zimmermann & Fimm, 2004)	Response time and accuracy
	Processing speed	TAP (Zimmermann & Fimm, 2004); Stroop test (naming and reading conditions) (Azouvi et al., 2015); D2-R (Brickenkamp et al., 2015)	Response time
	Attention fluctuation	TAP[a] (Zimmermann & Fimm, 2004)	Standard deviation scores
Executive functions	Inhibition	Stroop test (Azouvi et al., 2015) (interference condition)	Response time, accuracy, and interference index (interference RT – naming RT)
	Flexibility	Flexibility task of the TAP (Zimmermann & Fimm, 2004)	Response time and accuracy
	Working memory	Updating task of the TAP (Zimmermann & Fimm, 2004); Brown–Peterson test (Geurten et al., 2016)	Response time (updating) and accuracy (Brown–Peterson)
Language		Phonetic and semantic fluency (Azouvi et al., 2015)	Total number of words produced

[a]The tasks considered are all the TAP tasks referenced in this table.

(Collins & Lanza, 2009), such as the Bayesian Information Criterion, the Akaike Information Criteria, and entropy close to 1. When computing the profiles, our model specifications allowed the covariances among the indicator variables to be freely estimated within a profile, but both variances and covariances were constrained to be the same across profiles (Pastor et al., 2007).

We used robust analyses of variance (ANOVAs based on 5,000 replicates) and robust Pearson's chi-square tests (5,000 replicates) with the profiles identified with LPA as the between-subjects variable. This bootstrapping method is more robust than classic tests since (a) it does not assume normality or homoscedasticity of the data; (b) it is less sensitive to outliers and variance heterogeneity; and (c) it has higher validity in small sample sizes (Wilcox, 2005). The analyses were performed on the following variables: demographic characteristics (gender, age, education level, body mass index, severity of the infection); cognitive complaints (scores on BRIEF-A and MMQ questionnaires); psychological distress (score on OQ-45); sleep and fatigue (scores on PSQI and MFIS-21); quality of life (global QLSI score); and impact on work and daily activities (absenteeism and presenteeism scores on WPAI). In order to estimate the size of the difference between profiles, eta squared effect sizes were calculated for the results of the robust ANOVAs, and Cramer's V was used for the robust Pearson's chi-square tests (Cohen, 1988). Analyses of cognitive complaints and objective performances were carried out on Z-scores based on population norms with lower scores indicating higher difficulties. Analyses of somatic and psychological questionnaires were conducted on raw scores.

Finally, Pearson correlation coefficients were calculated between subjective (scores on the BRI and MI indices of the BRIEF-A and Ability index of the MMQ) and objective measures of cognitive problems (patient's worst score per cognitive domain: i.e., attention, memory, executive functions), and between subjective measures and psychological distress (scores on OQ-45). A Benjamini and Hochberg (1995) correction for multiple comparisons was used. Correlations were analyzed as small ($r < 0.3$), moderate (0.3–0.5), or large (>0.5) (Cohen, 1988). For these analyses, *Z*-scores from the neuropsychological tests were grouped by cognitive domain (i.e., attention, executive function, long-term memory, working memory), and the patient's worst *Z*-scores within each domain were retained for analyses. The worst *Z*-score per cognitive domain was used instead of a score averaging performance on a series of measures relevant to the domain. Indeed, a patient may exhibit specific impairments in a task (e.g., difficulties in divided attention) that can affect daily functioning, in the absence of generalized difficulties within the related cognitive domain (e.g., attentional tasks in general). Averaging scores would have masked such specific impairments and may only enable the identification of patients with more widespread cognitive deficits, which would not align with the objective of capturing clinically relevant difficulties.

Statistical analyses were conducted with R statistical software (R Core Team, 2021; version 4.1). The significance threshold was set at 0.05.

RESULTS

Sample Description

From a sample of 139 individuals with Long COVID assessed for eligibility, five patients did not meet the inclusion/exclusion criteria, one patient was excluded because of non-credible test performances, and three patients withdrew from the study after the first visit, resulting in a final sample of 130 patients. Seven patients were removed from the statistical analysis due to outlier results (identification of multivariate outliers using the

Table 2. Descriptive sociodemographic characteristics, history of COVID-19, and premorbidities of the total sample and the three profiles identified

		Total	Profile1	Profile2	Profile3
Demographics	Age (mean)	47.1	47.8	45.5	50.2
	Sex (female)	69.1%	79.4%	71.9%	48%
	Years of education (mean)	14	13.2	14.7	13.6
Severity of the disease	Asymptomatic[a]	1 (0.8%)	0	1 (1.6%)	0
	Mild infection[a]	67 (54.5%)	13 (38.2%)	37 (59.4%)	17 (68%)
	Moderate infection[a]	41 (33.3%)	15 (44.1%)	22 (34.4%)	4 (16%)
	Severe infection[a]	14 (11.4%)	6 (17.6%)	4 (6.3%)	4 (16%)
Premorbidities	Endocrine, nutritional, or metabolic diseases	35%	35%	33%	36%
	Mental and behavioral disorders	20%	11%	25%	16%
	Diseases of the circulatory system	17%	18%	19%	12%
	Surgical operations	11%	24%	5%	12%
	Sleep–wake cycle disorders	10%	12%	8%	12%
	Nervous system diseases	8%	18%	6%	0%
	Respiratory system diseases	8%	9%	9%	4%
	Neurodevelopmental disorders	8%	6%	6%	4%
	Infectious or parasitic diseases	6%	0%	8%	4%
	Chronic pain	5%	9%	3%	4%
	Diseases of the ear or mastoid process	5%	0%	8%	4%

Note. ICU = intensive care unit. Premorbidities were based on the International Classification of Diseases (ICD-11; WHO, 2019); premorbidities with a frequency < 5% are not displayed. [a]According to the criteria of the National Institutes of Health guideline.

Mahalanobis distance and critical X^2 value). A flowchart of the COVCOG study can be found in Supplemental Figure 1.

The 123 patients included had a mean age of 47 years and a mean education level of 14 years; 69.1% were women (for further details, see Table 2). The cohort had had predominantly mild to moderate SARS-CoV-2 infection, an average of 1.7 episodes of self-reported infection, of which at least one was medically certified. They were infected between March 2020 and November 2023 [no information was available on the variant responsible for the infection(s)], and the mean interval between the first reported infection and study inclusion was 20.9 months (SD = 8.6, median = 22). Forty-four patients (35.7%) were taking medication that could affect cognition (i.e., soporific, benzodiazepine, antidepressant, neuroleptic, anxiolytic). The medications were related to the treatment of post-COVID symptoms in most cases and had been taken for at least 2 months so that the patients were considered medically stable before their study inclusion. The most common premorbidities were endocrine, nutritional, or metabolic diseases as well as mental and behavioural disorders. Sociodemographic data, history of COVID-19, and premorbidities are presented in Table 2. Prior to their SARS-CoV-2 infection, 97.6% of the patients worked or studied in higher education and only 0.8% had been on sick leave. At the time of study inclusion, 59.3% were working, or studying in higher education and 34.15% were on sick leave.

Cognitive, Somatic, and Functional Complaints

Difficulties in daily life spontaneously reported during the semi-structured interviews are presented in Supplemental Table 2. In the cognitive domain, the most frequent complaints are problems affecting concentration, prospective memory, word-finding, long-term memory, and multitasking. For somatic aspects, sleep problems and fatigue are the most frequent complaints. When asked about the impact of their difficulties on their daily activities, 95% of the patients considered that they had impacts on work, 71% on social relationships, and 46% on family life.

In addition to the semi-structured interview, the existence of difficulties in daily life following COVID-19 was assessed with standardized questionnaires (see Table 3).

- *Cognitive complaint questionnaires*: Forty percent of the participants reported severe problems with attentional and executive functions (BRIEF-A questionnaire) and 35% with memory (MMQ).
- *Fatigue and sleep:* Pathological fatigue was observed in 95% of the patients (MFIS), while 81% identified as poor sleepers (PSQI).
- *Psychological distress and quality of life*: Over 70% of participants experienced pathological psychological distress (OQ-45), and 81% had problematic scores (above the 75th percentile) for quality of life (QLSI).
- *Work and activity*: Patients reported that persistent difficulties had a mean impact of approximately 60% on their daily activities (WPAI), and a 54% impact on work and study in those who were workers or students at the time of study inclusion ($N = 73$). No clinical threshold is proposed by the authors; interpretation will concern only qualitative aspects.

Cognitive Performance

The mean total score on the MoCA was 27.3 (range: 20–30). Nineteen patients (15.4%) obtained a score below the cut-off of 26.

The proportion of patients with a score < P2, between P2 and P5, between P5 and P8, and > P8 for measures from the neuropsychological tasks is shown in Fig. 1, representing conservative (P2), liberal (P5), and uncertainty (P8) threshold scores (Guilmette et al., 2020). Seventy-two percent of patients scored below the conservative threshold on at least one task. In the attentional domain, a sub-threshold performance was observed in 61% of patients, with the divided attention task accounting

Table 3. Mean, range, and percentage of sub-threshold scores on questionnaires addressing daily living problems

		Mean (*SD*)	Range	% of scores meeting the difficulty threshold (*N*)
Cognitive complaints	BRIEF-A (CEG)	138.2 (±21)	98–186.5	39.8% (49)
	BRIEF-A (BRI subscale)	55.9 (±10.6)	34.5–78	24.4% (30)
	BRIEF-A (MI subscale)	82.3 (±12.8)	54.5–114	56.1% (69)
	MMQ (satisfaction level)	20.3 (±11.3)	3.5–57.5	35% (43)
	MMQ (ability)	33.8 (±11.6)	7–63	25.2% (31)
	MMQ (strategies)	40.1 (±11.8)	16–70.5	0%
Fatigue and sleep	MFIS (global score)	62.7 (±13.1)	13–84	95% (117)
	PSQI (global score)	9.2 (±3.9)	1–20	81.3% (100)
Psychological distress and quality of life	OQ-45 (global score)	70.1 (±23	17–119	65.8% (81)
	OQ-45 (symptom distress)	44.8 (±15.8)	10–80	73.1% (90)
	OQ-45 (interpersonal relations)	11.9 (±6.3)	0–31	30% (37)
	OQ-45 (social role)	13.4 (±4.8)	0–31	69.9% (86)
	QLSI (global score)	11.6 (±8.2)	−8.3–37.6	81.3% (100)
Work and activity	Impact on daily activities (% ± *SD*)	57.8% (±27.2)	0–100	—
	Impact on work (% ± *SD*)[a]	54.2% (±32.1)	0–100	—

Note. *N* = number of participants (123); *SD* = standard deviation; CEG = Composite Executive Global; BRI = Behavioral Regulation Index; MI = Metacognition Index. [a]Results for the 73 patients who were actively employed/studying.

for the most frequent sub-threshold performance (45%). There are also substantial attention fluctuations: 34% of the patients had at least one attention or executive task with a large standard deviation. In the memory domain, 15% had at least one task below the threshold, and the most frequently impaired task was BVMT-R (13%). In the executive function domain, 41% had at least one sub-threshold score, most frequently on the Brown–Peterson task (26%).

