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REVIEW ARTICLE

What do we mean by long COVID? A scoping review of the cognitive sequelae of SARS-CoV-2 infection

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Abstract

Background and purpose: Many COVID-19 patients report persistent symptoms, including cognitive disturbances. We performed a scoping review on this topic, focusing primarily on cognitive manifestations.

Methods: Abstracts and full texts of studies published on PubMed (until May 2023) addressing cognitive involvement persisting after SARS-CoV-2 infection were reviewed, focusing on terms used to name the cognitive syndrome, reported symptoms, their onset time and duration, and testing batteries employed. Reported psychiatric symptoms, their assessment tools, and more general manifestations were also extracted.

Results: Among the 947 records identified, 180 studies were included. Only one third of them used a label to define the syndrome. A minority of studies included patients according to stringent temporal criteria of syndrome onset (34%), whereas more studies reported a minimum required symptom duration (77%). The most frequently reported cognitive symptoms were memory and attentional–executive disturbances, and among psychiatric complaints, the most frequent were anxiety symptoms, depression, and sleep disturbances. Most studies reported fatigue among general symptoms. Thirty-six studies employed cognitive measures: screening tests alone ($n = 19$), full neuropsychological batteries ($n = 25$), or both ($n = 29$); 30 studies performed psychiatric testing. Cognitive deficits were demonstrated in 39% of subjects, the most frequently affected domains being attention/executive functions (90%) and memory (67%).

Conclusions: Currently, no agreement exists on a label for post-COVID-19 cognitive syndrome. The time of symptom onset after acute infection and symptom duration are still discussed. Memory and attention–executive complaints and deficits, together with fatigue, anxiety, and depression symptoms, are consistently reported, but the objective evaluation of these symptoms is not standardized.

KEYWORDS
cognition, COVID-19, long COVID, neuropsychological, post-COVID, psychiatric

Alessia Nicotra and Federico Masserini contributed equally to this work.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has affected more than 500 million people worldwide [1].

The number of reports of neurological manifestations during the acute phase of COVID-19 has risen sharply. Neurologic manifestations of COVID-19 can be broadly divided in two categories: manifestations that occur during the acute phase of the infection (e.g., anosmia and ageusia, encephalopathy, stroke, central hypoventilation, delirium) and manifestations that occur following the acute phase (such as brainstem encephalitis, myelitis, Guillain–Barré syndrome, and so-called long COVID) [2]. Furthermore, after the beginning of the SARS-CoV-2 pandemic, any condition or symptom faintly related to neurological aspects (e.g., headache, confusion, and dizziness), either during the acute infection or in the postinfectious period [3, 4], has been collected and reported under the "neuro-COVID" umbrella [5, 6].

As the proportion of subjects reporting persistent disturbances after the acute infection grew [7], specific outpatient clinics for patients with symptoms following COVID-19 were instituted in many countries. However, although follow-up of infected patients is still being carried out, symptoms have not yet been systematized into well-defined syndromes yet, and therefore the difference between systemic residual consequences of SARS-CoV-2 infection and post-infectious symptoms, persisting after infection or emerging after its clearance, is often blurred [6, 8].

Strictly correlating to the large variability in symptom definition, syndromes after COVID-19 currently lack a shared definition and naming [9].

In the attempt to overcome these issues, in October 2021, the World Health Organization (WHO) proposed a definition of COVID-19 sequelae, using the terminology "post-COVID-19 condition" to name any symptom that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, lasting for at least 2 months, and not explained by an alternative diagnosis [10]. Almost at the same time and then regularly updated (last version: November 2022), the UK National Institute for Health Excellence (NICE) proposed to define "post-COVID-19 syndrome" as an unrestricted cluster of often overlapping signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis. By this definition, the term *long COVID* is commonly used to describe signs and symptoms that continue or develop after acute COVID-19 and includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or longer) [11].