Associations Between Complaints and Cognitive Performance

We computed the associations between the objective assessments (patient's worst *Z*-score per cognitive domain) and number of complaints (BRIEF-A and MMQ questionnaires) and between subjective complaints and psychological distress (OQ-45 questionnaire). After Benjamini & Hochberg correction, α was set at $p = .03$ for the first correlation matrix and $p = .05$ for the second one.[1]

The BRIEF-A MI subscale has a moderate correlation with executive performance ($r = 0.32$, $p < .001$), and a small correlation with attentional performance ($r = 0.28$, $p = .002$). The MMQ Ability subscale has a moderate correlation with executive performance ($r = 0.34$, $p < .001$) and a small correlation with attentional performance ($r = 0.25$, $p = .005$). All other correlations were non-significant (all $rs < 0.34$; all $ps > .042$).

OQ-45 (measuring psychological distress) have a large correlation with the BRIEF-A BRI subscale ($r = -0.72$, $p < .001$); a moderate correlation with BRIEF-A MI subscale, MMQ Satisfaction subscale, and MMQ Ability subscale ($rs = -0.44, -0.44, -0.34$, all $ps < .001$, respectively); and a small correlation with the MMQ Strategies subscale ($r = 0.23$, $p = .012$). Increased cognitive complaints are associated with higher psychological distress.

Profiles of Individuals With Long COVID

The EFA revealed two composite factors (processing speed and executive attentional) (for more details, see Supplemental Figure 2) and three variables that were not related to these factors (delayed recall in verbal long-term memory, index of updating in working memory including RT and accuracy, and index of interference management in working memory, combining scores for 20- and 10-s intervals on the Brown–Peterson task). Consequently, scores entered in the LPA were from the two composite factors and three individual variables.

The LPA showed three different profiles that differ, with large effect sizes, in terms of processing speed factor [$F(38.2120)$, $p < .001$, $\eta^2_g = 0.39$[2]], executive attentional factor [$F(25.4120)$, $p < 0.001$, $\eta^2_g = 0.30$], delayed verbal long-term memory [$F(85.6120)$, $p < 0.001$, $\eta^2_g = 0.59$], updating (speed and precision combined) [$F(26.2120)$, $p < .001$, $\eta^2_g = 0.30$] and interference in working memory [$F(30.3120)$, $p < .001$, $\eta^2_g = 0.34$] (see Fig. 2). Patients in Profile 1 ($N = 34$; 28%) have the lowest performance for all factors and variables except for the verbal long-term memory variable, which is associated with the lowest score for patients in Profile 3 (all $ps < .001$). Patients in Profile 2 ($N = 64$; 52%) also showed a widespread pattern of problems but less pronounced than for patients in Profile 1 (all $ps < .001$). Finally, patients in Profile 3 ($N = 25$; 20%) seem to be specifically impaired in verbal long-term memory.

[1] Correlations were analyzed as small ($r < 0.3$), moderate (0.3–0.5), or large (>0.5) (Cohen, 1988).

[2] Generalized eta squared effect sizes (η^2_g) were analyzed as small (0.02), moderate (0.13), and large (0.26) (Cohen, 1988)

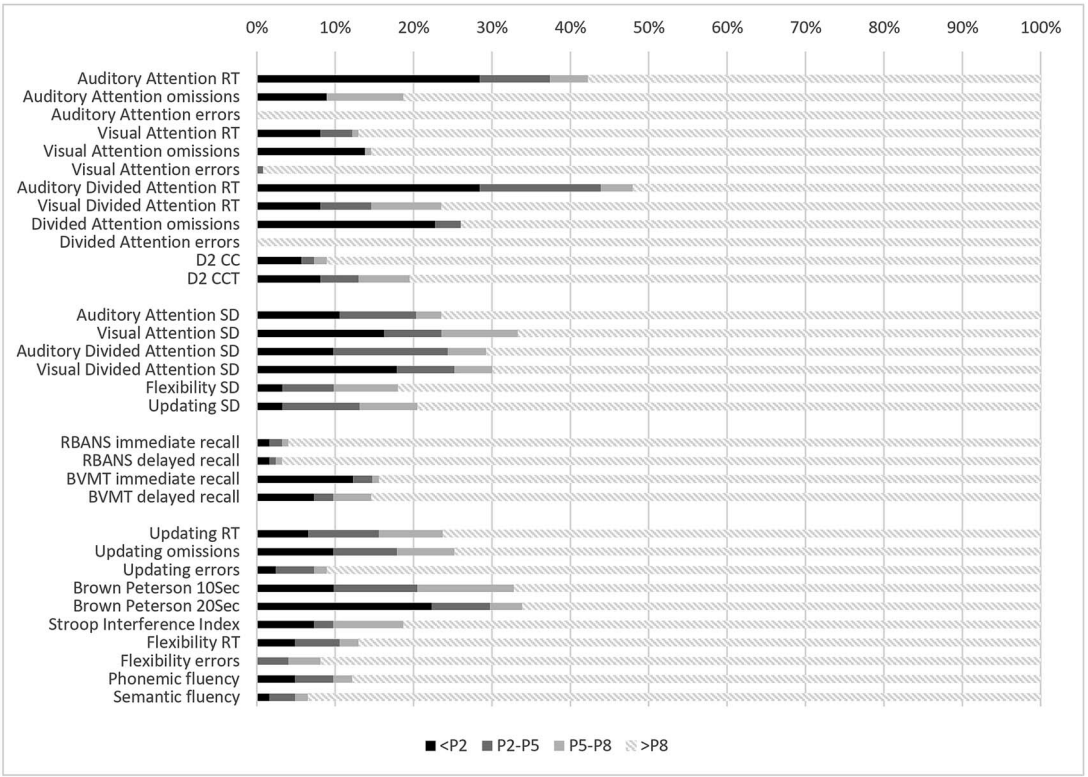

Fig. 1. Percentage of patients with a score below the 2nd, 5th, and 8th percentiles.

Demographic and medical data of the three profiles

No significant difference was observed between the three profiles for age ($F = 1.99$, $p = .165$, $\eta^2 = 0.239$[3]), educational level ($\chi^2 = 8.58$, $p = .199$, $V = 0.169$[4]), body mass index ($F = 0.90$, $p = .415$, $\eta^2 = 0.163$), presence of anosmia ($\chi^2 = 0.0695$, $p = .966$), severity of the infection ($\chi^2 = 9.29$, $p = .052$, $V = 0.22$), and number of infections ($\chi^2 = 4.81$, $p = .78$, $V = 0.14$). However, significant differences were observed for sex ($\chi^2 = 7.14$, $p = .028$, $V = 0.251$) with a small effect size. Post hoc analyses showed more men in Profile 3 (52%) than in Profiles 1 (20.6%, $\chi^2 = 6.34$, $p = .012$, $V = 0.23$) and 2 (28.1%, $\chi^2 = 4.51$, $p = .034$, $V = 0.19$). Significant differences were also observed for hospitalization in the acute phase ($\chi^2 = 6.56$, $p = .038$, $V = 0.23$; small effect size) with less hospitalized patients in Profile 2 ($N = 4$, 6.3%) than in Profiles 1 ($N = 7$, 20.6%; $\chi^2 = 4.58$, $p = .032$, $V = 0.22$) and 3 ($N = 6$, 24%; $\chi^2 = 5.68$, $p = .017$, $V = 0.253$). No differences were observed in the need for intensive care during the acute phase ($\chi^2 = 3.46$, $p = .177$, $V = 0.168$).

Sociodemographic and medical data for the three profiles are presented in Table 2.

Cognitive complaints of the three profiles

Spontaneous complaints mentioned during the semi-structured clinical interview for the three profiles are presented in Supplemental Table 2 and will not be described here.

The BRIEF-A questionnaire used to assess complaints about executive functioning showed a profile effect for the global score ($F = 8.45$, $p = .002$, $\eta^2 = 0.445$), and the MI subscale ($F = 18.0$, $p < .001$, $\eta^2 = 0.553$) with patients from Profile 1 having the highest level of complaints (all $ps < .03$) (see Fig. 3). Regarding memory complaints, the profiles differed significantly for the MMQ subscales of satisfaction ($F = 4.09$, $p = .023$, $\eta^2 = 0.346$) and ability ($F = 5.69$, $p = .012$, $\eta^2 = 0.456$): patients in Profile 1 had more marked complaints than patients in Profile 3 (all $ps < .03$) (see Fig. 3).

Psychological, somatic, and functional complaints of the three profiles

Assessment of fatigue complaints showed a profile effect for the global score on the MFIS ($F = 6.36$, $p = .010$, $\eta^2 = 0.471$): patients in Profile 3 had the fewest complaints (all $ps < .03$; see Fig. 3). On the subscales, differences were observed only for physical ($F = 3.59$, $p = .040$, $\eta^2 = 0.353$) and cognitive fatigue ($F = 4.03$, $p = .033$, $\eta^2 = 0.406$). Profiles do not differ significantly for any of the other measures addressing quality of sleep, psychological distress, quality of life, and impact on activities (all $ps > .1$).

Cognitive performance of the three profiles

A significant difference was observed for the MoCA global score ($F = 8.33$, $p = .001$, $\eta^2 = 0.472$), with decreased performance for patients in Profile 1 compared to those in Profile 2 (26 [20–30] vs. 28 [23–30], $p < .001$), and lower performance in patients in Profile 3 than Profile 2 (27 [23–30], $p = .046$). Performance

[3] Eta squared effect sizes (η^2) were analyzed as small (0.01), medium (0.06), and large (0.14) (Cohen, 1988).

[4] Cramer's V was analyzed as small (0.10–0.30), moderate (0.30–0.50), large (0.50–0.70), and very large (0.70–1) (Cohen, 1988)

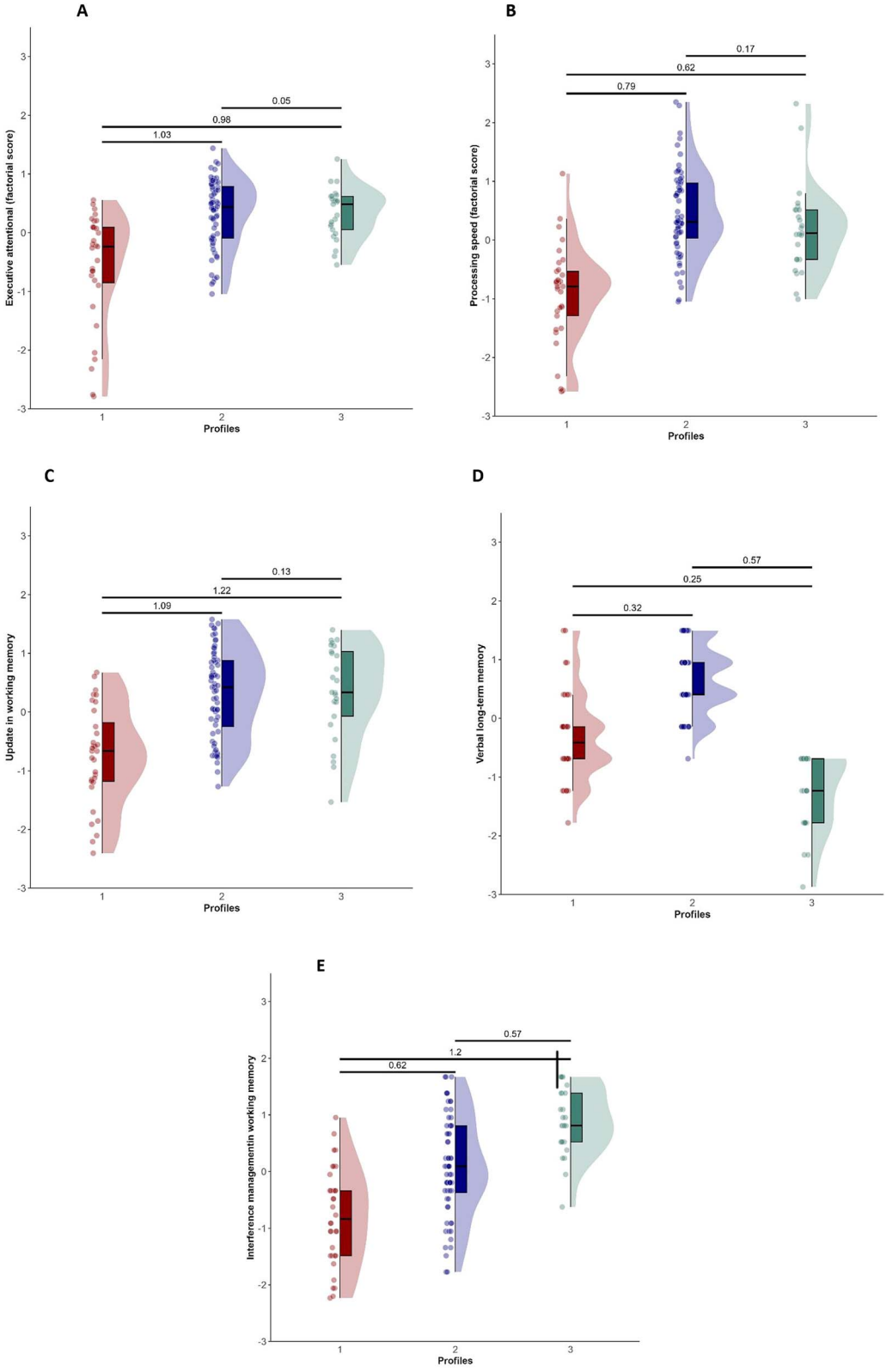

Fig. 2. Results of the LPA analysis showing three different profiles. The 3 profiles differ for the two composite factors – executive attentional (A) and processing speed (B) and for the three individual variables: – measure of updating (C), delayed verbal long-term memory (D), and interference in working memory (E).

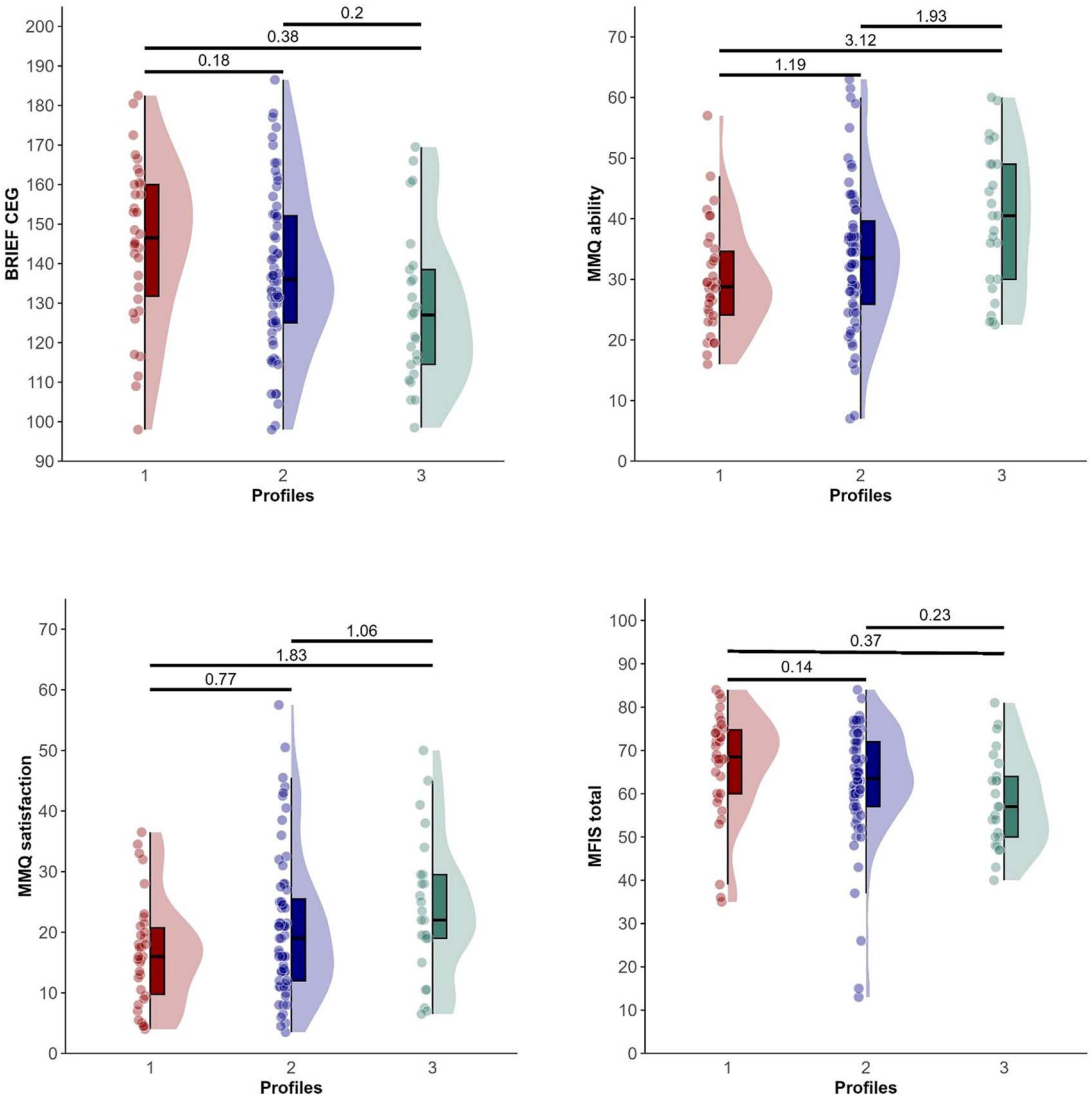

Fig. 3. Violin plots comparing scores for the Composite Executive Global (CEG) of the BRIEF-A questionnaire, the Satisfaction and Ability subscales of the MMQ questionnaire, and the global score of the MFIS questionnaire, for the three profiles. Higher scores on the BRIEF-A indicate more serious complaints, while higher scores on the MMQ indicate better self-reported memory functioning. Higher scores indicate a greater impact of fatigue on a patient's activities.

below the cut-off score (<P2) was observed for 11 patients in Profile 1 (32%), 5 in Profile 2 (8%), and 3 in Profile 3 (12%).

For attentional and executive tasks, Profile 1 patients had the highest number of sub-threshold scores, particularly for auditory attention, in contrast to Profile 3 patients, who generally performed within the norms. In the field of memory, sub-threshold scores were more frequent for verbal long-term memory in patients from Profile 3; for visuo-spatial long-term memory, sub-threshold scores were more frequent in Profile 1. Supplemental Figure 3 shows the proportion of patients in each profile with a score < P2, between P2 and P5, between P5 and P8, and > P8 for the cognitive battery.