Despite these efforts, the definition of this complex syndrome is still evolving. Both of the above-reported definitions fall short in describing syndrome characteristics, because symptoms are not included in the definitions. This has led the number of symptoms attributed to long COVID to grow disproportionately (more than 200 manifestations have been described up to now [12]). Moreover, a definition of temporal boundaries for syndrome onset and persistence that is rooted in direct patient observation more than deriving from biological plausibility is still lacking.

We therefore decided to undertake a scoping review of the literature focusing on labels used to define post-COVID-19 syndrome, reported symptoms, time of onset from acute infection, and tools used to assess and collect these symptoms, with a specific focus on the cognitive ones.

METHODS

Search strategy and information sources

This work was performed according to the PRISMA Guidelines for Systematic Reviews [13]. A scoping review of the medical literature was conducted to identify all published studies addressing primarily cognitive involvement during and after SARS-CoV-2 infection. We included any kind of study that reported (i) patients affected by COVID-19 with proven infection, (ii) cognitive involvement manifested during and persisting after primary infection, and (iii) studies that reported on or employed any kind of cognitive testing to further investigate reported manifestations. Studies that also reported psychiatric or other general manifestations, in addition to cognitive involvement, were also included. Finally, we included literature entries that did not collect direct observational data but that surveyed, also narratively, the topics of interest, if novel elements for syndrome definition were provided by such publications.

We excluded (i) non-English language studies, (ii) nonhuman studies, and (iii) single-case studies or case series with small sample size ($n \leq 5$), and (iv) studies on patients <18 years old.

We searched MEDLINE (PubMed) database on 4 May 2023, using a combination of the following keywords, structured in a complex research string (complete research string is reported in Data S1): "neurocovid", "neuro", "neurocognitive", "COVID-19", "cognitive", and "long COVID", to find any published article that pertained chiefly to neurological or cognitive symptoms/syndromes started during or after COVID-19 infection.

Search results were then uploaded to Covidence systematic review software (Veritas Health Innovation; available at www.covidence.org). Duplicated entries were automatically reviewed and eliminated before screening began. Abstracts of retrieved entries were then reviewed for adherence to inclusion/exclusion criteria independently by two reviewers (A.N. and F.M.). Full texts of included abstracts were then retrieved; search entries for which the full text was not available (online or printed) were excluded. Retrieved full-text reports were finally assessed for adherence independently by the same reviewers, similarly as above. Any conflict was discussed and resolved by consensus. Included reports were finally extracted and data collected in an electronic database. All logs relative to every search step were recorded. Data were extracted focusing on specific terminology employed to define cognitive/neuropsychiatric syndrome following COVID-19, type of symptoms displayed, timing

of symptom onset and duration relative to acute SARS-CoV-2 infection, any cognitive tests or neuropsychiatric scales employed, and outcomes of screening and extensive neuropsychological tests, if available. For each study we extracted title, authors, country in which the study was conducted, aims of the study, study design/type, sample size, terminology adopted, time of onset of symptoms defined or observed after infection or persistence of symptoms, severity of acute infection considered in inclusion criteria, reported symptomatology, cognitive tests/instruments or psychiatric scales employed (if any), results of screening, and extensive neuropsychological tests grouped into major cognitive domains. As far as symptomatology was concerned, we collected data on symptoms that were classifiable into cognitive, psychiatric/behavioral, or general/systemic symptoms.

Statistical analysis

Data synthesis and quantitative analysis of extracted data were performed; descriptive analyses for reported variables were then run with IBM SPSS Statistics software (v28.0). Chi-squared test and kappa statistics were used to assess concordance between dichotomous variables (specifically cognitive symptoms and relative cognitive deficits at neuropsychological testing). Statistical significance was set at $\alpha = 5\%$ ($p = 0.05$).

RESULTS

We identified 947 unique records that underwent title and abstract screening; 557 records were excluded because they contained irrelevant information for the purpose of the study or were unrelated to COVID-19. Five full texts were not available for retrieval. Of the 385 remaining reports, 205 reports were excluded after full text review, and a total of 180 articles were included for data extraction (Figure 1). A list of included works along with summary of relevant data is reported in Table S1 of the supplementary materials.

Types of included studies are reported in Table 1, along with mean study duration and study size.

A label to name a post-COVID-19 syndrome that comprised, among other symptoms, cognitive complaints was reported in 62 studies (Table 2a); five used the label "neuro-COVID," 14 used the term "postacute sequelae of COVID-19" (PASC) and its variant "neuro-PASC," 20 referred to the terminology "post-COVID" with various specifiers and with specific reference to cognitive/neuropsychiatric sequelae (e.g., post-COVID-19 syndrome/condition with cognitive/neuropsychiatric symptoms), 16 mentioned "long COVID with cognitive impairment," and four used the label postacute COVID syndrome (PACS) and its variations. Time trend of use of different labels is reported in Figure S1.

Among studies reporting patients' symptoms ($n = 132$), 121 reported cognitive symptoms, 99 psychiatric symptoms. We surveyed the most frequently reported cognitive, psychiatric, and general symptoms; the relative frequency of symptoms belonging to each category is depicted in Figure 2. Some studies ($n = 33$, 38%) failed to further specify the type of cognitive symptoms. Among studies that characterized them, the most often reported were memory difficulties ($n = 72$, 82%), attentional–executive deficits ($n = 61$, 69%), and psychomotor slowing ($n = 52$, 59%), often also referred to as "brain fog." In terms of psychiatric complaints, depression symptoms were the most frequent ($n = 77$, 78%), followed by anxiety ($n = 76$, 77%), sleep disturbances ($n = 65$, 66%), and stress-related disturbances ($n = 25$, 25%). More general symptoms were also frequently reported, with fatigue being the most common ($n = 96$, 86%), followed by anosmia ($n = 70$, 63%), headache ($n = 69$, 62%), and myalgias ($n = 63$, 56%).

Among studies that were designed for enrollment and observation of patients ($n = 124$), different degrees of COVID-19 severity were reported (Table 2b). Precise temporal criteria for patient enrollment that defined onset and duration of the clinical syndrome were employed in 42 and 96 studies, respectively; on the other hand, timing of symptom onset after COVID-19 infection and duration of post-COVID-19 syndrome were directly derived from patient observation in five and 10 studies, respectively. Timing cutoffs reported in each study for each of these variables are reported in Table 2c,d. Trends of use over time of criteria for patient enrollment and in variations of temporal boundaries for syndrome definition are reported in Figure S2a–c.

Overall, only 24 studies used a definition for the syndrome that included both information about timing (i.e., precise time of onset and precise time of persistence) and a codified list of symptoms to identify patients. Of these latter studies, most derived the definition from the literature ($n = 22$), whereas only two derived it post hoc from the observational data reported in the study itself.

Neuropsychological tests

Seventy-three studies (59% of studies featuring patients' enrollment) employed cognitive measures in patients' assessment, either cognitive screening tests alone ($n = 19$), neuropsychological batteries ($n = 25$), or both ($n = 29$). Overall, Montreal Cognitive Assessment was the most widely used screening test ($n = 33$, 69%), either in its original form or analyzed in its various subdomains ($n = 5$ studies), whereas Mini-Mental State Examination was used in six studies.

The employed neuropsychological batteries tested different domains; proportion of domains investigated, along with most widely used tests for assessing them, is depicted in Figure 3. Notably, 30% of studies employing cognitive testing ($n = 16$) reported only the outcome of testing, without citing cognitive symptoms reported by patients.

Independent of cognitive testing, 71 studies reported assessment of psychiatric comorbidities. Most frequently investigated conditions included depression (21%) and anxiety (19%). Quality of life scales, multidimensional scales, and scales for posttraumatic stress disorder were also employed (respectively in 16%, 7%, and 7% of studies). Relative proportion of each psychiatric domain investigated, along with most reported scales for assessment, is reported in Figure 4.