Associations between complaints and cognitive performance for the three profiles

After Benjamini & Hochberg correction, for the correlation matrix including measures from objective assessment and subjective complaints, α was set at $p = .016$, $p = .014$ and $p = .013$ for the three profiles respectively; and, for the second correlation matrix (subjective complaints and psychological distress measures), $p = .03$, $p = .05$, and $p = .02$ for the three profiles, respectively.[5]

Regarding the association between subjective complaints and objective assessment, in Profile 1, MMQ Satisfaction and MMQ Ability subscales had both a moderate correlation with executive performance ($rs = 0.43$ and 0.44; $ps = .012$ and $.010$, respectively). All other correlations were non-significant (all $rs < 0.19$; all $ps > .27$). In Profile 2, no significant correlation between subjective and objective measures was observed (all $rs < 0.21$; all $ps > .09$). In Profile 3, BRIEF-A BRI and BRIEF-A MI subscales had both a moderate correlation with attention performance

[5] Correlations were analysed as small ($r < 0.3$), moderate (0.3–0.5), or large (>0.5) (Cohen, 1988).

($rs = 0.53$ and 0.50; $ps = .007$ and .012, respectively), and MMQ Strategies had a large correlation with long-term memory performance ($r = 0.58$, $p = .002$). All other correlations were non-significant (all $rs < 0.36$; all $ps > .08$).

Concerning the association between cognitive complaints and psychological distress (OQ-45), in Profile 1, psychological distress had a large correlation with the BRIEF BRI subscale ($r = -0.70$; $p < .001$) and a moderate correlation with the BRIEF MI subscale ($r = -0.46$; $p = .006$). All other correlations were non-significant (all $rs < 0.24$; all $ps > .04$). In Profile 2, psychological distress had a large correlation with the BRIEF BRI subscale ($r = -0.71$; $p < .001$) and a moderate correlation with the BRIEF-A MI subscale ($r = -0.50$; $p < .001$) and with two MMQ subscales (Satisfaction: $r = -0.51$, $p < .001$; Ability: $r = -0.41$, $p < .001$). Correlation with the Strategies subscale was non-significant ($r = 0.0.20$, $p = .12$). In Profile 3, psychological distress had a large correlation with the BRIEF-A BRI subscale ($r = -0.75$, $p < .001$). All other correlations were non-significant (all $rs < 0.29$; all $ps > .07$). More cognitive complaints are associated with higher psychological distress.

DISCUSSION

Given the inconsistent and heterogeneous findings in the literature on Long COVID concerning the presence and prevalence of objective cognitive impairment, subjective cognitive complaints, and their interplay, this study aimed to better understand individuals with Long COVID and their persistent cognitive difficulties. We sought to explore whether different patient profiles exist and, if so, what characteristics define them and influence their daily functional difficulties.

Patients included in the study had been infected with SARS-CoV-2 on average 20.9 months earlier; they still experienced significant difficulties, which had a considerable impact on their work and social life. Fatigue and sleep problems were reported spontaneously, with sub-threshold scores on the fatigue and sleep questionnaires for the majority. In the cognitive domain, spontaneous complaints mainly concerned concentration, memory, word retrieval, and multitasking abilities. More than a third of the patients had statistically very uncommon low scores on memory and executive function questionnaires (<percentile 2). In addition, more than two-thirds of the patients also scored below the threshold for psychological distress and quality of life.

We found that most patients presented poor cognitive performance, at a level that is statistically very infrequent in the general population, mainly in the attentional and executive domains; some also showed memory problems. Importantly, the poorest performance correlated with self-reported complaints on questionnaires.

Finally, we also observed that the performance profile is not perfectly uniform. Two patient profiles showed more wide-ranging difficulties, mainly in the attentional and executive domains; one of them was composed quite consistently of patients with lower overall performance and the most severe cognitive and fatigue complaints. A third profile featured a specific impairment affecting verbal long-term memory, despite a lack of specific complaints at this level. All three profiles showed similar levels of psychological distress and quality of life.

Subjective Cognitive Complaints

With regard to spontaneous complaints and those collected with questionnaires, our results are in line with previous studies observing that lack of concentration, memory deficits, and fatigue are among the most common self-reported Long COVID symptoms (Carmona-Cervelló et al., 2024; Herrera et al., 2023; Krishnan et al., 2022) and that these perceived difficulties persist even after 2 years (Wahlgren et al., 2023; Fernandez-de-las-Peñas et al., 2024). Moreover, 95% of our patients considered that those cognitive and somatic difficulties had direct impacts on their work and 71% that they interfered with their social relationships. While less than 1% of patients were on medical leave prior to the SARS-CoV-2 infection, 34% were on leave at study inclusion, while 54% of those who were working perceived that their cognitive difficulties affected their professional activities. These results are in line with the numerous obstacles that people with Long COVID perceive to their returning to work (Kohn et al., 2024).

Objective Cognitive Impairments

Some studies have noted that less than half of cognitive complaints are actually objectively detectable in cognitive performance (Schild et al., 2023). In some of those studies, the results may be explained by the use of a global screening tool (e.g., MoCA). This tool is commonly used in Long COVID research, but it is not specifically designed for this population (Gulick et al., 2021) and may lack sensitivity for young adults. In this study, which included a full cognitive assessment and used a conservative threshold, we found that 72% of patients performed at least one task with a score below the threshold, whereas only 19.5% scored below the threshold on the MoCA (15.4% when adjusting for education level). This contrast highlights the importance of a full assessment of cognitive functions rather than relying solely on screening tools.

The observed prevalence with a comprehensive evaluation exceeds what could statistically be expected in the general population. Given the increased risk of Type 1 error when multiplying the number of tests, we have computed that the probability in the general population of having a score below the percentile 2—for the same number of measures as those used in our study—is approximately 48%. This is substantially lower than the 72% observed in our sample. Similar prevalence rates have been reported in prior research (Carmona-Cervelló et al., 2024). We also found that 61% of patients had at least one score below the significance threshold (<P2) in the attentional domain, 41% in executive function, and 16% in memory. The difficulties observed in Long COVID may therefore primarily concern attentional and executive functions, as other studies have suggested (Delgado-Alonso et al., 2022; Herrera et al., 2023; Jaywant et al., 2021; Krishnan et al., 2022). These results can hardly be explained by a lack of involvement and effort in performance tests. Indeed, a verification of embedded validity indices on the Stroop (Arentsen et al., 2013) and verbal fluency tasks (Sugarman & Axelrod, 2015) identified eight

participants with one potentially questionable result, but only two participants with the two indices, which is the recommended practice for the detection of invalid results with high specificity (Bertrand et al., 2023; Chafetz, 2011). However, the aim of our study was not to evaluate the validity of cognitive performances in Long COVID; consequently, our procedure is probably not the most suitable and answering this question would require a more thorough assessment using sensitive performance validity tests.

Association of Cognitive Impairments and Complaints

Concerning the association between complaints of cognitive issues in daily life and difficulties observed in performance tests, we found moderate to extreme evidence of association between objective measures of attention and executive function and subjective measures of cognitive difficulties (Behavioral regulation Index and Metacognition Index of the BRIEF-A, which measure perceived executive control, organization, and planning capacity; and Ability index of the MMQ, which measures memory capacity). Several past studies support the alignment of subjective cognitive complaints with objective neuropsychological measures (García-Sánchez et al., 2022; Miskowiak et al., 2023). However, other studies failed to find a correlation (Bland et al., 2024; Gouraud et al., 2021; Whiteside et al., 2022). It is important to note that this inconsistency is also seen in other neurological populations, such as acquired brain injury (ABI) and post-concussion syndrome (PCS), where subjective complaints do not always necessarily align with objective testing results (Anderson, 2021; Byrne et al., 2017; van Rijsbergen et al., 2014). Methodology and choice of evaluation instruments for both objective performance and cognitive complaints may largely account for these discrepancies. Indeed, with regard to cognitive tasks, the choice of tools is crucial in determining the prevalence of cognitive disorders (Honarmand et al., 2020). For example, as previously discussed, the use of cognitive screening tools alone is not equivalent to a comprehensive neuropsychological evaluation and may explain the lack of association in some studies (e.g., Schild et al., 2023). Another problem concerns the use of composite scores that may mask certain isolated deficits that have a massive impact on an activity the patient finds crucial (e.g., interference sensitivity for a mother of several young children). For this reason, in this study, we used the patient's lowest score in each domain for the correlation analyses.

Similarly, to measure cognitive complaints, several studies used questionnaires that assess a wide range of cognitive symptoms (e.g., Cognitive Failures Questionnaire or Everyday Cognition Questionnaire; Miskowiak et al., 2021; Marquine et al., 2023). However, the instruments used should be specific to each cognitive domain and sensitive to particular and diverse difficulties in daily life (as is the case here: we used sensitive, specific questionnaires for executive functions and memory). However, it should be noted that the assessment of difficulties in daily life remains complex and debated. Poor awareness and associated metacognitive knowledge, and poor episodic memory of events related to problems are variables that can lead some patients to underestimate their problems (Chi et al., 2021). Thus, anosognosia seems to affect a proportion of individuals with Long COVID (Voruz et al., 2022). Conversely, catastrophizing and the "good old days" bias are examples of cognitive biases that can lead to unintentional overestimation of impairments (Shi et al., 2024).

In addition, depression and anxiety may also play a role in perceived cognitive decline (Dotson et al., 2014). In agreement with previous studies (Mazza et al., 2020; Poletti et al., 2022), we found that 66% of patients had psychological distress scores above clinical significance. Furthermore, we found robust evidence of an association between cognitive complaints and psychological distress. However, the relationship between cognitive problems and psychological factors is most probably two-directional, and cognitive impairment by itself may also lead to psychological distress. Only 20% of the sample had pre-existing mental and behavioural disorders before their SARS-CoV-2 infection. Further studies are therefore needed to explore the association between subjective and objective measures and the contributions of those varied factors.

Different Profiles of Individuals With Long COVID

One of the main findings is the identification of three different profiles of individuals with Long COVID based on their cognitive performance. On the basis of a systematic review, Espinoza and Martella (2023) had already suggested that different profiles exist. These profiles characterized three types of clinical presentation: predominant executive attentional dysfunction; memory and language disorders; and mixed presentation. However, Espinoza and Martella stressed the difficulty of establishing profiles due to the very heterogeneous assessment tools used in the various studies in their review. Our study, however, points in a broadly similar direction.

Our Profile 1 (28% of the sample) includes patients who have the largest number of sub-threshold scores (<P2) in executive functions and attentional domains, with highly impaired auditory attention. Consistently, these patients also report higher levels of executive and memory complaints, as well as more complaints about physical and cognitive fatigue (MFIS). Our results also indicate the presence of a second profile (52% of the sample), in which patients also have a widespread pattern of difficulties but less pronounced than in Profile 1. A final profile (20% of the sample) includes patients who have more frequent deficits in verbal long-term memory but no executive function deficits. Clinically, they have the lowest level of complaints, including for their memory functioning, which may be seen as indirect evidence of poor awareness of memory difficulties. This third profile includes proportionately more men.

Voruz and colleagues (2022) also found that individuals with Long COVID have distinct cognitive and psychiatric profiles, and suggested that anosognosia for memory and olfactory dysfunction were key differentiators between clinical phenotypes. In essence, they identified a profile characterized by not only anosognosia for cognitive disorders but also psychiatric and somatic (e.g., olfactory) difficulties, along with impaired brain connectivity. Our last group (Profile 3) also had fewer memory complaints despite the difficulties observed, but they also exhibited fewer cognitive impairments, suggesting that their

reduced number of complaints could be explained by their experiencing fewer difficulties overall. This profile is therefore not perfectly equivalent to the one observed by Voruz's team. It should be noted, however, that differences between the two studies may be attributable to the participant selection, as cognitive complaints in daily life were not an inclusion criterion in Voruz and coworkers (2022). Indeed, profiles in our study differentiate among patients on a cognitive level, given that no significant differences were found in their sleep difficulties, psychological distress, quality of life, or activity impairment, suggesting that these kinds of psychosomatic difficulties may be common to all individuals with Long COVID.

Clinical Implications

Given the still significant impact of cognitive impairment 20 months post-infection, there is an urgent need to develop specific rehabilitation programmes for individuals with Long COVID. Evidence on effective treatments is still limited. However, preliminary data on cognitive training are encouraging (e.g., Rabaiotti et al., 2023; Victoria et al., 2024). Furthermore, multidisciplinary approaches combining cognitive remediation interventions with interventions that also focus on other targets (e.g., physical exercise, nutrition, fatigue) appear to be able to improve cognitive issues. Unfortunately, recent studies are still difficult to interpret, given their heterogeneous assessments and inclusion criteria and the lack of long-term follow-up (Melillo et al., 2024).

A complementary approach to these multidisciplinary interventions consists of the treatment of psychological factors. In a consensus statement, Cheng and coworkers (2023) recommend interventions comprising supportive psychotherapy and Cognitive Behavioral Therapy (CBT), including treatments based on acceptance and mindfulness. Integrating this type of approach with cognitive rehabilitation can provide a holistic treatment approach adapted to the needs of the patient, similar to what is effective in other neurological diseases such as ABI (Davies et al., 2023). In this vein, a rehabilitation program for Long COVID including neuropsychological and mood interventions resulted in cognitive improvements in some performance tasks while reducing the likelihood of presenting anxio-depressive symptoms (García-Molina et al., 2021).

A comprehensive assessment of neuropsychological, psychological, and functional aspects in patients with long-standing COVID may help identify key factors of the patient profile that could influence their recovery trajectory and subsequently support the design of targeted interventions. The identification of different patient profiles in our study might suggest that modular psychoeducation tailored to each patient could be the most effective approach with, for example, some patients that may benefit more from the use of memory aids, while others may need help for managing the reduction in attentional resources. These individual cognitive difficulties—defining distinct patient profiles—require further investigation. The existence of different phenotypes also raises questions about the long-term evolution of cognitive difficulties, particularly regarding the potential increased risk of developing neurodegenerative disorders following SARS-CoV-2 infection, as suggested by recent studies (Duff et al., 2024) and observed in the context of other viral infections (Levine et al., 2023).

Strengths

This study reinforces the observation that it is essential to consider the cognitive profiles of people with Long COVID. Few studies have done this using a comprehensive assessment of objective neuropsychological performance, supplemented by measures of cognitive complaints, psychological, functional, and somatic aspects. Unlike some previous studies that may have focused only on self-reported impact of cognitive difficulties or brief cognitive assessments, our results offer a broader perspective, more clinically relevant for tailoring rehabilitation, taking into account the complex interplay between cognitive, emotional, and functional domains.

Study Limitations

Our study has some limitations. First, our findings are limited to patients who reported cognitive complaints following COVID-19 and therefore cannot be generalized to all individuals affected by the disease nor to those with other sequelae (e.g., respiratory or cardiac issues). Nevertheless, we believe that our results are clinically relevant for the health care of individuals with Long COVID, particularly since approximately 50% of patients with persistent difficulties (most commonly respiratory problems) present clinically relevant cognitive impairments (Miskowiak et al., 2023).

Secondly, 88% of our patients had mild or moderate COVID infections and only 14% had been hospitalized; accordingly, results may differ for patients with more severe acute disease. However, several studies have shown that patients with more severe disease in the acute phase (i.e., hospitalized patients) do not necessarily show greater cognitive deficits after 3–7 months (Krishnan et al., 2022; Miskowiak et al., 2023; Woo et al., 2020). Similarly, our sample had a high level of education (mean = 14 years, SD = 3), which is generally considered a proxy of cognitive reserve. It would be worth exploring whether our findings apply to individuals with a lower level of education.

Profile 3 includes mostly men, making it difficult to rule out gender bias unrelated to Long COVID. Indeed, the disadvantage in verbal memory for men is well documented (e.g., Siedlecki et al., 2019). However, we observed no gender differences in verbal memory across the entire sample. This suggests that our findings are probably specific to this patient subgroup and do not reflect broader gender-based differences. Similarly, gender differences in fatigue have also been reported in the general population, with men generally reporting lower complaints (e.g., Bensing et al., 1999) which also corresponds to our findings for Profile 3. This finding is difficult to interpret given that the same gender effect is observed in Long COVID with overall less fatigue reported among men (Price et al., 2023).

It is also important to acknowledge that the assessment of anxio-depressive symptoms in our study was based on a global self-reported questionnaire assessing psychological distress. This approach does not substitute for disorder-specific psychometric instruments or structural clinical interviews, which would be required to establish a diagnosis, and therefore may limit our

results regarding the impact of anxiety and depression on cognitive complaints.

Another potential limitation to consider could be the large number of patients (46% of the sample) who had a pre-existing health problem such as diabetes, obesity, inflammatory, autoimmune, or cardiovascular problems that could potentially affect cognitive functioning. A similar prevalence is found in previous studies. For instance, Whiteside and coworkers (2022) reported that 57.1% of their sample had premorbid psychiatric diagnoses and 51% premorbid vascular risk factors. Consequently, we cannot exclude that cognitive difficulties and heterogeneity are partly driven by pre-existing health problems. In fact, Long COVID is a systemic disease, and these medical conditions have been reported as vulnerability and risk factors for the disease (Peluso & Deeks, 2024). Excluding patients with pre-existing or comorbid health problems (other than neurological, cognitive, or psychiatric premorbidities) would have prevented the generalization of the results. How comorbidities may be considered as a risk factor for cognitive difficulties in Long COVID seems particularly relevant to assess in future studies. Finally, a proportion of patients (36%) were taking medications potentially affecting cognition as part of their treatment for Long COVID symptoms. While we ensured that they were on a stable regimen prior to study inclusion, we cannot exclude the possibility that these medications influenced the patterns of results we observed.

This study did not assess the potential impact of different SARS-CoV-2 variants and participants' vaccination status. However, prior studies suggest that the presence or number of Long COVID symptoms, particularly cognitive impairment, seems to occur at similar rates across variants (de Erausquin et al., 2023; Saigal et al., 2023). Regarding vaccination, existing evidence suggests a protective effect, with vaccinated individuals showing a reduced risk of developing Long COVID (Ayoubkhani et al., 2022; Ceban et al., 2023).

We acknowledge that the relatively modest sample size of 123 analyzed patients may raise concerns given the complexity of the analyses performed. However, our study adopts an exploratory, hypothesis-generating approach and we conducted robust statistical analyses to ensure reliability of our findings (i.e., for LPA analysis, we followed the recommendations by Dalmaijer and associates (2022)).

Finally, 16% of our patients had impairment in the memory domain; 13% had impaired performance on the visuo-spatial memory task and only 3% on the verbal memory task. The proportion of patients with impaired verbal episodic memory is lower than in other studies, which have reported deficits in around 20% of patients (Delgado-Alonso et al., 2022; Herrera et al., 2023; Jaywant et al., 2021). Therefore, we cannot rule out a ceiling effect with the Repeatable Battery for the Assessment of Neuropsychological Status word list subtest. The task was selected because multiple versions are available with normative data for French-speaking populations, allowing for baseline and two follow-up evaluations in an RCT study (Willems et al., 2023). We also wanted to find a task that is rarely used in neuropsychological settings as we were assessing patients who frequently consult health care providers.

CONCLUSION

In conclusion, our study illustrates that objective cognitive impairments, along with subjective cognitive, somatic, and psychological complaints, can persist approximately 20 months after a SARS-CoV-2 infection. Moreover, we identified three distinct profiles of individuals with Long COVID: two with a widespread dysfunction and the third with long-term memory difficulties (and lack of awareness of memory difficulties). Additional studies are needed to better understand the full spectrum of individuals with Long COVID and the different factors involved in their trajectories, but above all, to guide clinical management strategies.

SUPPLEMENTARY DATA

Supplementary data are available at *Archives of Clinical Neuropsychology* online.

FUNDING

This work was supported by the Belgian Health Care Knowledge Centre (KCE; KCE trial number: LCOV21–1303). The funding source had no role in the study design, data collection, analysis, or interpretation, nor in the writing of the manuscript. FC is supported by the F.R.S.-FNRS-Belgium. CC is supported by KCE trials.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

Our gratitude goes to all the participants for their time and effort in contributing to this study. We are deeply grateful to our patient partners, all the clinicians, the Clinical Trial Center from Antwerp University Hospital, and the COV-COG team for their support and collaboration throughout the research process.

REFERENCES

Anderson, J. F. (2021). Cognitive complaint and objective cognition during the post-acute period after mild traumatic brain injury in premorbidly healthy adults. *Brain Injury*, 35(1), 103–113. https://doi.org/10.1080/02699052.2020.1859613.