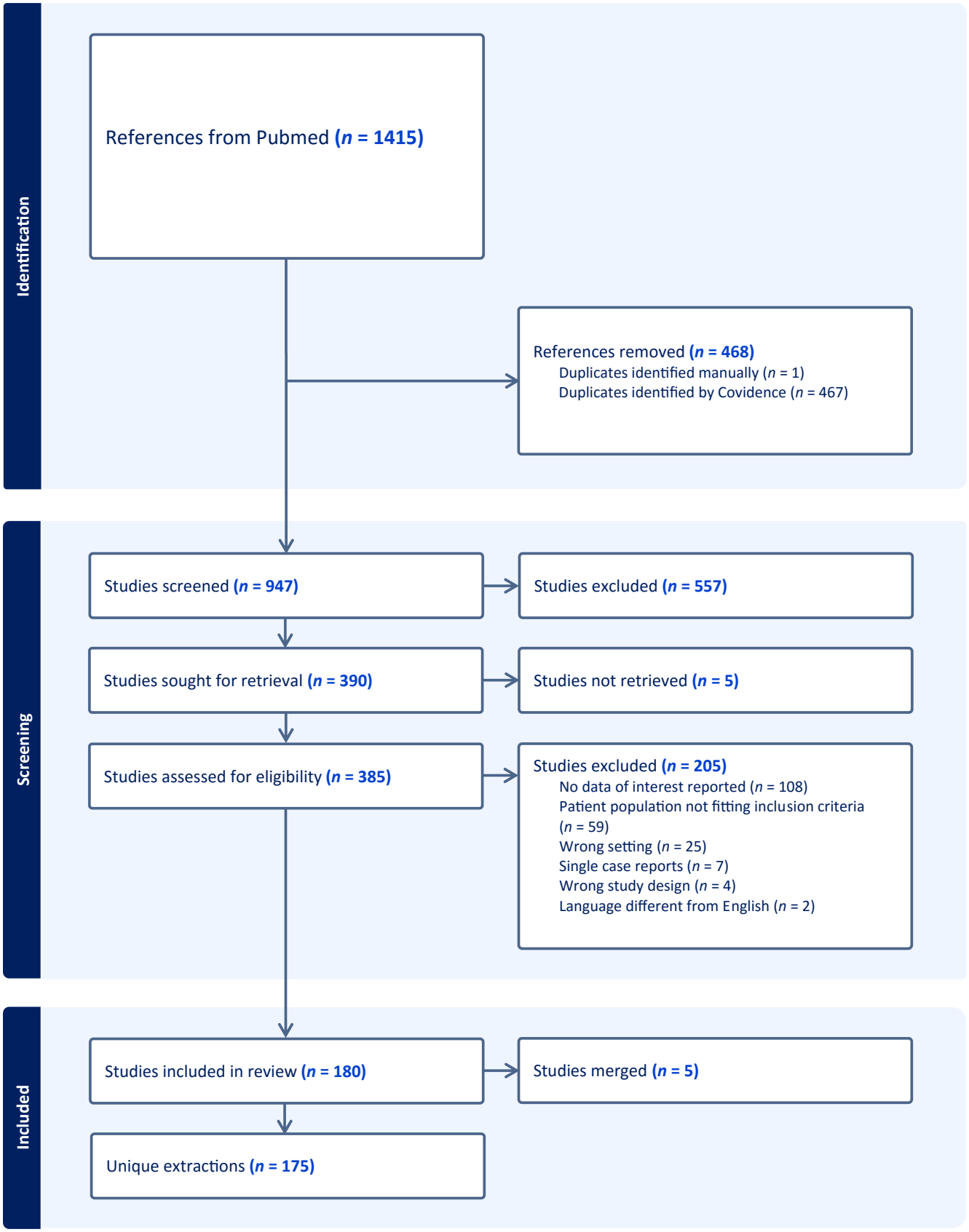

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

TABLE 1 Type of included studies, mean study size, and study duration.