Arentsen, T. J., Boone, K. B., Lo, T. T. Y., Goldberg, H. E., Cottingham, M. E., Victor, T. L., et al. (2013). Effectiveness of the comalli stroop test as a measure of negative response bias. *The Clinical Neuropsychologist*, 27(6), 1060–1076. https://doi.org/10.1080/13854046.2013.803603.

Ayoubkhani, D., Bosworth, M. L., King, S., Pouwels, K. B., Glickman, M., Nafilyan, V., et al. (2022). Risk of long COVID in people infected with severe acute respiratory syndrome coronavirus 2 after 2 doses of a coronavirus disease 2019 vaccine: Community-based, matched cohort study. *Open Forum Infectious Diseases*, 9(9), ofac464. https://doi.org/10.1093/ofid/ofac464.

Azouvi, P., Vallat-Azouvi, C., Joseph, P. A., Meulemans, T., Bertola, C., Gall, D. L., et al. (2015). Executive functions deficits after severe traumatic brain injury: The GREFEX study. *The Journal of Head Trauma Rehabilitation*, 31(3), E10–E20.

Benedict, R. H., Schretlen, D., Groninger, L., Dobraski, M., & Shpritz, B. (1996). Revision of the brief visuospatial memory test: Studies of normal performance, reliability, and validity. *Psychological Assessment*, 8(2), 145–153. https://doi.org/10.1037/1040-3590.8.2.145.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B: Methodological*, 57(1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x.

Bensing, J. M., Hulsman, R. L., & Schreurs, K. M. G. (1999). Gender differences in fatigue: Biopsychosocial factors relating to fatigue in men and women. *Medical Care*, 37(10), 1078–1083. https://doi.org/10.1097/00005650-199910000-00011.

Bertrand, J. A., Chartrand, J. P., Gauthier, A. K., Kennepohl, S., & Monette, S. (2023). Validité de performance aux tests neuropsychologiques : Prise de position de l ' association québécoise des neuropsychologues. *Neuropsychologie Clinique et Appliquée*, (5), 1–16. https://doi.org/10.46278/j.ncacn.20231211.

Bland, A. R., Barraclough, M., Trender, W. R., Mehta, M. A., Hellyer, P. J., Hampshire, A., et al. (2024). Profiles of objective and subjective cognitive function in post-COVID syndrome, COVID-19 recovered, and COVID-19 naïve individuals. *Scientific Reports*, 14(1), 13368. https://doi.org/10.1038/s41598-024-62050-x.

Brickenkamp, R., Schmidt-Atzert, L., & Liepmann, D. (2015). *D2-R: Test d'attention concentrée*Éditions. France: Hogrefe.

Buysse, D. J., Reynolds, C. F., III, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, 28(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4.

Byrne, C., Coetzer, R., & Addy, K. (2017). Investigating the discrepancy between subjective and objective cognitive impairment following acquired brain injury: The role of psychological affect. *NeuroRehabilitation*, 41(2), 501–512. https://doi.org/10.3233/NRE-162015.

Carmona-Cervelló, M., León-Gómez, B. B., Dacosta-Aguayo, R., Lamonja-Vicente, N., Montero-Alía, P., Molist, G., et al. (2024). Long COVID: Cognitive, balance, and retina manifestations. *Frontiers in Medicine*, 11(July), 1–12. https://doi.org/10.3389/fmed.2024.1399145.

Castanares-Zapatero, D., Chalon, P., Kohn, L., Dauvrin, M., Detollenaere, J., Maertens de Noordhout, C., et al. (2022). Pathophysiology and mechanism of long COVID: A comprehensive review. *Annals of Medicine*, 54(1), 1473–1487. https://doi.org/10.1080/07853890.2022.2076901.

Ceban, F., Kulzhabayeva, D., Rodrigues, N. B., Di Vincenzo, J. D., Gill, H., Subramaniapillai, M., et al. (2023). COVID-19 vaccination for the prevention and treatment of long COVID: A systematic review and meta-analysis. *Brain, Behavior, and Immunity*, 111(September 2022), 211–229. https://doi.org/10.1016/j.bbi.2023.03.022.

Chafetz, M. (2011). Reducing the probability of false positives in malingering detection of social security disability claimants. *The Clinical Neuropsychologist,* 25(7), 1239–1252. https://doi.org/10.1080/13854046.2011.586785.

Cheng, A. L., Anderson, J., Didehbani, N., Fine, J. S., Fleming, T. K., Karnik, R., et al. (2023). Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of mental health symptoms in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). *PM & R: The Journal of Injury, Function, and Rehabilitation*, 15(12), 1588–1604. https://doi.org/10.1002/pmrj.13085.

Chi, S. Y., Chua, E. F., Kieschnick, D. W., & Rabin, L. A. (2021). Prospective metamemory monitoring of episodic visual memory in community-dwelling older adults with subjective cognitive decline and mild cognitive impairment. *Archives of Clinical Neuropsychology*, 36(8), 1404–1425. https://doi.org/10.1093/arclin/acab008.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). New York, NY: Routledge.

Collins, L. M., & Lanza, S. T. (2009). *Latent class and latent transition analysis: With applications in the social, behavioral, and health sciences* (Vol. 718). Hoboken, NJ: John Wiley & Sons. https://doi.org/10.1002/9780470567333.

COVID-19 Treatment Guidelines Panel. Coronavirus Disease (2019). *(COVID-19) treatment guidelines*. Bethesda, MD: National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/.

Crawford, J. R., & Garthwaite, P. H. (2005). Testing for suspected impairments and dissociations in single-case studies in neuropsychology: Evaluation of alternatives using Monte Carlo simulations and revised tests for dissociations. *Neuropsychology*, 19(3), 318–331. https://doi.org/10.1037/0894-4105.19.3.318.

Dalmaijer, E. S., Nord, C. L., & Astle, D. E. (2022). Statistical power for cluster analysis. *BMC Bioinformatics*, 23(1), 1–28. https://doi.org/10.1186/s12859-022-04675-1.

Dani, M., Dirksen, A., Taraborrelli, P., Torocastro, M., Panagopoulos, D., Sutton, R., et al. (2021). Autonomic dysfunction in 'long COVID': Rationale, physiology and management strategies. *Clinical Medicine*, 21(1), e63–e67. https://doi.org/10.7861/clinmed.2020-0896.

Davies, A., Rogers, J. M., Baker, K., Li, L., Llerena, J., das Nair, R., et al. (2023). Combined cognitive and psychological interventions improve meaningful outcomes after acquired brain injury: A systematic review and meta-analysis. *Neuropsychology Review*, 34(4), 1095–1114.

Delgado-Alonso, C., Valles-Salgado, M., Delgado-Álvarez, A., Yus, M., Gómez-Ruiz, N., Jorquera, M., et al. (2022). Cognitive dysfunction associated with COVID-19: A comprehensive neuropsychological study. *Journal of Psychiatric Research*, 150, 40–46. https://doi.org/10.1016/j.jpsychires.2022.03.033.

Diar Bakerly, N., Smith, N., Darbyshire, J. L., Kwon, J., Bullock, E., Baley, S., et al. (2024). Pathophysiological mechanisms in long COVID: A mixed method systematic review. *International Journal of Environmental Research and Public Health*, 21(4), 473. https://doi.org/10.3390/ijerph21040473.

Dondaine, T., Ruthmann, F., Vuotto, F., Carton, L., Gelé, P., Faure, K., et al. (2022). Long-term cognitive impairments following COVID-19: A possible impact of hypoxia. *Journal of Neurology*, 269(8), 3982–3989. https://doi.org/10.1007/s00415-022-11077-z.

Dotson, V. M., Szymkowicz, S. M., Kirton, J. W., McLaren, M. E., Green, M. L., & Rohani, J. Y. (2014). Unique and interactive effect of anxiety and depressive symptoms on cognitive and brain function in young and older adults. *Journal of Depression & Anxiety*, S1(01). https://doi.org/10.4172/2167-1044.S1-003.

Duff, E. P., Zetterberg, H., Heslegrave, A., Dehghan, A., Elliot, P., Allen, N., et al. (2024). Plasma proteomic evidence for increased Alzheimer's disease-related brain pathology after SARS-CoV-2 infection. *MedRxiv*, 31(March), 2024.02.02.24302132.

Duquette, R. L., Dupuis, G., & Perrault, J. (1994). A new approach for quality of life assessment in cardiac patients: Rationale and validation of the quality of life systemic inventory. *The Canadian Journal of Cardiology*, 10(1), 106–112.

de Erausquin, G. A., Zwir, J. I., Snyder, H. M., Gonzalez-Aleman, G., Zamponi, H. P., Figueredo-Aguiar, M., et al. (2023). Cognitive sequelae of COVID-19 is not predicted by SARS-CoV-2 variants. *Alzheimer's & Dementia*, 19(S24), 1–2. https://doi.org/10.1002/alz.083028.

Espinoza, C., & Martella, D. (2023). Cognitive functions in COVID-19 survivors, approaches strategies, and impact on health systems: A qualitative systematic review. *European Archives of Psychiatry and Clinical Neuroscience*, 275(1), 1–45.

Fernandez-de-las-Peñas, C., Notarte, K. I., Macasaet, R., Velasco, J. V., Catahay, J. A., Ver, A. T., et al. (2024). Persistence of post-COVID symptoms in the general population two years after SARS-CoV-2 infection: A systematic review and meta-analysis. *Journal of Infection*, 88(2), 77–88. https://doi.org/10.1016/j.jinf.2023.12.004.

Fery, P., & Claes, T. (2025). AUTONORMES: an open-access spreadsheet performing statistical analysis of scores from a wide range of cognitive tests. *Revue de Neuropsychologie*, 17(1), 19–29. https://doi.org/10.1684/nrp.2025.0801

García-Molina, A., Espiña-Bou, M., Rodríguez-Rajo, P., Sánchez-Carrión, R., & Enseñat-Cantallops, A. (2021). Neuropsychological rehabilitation program for patients with post-COVID-19 syndrome: A clinical

experience. *Neurologia (English Edition)*, 36(7), 565–566. https://doi.org/10.1016/j.nrleng.2021.03.003.