Type of included studies (*n*)	
	Prospective observational studies (104)
	Narrative reviews (23)
	Research letters/expert opinions (11)
	Systematic reviews/meta-analyses (17)
	Interventional studies (7)
	Study protocols (7)
	Case–control studies (6)
Median study size (IQR; range) [patients]	98 (49.75–331.25; 8–299,870)
Median study duration (IQR; range) [days]	223 (163–365; 53–665); studies reporting duration of follow-up: $n = 51$

Abbreviation: IQR, interquartile range.

Finally, 25 studies used quantitative measures for cognitive and psychiatric assessment to assess in depth previously screened cognitive and psychiatric symptoms.

A clear deficit on cognitive screening testing (as reported either by an equivalent score of 0 or by *Z*-score < −1.5) was identified in eight studies (17% of studies employing cognitive screening tests), and in nine studies ($n = 18\%$) a significant difference with a control group, although with absolute values within normal limits, was identified. Among studies reporting results of extensive neuropsychological testing, a clear deficit (by the same aforementioned criteria) was identified in at least one cognitive domain in 21 studies (39% of studies employing neuropsychological testing), with 16 of these reporting multidomain impairment. The most affected cognitive domain was attention and executive functions (affected in 90% cases, $n = 19$) followed by memory ($n = 14$, 67%); a bar chart depicting the number of studies finding deficits for each cognitive domain is provided in the supplementary materials (Figure S3).

In studies characterizing cognitive symptoms and reporting results of neuropsychological testing, symptoms of decreased attention, psychomotor slowing, or memory loss were present respectively in seven (33%), three (14%), and eight cases (38%). Assessing for concordance between attention complaints and attention deficits, no concordance or association was found between reported symptoms and corresponding deficits at neuropsychological testing (chi-squared = 0.367, $p > 0.05$, kappa statistic = −0.11); the same held true also for memory and language ($p > 0.05$).

DISCUSSION

Data from our review show that a unified description of the cognitive manifestations that persist after COVID-19, often reported in combination with psychiatric or other more general manifestations, is still lacking.

TABLE 2 Labels to name a post-COVID syndrome, timing cutoffs after COVID-19, and severity of acute infection.

(a) Diagnostic label	*n*	
No label reported	113	
Post-COVID-19 condition/ syndrome (with cognitive/ neuropsychiatric specifiers)	20	
Long COVID with cognitive impairment	16	
PASC	8	
Neuro-PASC	6	
Neuro-COVID	5	
PACS and composites	4	
Other	3	
(b) Acute COVID-19 severity		
Mild	12	
Mild to moderate	4	
Moderate to severe	9	
All of the above	79	
Not reported	20	
(c) Time of post-COVID symptoms onset	Prespecified	Observed
Within 4 weeks	5	1
Within 8 weeks	4	1
Within 12 weeks	33	2
Within >12 weeks	-	1
Any time of onset	7	1
Not reported	126	169
(d) Post-COVID symptoms duration	Prespecified	Observed
0–3 months	47	2
3–6 months	46	1
6–12 months	2	4
>12 months	1	3
Any persistence	2	–
Not reported	77	165

Note: For time of post-COVID symptoms onset (c) and duration (d), values reported in each study have been grouped in appropriate time categories (as shown in the Table) and stratified according to their definition within each study, either derived from available literature and prespecified in the methods section, or inferred after patient observation, and thus reported within study results.

Abbreviations: PACS, postacute COVID syndrome; PASC, postacute sequelae of COVID-19.

We found considerable heterogeneity even in the labels used to name the syndrome and specifically its cognitive counterpart. The few studies that provide a label used different terms. All the terms used refer to widely variable and often ill-defined syndromes that appear after the acute phase of COVID-19, except for "neuro-COVID," which specifically refers to neurological symptoms, signs, and conditions, yet without distinction between the acute infection phase and the neurological sequelae [14].