García-Sánchez, C., Calabria, M., Grunden, N., Pons, C., Arroyo, J. A., Gómez-Anson, B., et al. (2022). Neuropsychological deficits in patients with cognitive complaints after COVID-19. *Brain and Behavior: A Cognitive Neuroscience Perspective*, 12(3), e2508. https://doi.org/10.1002/brb3.2508.

Geurten, M., Vincent, E., Van Der Linden, M., Coyette, F., & Meulemans, T. (2016). Working memory assessment: Construct validity of the Brown-Peterson test. *Canadian Journal of Behavioural Science/Revue Canadienne Des Sciences Du Comportement*, 48(4), 328–336. https://doi.org/10.1037/cbs0000057.

Gheorghita, R., Soldanescu, I., Lobiuc, A., Caliman Sturdza, O. A., Filip, R., Constantinescu – Bercu, A., et al. (2024). The knowns and unknowns of long COVID-19: From mechanisms to therapeutical approaches. *Frontiers in Immunology*, 15(March), 1–21. https://doi.org/10.3389/fimmu.2024.1344086.

Gibney, S. M., & Drexhage, H. A. (2013). Evidence for a dysregulated immune system in the etiology of psychiatric disorders. *Journal of Neuroimmune Pharmacology*, 8(4), 900–920. https://doi.org/10.1007/s11481-013-9462-8.

Gouraud, C., Bottemanne, H., Lahlou-Laforêt, K., Blanchard, A., Günther, S., Batti, S. E., et al. (2021). Association between psychological distress, cognitive complaints, and neuropsychological status after a severe COVID-19 episode: A cross-sectional study. *Frontiers in Psychiatry*, 12, 725861. https://doi.org/10.3389/fpsyt.2021.725861.

Guilmette, T. J., Sweet, J. J., Hebben, N., Koltai, D., Mahone, E. M., Spiegler, B. J., et al. (2020). American Academy of clinical neuropsychology consensus conference statement on uniform labeling of performance test scores. *The Clinical Neuropsychologist*, 34(3), 437–453. https://doi.org/10.1080/13854046.2020.1722244.

Gulick, S. H., Mandel, S., Maitz, E. A., & Brigham, C. R. (2021). Cognitive screening after COVID-19. *Practical Neurology*, 19–23.

Han, Q., Zheng, B., Daines, L., & Sheikh, A. (2022). Long-term sequelae of COVID-19: A systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. *Pathogens*, 11(2), 269. https://doi.org/10.3390/pathogens11020269.

Herrera, E., Pérez-Sánchez, M. D. C., San Miguel-Abella, R., Barrenechea, A., Blanco, C., Solares, L., et al. (2023). Cognitive impairment in young adults with post COVID-19 syndrome. *Scientific Reports*, 13(1), 6378. https://doi.org/10.1038/s41598-023-32939-0.

Honarmand, K., Lalli, R. S., Priestap, F., Chen, J. L., McIntyre, C. W., Owen, A. M., et al. (2020). Natural history of cognitive impairment in critical illness survivors a systematic review. *American Journal of Respiratory and Critical Care Medicine*, 202(2), 193–201. https://doi.org/10.1164/rccm.201904-0816CI.

Howard, M. C., & Hoffman, M. E. (2018). Variable-centered, person-centered, and person-specific approaches: Where theory meets the method. *Organizational Research Methods*, 21(4), 846–876. https://doi.org/10.1177/1094428117744021.

Jaywant, A., Vanderlind, W. M., Alexopoulos, G. S., Fridman, C. B., Perlis, R. H., & Gunning, F. M. (2021). Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. *Neuropsychopharmacology*, 46(13), 2235–2240. https://doi.org/10.1038/s41386-021-00978-8.

Kohn, L., Dauvrin, M., Detollenaere, J., Primus-de Jong, C., Maertens de Noordhout, C., Castanares-Zapatero, D., et al. (2024). Long COVID and return to work: A qualitative study. *Occupational Medicine*, 74(1), 29–36. https://doi.org/10.1093/occmed/kqac119.

Kos, D., Kerckhofs, E., Carrea, I., Verza, R., Ramos, M., & Jansa, J. (2005). Evaluation of the modified fatigue impact scale in four different European countries. *Multiple Sclerosis Journal*, 11(1), 76–80. https://doi.org/10.1191/1352458505ms1117oa.

Krishnan, K., Miller, A. K., Reiter, K., & Bonner-Jackson, A. (2022). Neurocognitive profiles in patients with persisting cognitive symptoms associated with COVID-19. *Archives of Clinical Neuropsychology*, 37(4), 729–737. https://doi.org/10.1093/arclin/acac004.

Lambert, M. J., Burlingame, G. M., Umphress, V., Hansen, N. B., Vermeersch, D. A., Clouse, G. C., et al. (1996). The reliability and validity of the outcome questionnaire. *Clinical Psychology & Psychotherapy: An International Journal of Theory and Practice*, 3(4), 249–258. https://doi.org/10.1002/(SICI)1099-0879(199612)3:4<249::AID-CPP106>3.0.CO;2-S.

Levine, K. S., Leonard, H. L., Blauwendraat, C., Iwaki, H., Johnson, N., Bandres-Ciga, S., et al. (2023). Virus exposure and neurodegenerative disease risk across national biobanks. *Neuron*, 111(7), 1086–1093.e2. https://doi.org/10.1016/j.neuron.2022.12.029.

Marquine, M. J., Madriaga, C., Blumstein, Y., Hughes, C., Cancela, V., Muniz-Terrera, G., et al. (2023). Cognitive symptoms among middle- and older-age adults in Latin America during the coronavirus disease 2019 (COVID-19) pandemic: Risk and protective factors. *Alzheimer's & Dementia*, 19(S8), e061678. https://doi.org/10.1002/alz.061678.

Mazza, M. G., De Lorenzo, R., Conte, C., Poletti, S., Vai, B., Bollettini, I., et al. (2020). Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain, Behavior, and Immunity*, 89, 594–600. https://doi.org/10.1016/j.bbi.2020.07.037.

McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders*, 119(1–3), 1–8. https://doi.org/10.1016/j.jad.2009.04.022.

Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., et al. (2021). Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nature Neuroscience*, 24(2), 168–175. https://doi.org/10.1038/s41593-020-00758-5.

Melillo, A., Perrottelli, A., Caporusso, E., Coltorti, A., Giordano, G. M., Giuliani, L., et al. (2024). Research evidence on the management of the cognitive impairment component of the post-COVID condition: A qualitative systematic review. *European Psychiatry*, 67(1), e601-11. https://doi.org/10.1192/j.eurpsy.2024.1770.

Miskowiak, K. W., Johnsen, S., Sattler, S. M., Nielsen, S., Kunalan, K., Rungby, J., et al. (2021). Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. *European Neuropsychopharmacology*, 46, 39–48. https://doi.org/10.1016/j.euroneuro.2021.03.019.

Miskowiak, K. W., Pedersen, J. K., Gunnarsson, D. V., Roikjer, T. K., Podlekareva, D., Hansen, H., et al. (2023). Cognitive impairments among patients in a long-COVID clinic: Prevalence, pattern and relation to illness severity, work function and quality of life. *Journal of Affective Disorders*, 324, 162–169. https://doi.org/10.1016/j.jad.2022.12.122.

Molnar, T., Lehoczki, A., Fekete, M., Varnai, R., Zavori, L., Erdo-Bonyar, S., et al. (2024). Mitochondrial dysfunction in long COVID: Mechanisms, consequences, and potential therapeutic approaches. *GeroScience*, 46(5), 5267–5286. https://doi.org/10.1007/s11357-024-01165-5.

Multiple Sclerosis Council for Clinical Practice Guidelines (1998). *Fatigue and multiple sclerosis: Evidence-based management strategies for fatigue in multiple sclerosis*. Washington, DC: Paralyzed Veterans of America.

Najjar, S., Najjar, A., Chong, D. J., Pramanik, B. K., Kirsch, C., Kuzniecky, R. I., et al. (2020). Central nervous system complications associated with SARS-CoV-2 infection: Integrative concepts of pathophysiology and case reports. *Journal of Neuroinflammation*, 17(1), 1–14. https://doi.org/10.1186/s12974-020-01896-0.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, 53(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x.

Nuber-Champier, A., Breville, G., Voruz, P., Jacot de Alcântara, I., Cionca, A., Allali, G., et al. (2024). Systemic cytokines related to memory function 6-9 months and 12-15 months after SARS-CoV-2 infection. *Scientific Reports*, 14(1), 22660. https://doi.org/10.1038/s41598-024-72421-z.

Nuber-Champier, A., Cionca, A., Breville, G., Voruz, P., de Alcântara, I. J., Allali, G., et al. (2023). Acute TNFα levels predict cognitive impairment 6–9 months after COVID-19 infection. *Psychoneuroendocrinology*, 153(March), 106104. https://doi.org/10.1016/j.psyneuen.2023.106104.

Pastor, D. A., Barron, K. E., Miller, B. J., & Davis, S. L. (2007). A latent profile analysis of college students' achievement goal orientation. *Contemporary Educational Psychology*, 32(1), 8–47. https://doi.org/10.1016/j.cedpsych.2006.10.003.

Peluso, M. J., & Deeks, S. G. (2024). Mechanisms of long COVID and the path toward therapeutics. *Cell*, 187(20), 5500–5529. https://doi.org/10.1016/j.cell.2024.07.054.

Pihlaja, R. E., Kauhanen, L. L. S., Ollila, H. S., Tuulio-Henriksson, A. S., Koskinen, S. K., Tiainen, M., et al. (2023). Associations of subjective and objective cognitive functioning after COVID-19: A six-month follow-up of ICU, ward, and home-isolated patients. *Brain, Behavior, & Immunity-Health*, 27, 100587. https://doi.org/10.1016/j.bbih.2023.100587.

Poletti, S., Palladini, M., Mazza, M. G., De Lorenzo, R., Irene, B., Sara, B., et al. (2022). Long-term consequences of COVID-19 on cognitive functioning up to 6 months after discharge: Role of depression and impact on quality of life. *European Archives of Psychiatry and Clinical Neuroscience*, 272(5), 773–782. https://doi.org/10.1007/s00406-021-01346-9.

Poletti, S., Vai, B., Mazza, M. G., Zanardi, R., Lorenzi, C., Calesella, F., et al. (2021). A peripheral inflammatory signature discriminates bipolar from unipolar depression: A machine learning approach. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 105, 110136. https://doi.org/10.1016/j.pnpbp.2020.110136.

Politi, L. S., Salsano, E., & Grimaldi, M. (2020). Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. *JAMA Neurology*, 77(8), 1028–1029. https://doi.org/10.1001/jamaneurol.2020.2125.

Price, J. K., de Avila, L., Stepanova, M., Weinstein, A. A., Pham, H., Keo, W., et al. (2023). Severe, persistent, disruptive fatigue post-SARS-CoV-2 disproportionately affects young women. *International Journal of General Medicine*, Volume 16(September), 4393–4404. https://doi.org/10.2147/IJGM.S423910.

R Core Team (2021). *R: A language and environment for statistical computing*. (Version 4.1), Vienna, Austria. Retrieved from https://www.R-project.org/.

Rabaiotti, P., Ciracì, C., Donelli, D., Oggioni, C., Rizzi, B., Savi, F., et al. (2023). Effects of multidisciplinary rehabilitation enhanced with neuropsychological treatment on post-acute SARS-CoV-2 cognitive impairment (brain fog): An observational study. *Brain Sciences*, 13(5), 791. https://doi.org/10.3390/brainsci13050791.

Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The repeatable battery for the assessment of neuropsychological status (RBANS): Preliminary clinical validity. *Journal of Clinical and Experimental Neuropsychology*, 20(3), 310–319. https://doi.org/10.1076/jcen.20.3.310.823.

Reilly, M. C., Zbrozek, A. S., & Dukes, E. M. (1993). The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics*, 4(5), 353–365. https://doi.org/10.2165/00019053-199304050-00006.

Saigal, A., Nagoda Niklewicz, C., Naidu, S. B., Bintalib, H. M., Shah, A. J., Seligmann, G., et al. (2023). Cross-sectional study evaluating the impact of SARS-CoV-2 variants on long COVID outcomes in UK hospital survivors. *BMJ Open Respiratory Research*, 10(1), 1–12. https://doi.org/10.1136/bmjresp-2023-001667.

Schild, A. K., Scharfenberg, D., Kirchner, L., Klein, K., Regorius, A., Goereci, Y., et al. (2023). Subjective and objective cognitive deficits in patients with post-COVID syndrome. *Zeitschrift für Neuropsychologie*, 34(2), 99–110. https://doi.org/10.1024/1016-264X/a000374.

Schultheiß, C., Willscher, E., Paschold, L., Gottschick, C., Klee, B., Henkes, S. S., et al. (2022). The IL-1β, IL-6, and TNF cytokine triad is associated with post-acute sequelae of COVID-19. *Cell Reports Medicine*, 3(6), 100663. https://doi.org/10.1016/j.xcrm.2022.100663.

Shi, S., Picon, E. L., Rioux, M., Panenka, W. J., & Silverberg, N. D. (2024). Catastrophizing is associated with excess cognitive symptom reporting after mild traumatic brain injury. *Neuropsychology*, 38(2), 126–133. https://doi.org/10.1037/neu0000930.

Siedlecki, K. L., Falzarano, F., & Salthouse, T. A. (2019). Examining gender differences in neurocognitive functioning across adulthood. *Journal of the International Neuropsychological Society*, 25(10), 1051–1060. https://doi.org/10.1017/S1355617719000821.

Song, X., Song, W., Cui, L., Duong, T. Q., Pandy, R., Liu, H., et al. (2024). A comprehensive review of the global epidemiology, clinical management, socio-economic impacts, and National Responses to long COVID with future research directions. *Diagnostics*, 14(11), 1–17. https://doi.org/10.3390/diagnostics14111168.

Spurk, D., Hirschi, A., Wang, M., Valero, D., & Kauffeld, S. (2020). Latent profile analysis: A review and "how to" guide of its application within vocational behavior research. *Journal of Vocational Behavior*, 120, 103445. https://doi.org/10.1016/j.jvb.2020.103445.

Sugarman, M. A., & Axelrod, B. N. (2015). Embedded measures of performance validity using verbal fluency tests in a clinical sample. *Applied Neuropsychology. Adult*, 22(2), 141–146. https://doi.org/10.1080/23279095.2013.873439.

Taquet, M., Skorniewska, Z., Hampshire, A., Chalmers, J. D., Ho, L. P., Horsley, A., et al. (2023). Acute blood biomarker profiles predict cognitive deficits 6 and 12 months after COVID-19 hospitalization. *Nature Medicine*, 29(10), 2498–2508. https://doi.org/10.1038/s41591-023-02525-y.

Téllez, N., Río, J., Tintoré, M., Nos, C., Galán, I., & Montalban, X. (2005). Does the modified fatigue impact scale offer a more comprehensive assessment of fatigue in MS? *Multiple Sclerosis Journal*, 11(2), 198–202. https://doi.org/10.1191/1352458505ms1148oa.

Troyer, A. K., & Rich, J. B. (2002). Psychometric properties of a new metamemory questionnaire for older adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, 57(1), P19–P27. https://doi.org/10.1093/geronb/57.1.P19.

van Rijsbergen, M. W., Mark, R. E., de Kort, P. L., & Sitskoorn, M. M. (2014). Subjective cognitive complaints after stroke: A systematic review. *Journal of Stroke and Cerebrovascular Diseases*, 23(3), 408–420. https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.05.003.

Vandierendonck, A. (2018). Further tests of the utility of integrated speed-accuracy measures in task switching. *Journal of Cognition*, 1(1), 8. https://doi.org/10.5334/joc.6.

Veleri, S. (2022). Neurotropism of SARS-CoV-2 and neurological diseases of the central nervous system in COVID-19 patients. *Experimental Brain Research*, 240(1), 9–25. https://doi.org/10.1007/s00221-021-06244-z.

Victoria, L. W., Oberlin, L. E., Ilieva, I. P., Jaywant, A., Kanellopoulos, D., Mercaldi, C., et al. (2024). A digital intervention for cognitive deficits following COVID-19: A randomized clinical trial. *Neuropsychopharmacology*, 50(2), 472–479. https://doi.org/10.1038/s41386-024-01995-z.

Voruz, P., Cionca, A., Jacot de Alcântara, I., Nuber-Champier, A., Allali, G., Benzakour, L., et al. (2022). Functional connectivity underlying cognitive and psychiatric symptoms in post-COVID-19 syndrome: Is anosognosia a key determinant? *Brain Communications*, 4(2), fcac057. https://doi.org/10.1093/braincomms/fcac057.

Voruz, P., de Alcântara, I. J., Nuber-Champier, A., Cionca, A., Guérin, D., Allali, G., et al. (2024). Persistence and emergence of new neuropsychological deficits following SARS-CoV-2 infection: A follow-up assessment of the Geneva COVID-COG cohort. *Journal of Global Health*, 14, 05008. https://doi.org/10.7189/jogh.14.05008.

Wahlgren, C., Forsberg, G., Divanoglou, A., Balkhed, Å. Ö., Niward, K., Berg, S., et al. (2023). Two-year follow-up of patients with post-COVID-19 condition in Sweden: A prospective cohort study. *The Lancet Regional Health–Europe*, 28, 100595. https://doi.org/10.1016/j.lanepe.2023.100595.

Waid-Ebbs, J. K., Wen, P. S., Heaton, S. C., Donovan, N. J., & Velozo, C. (2012). The item level psychometrics of the behaviour rating inventory of executive function-adult (BRIEF-A) in a TBI sample. *Brain Injury*, 26(13–14), 1646–1657. https://doi.org/10.3109/02699052.2012.700087.

Whiteside, D. M., Basso, M. R., Naini, S. M., Porter, J., Holker, E., Waldron, E. J., et al. (2022). Outcomes in post-acute sequelae of COVID-19 (PASC) at 6 months post-infection part 1: Cognitive functioning. *The Clinical Neuropsychologist*, 36(4), 806–828. https://doi.org/10.1080/13854046.2022.2030412.

Wilcox, R. R. (2005). *Introduction to robust estimation and hypothesis testing* (4th ed.). San Diego, CA: Academic Press.

Willems, S., Didone, V., Cabello Fernandez, C., Delrue, G., Slama, H., Fery, P., et al. (2023). COVCOG: Immediate and long-term cognitive improvement after cognitive versus emotion management psychoeducation programs-a randomized trial in covid patients with neuropsychological difficulties. *BMC Neurology*, 23(1), 307. https://doi.org/10.1186/s12883-023-03346-9.

Woo, M. S., Malsy, J., Pöttgen, J., Seddiq Zai, S., Ufer, F., Hadjilaou, A., et al. (2020). Frequent neurocognitive deficits after recovery from mild COVID-19. *Brain Communications*, 2(2), fcaa205. https://doi.org/10.1093/braincomms/fcaa205.

World Health Organization (2019). *International statistical classification of diseases and related health problems, ICD-11* (11th ed.). Geneva, Switzerland: World Health Organization.

World Health Organization (2021). *Une définition de cas clinique pour l'affection post-COVID-19 établie par un consensus Delphi, 6 octobre 2021 (No. WHO/2019-nCoV/Post_COVID-19_condition/Clinical_case_definition/2021.1)*. Geneva, Switzerland: Organisation mondiale de la Santé.

Wu, X., Xiang, M., Jing, H., Wang, C., Novakovic, V. A., & Shi, J. (2024). Damage to endothelial barriers and its contribution to long COVID. *Angiogenesis*, 27(1), 5–22. https://doi.org/10.1007/s10456-023-09878-5.

Zimmermann, P., & Fimm, B. (2004). A test battery for attentional performance. In M. Leclercq & P. Zimmermann (Eds.), *Applied neuropsychology of attention* (pp. 124–165). London, UK: Psychology Press.

Archives of Clinical Neuropsychology, 2025, 00, 1–18
https://doi.org/10.1093/arclin/acaf064
Original Empirical Article