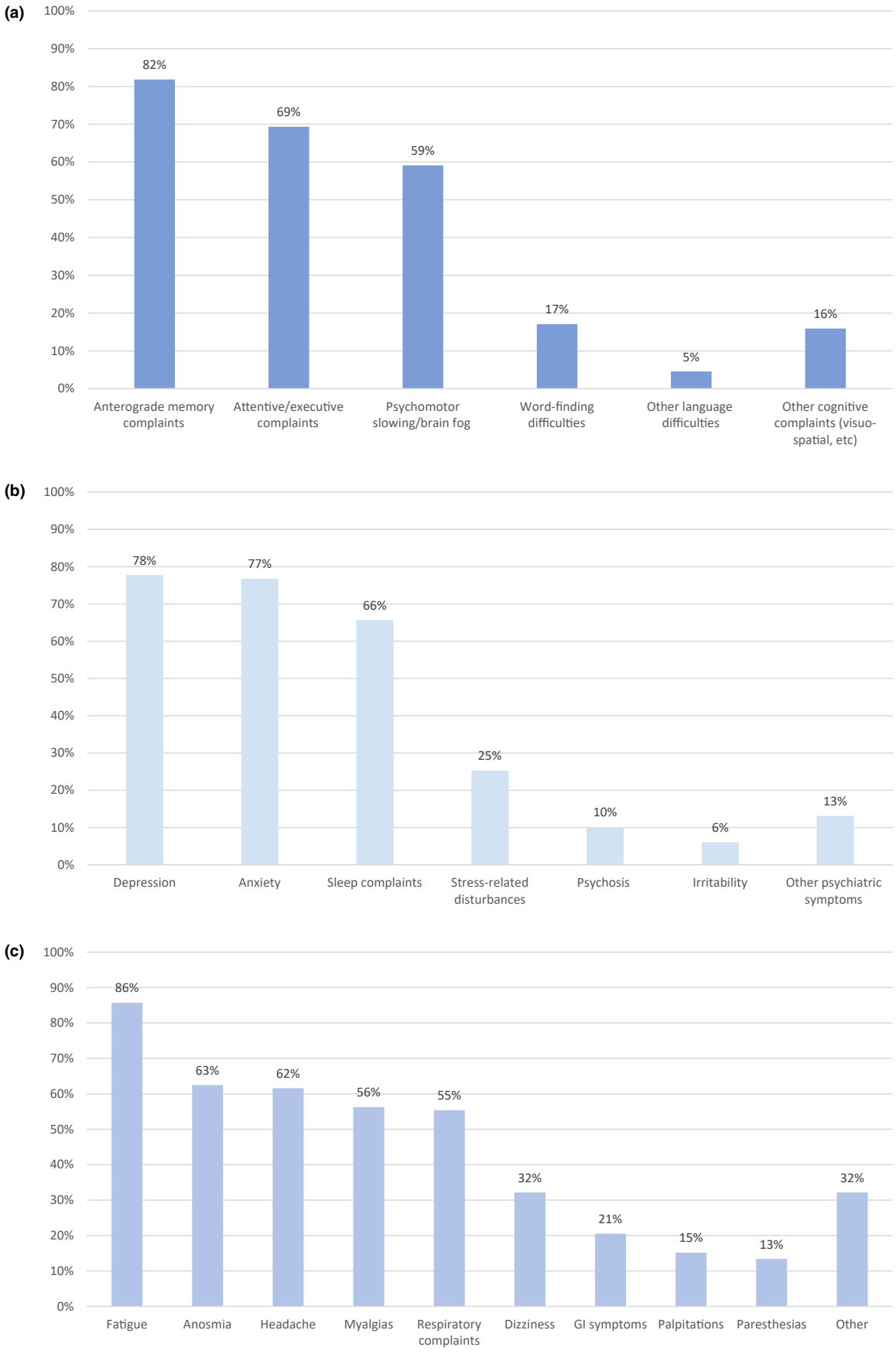

FIGURE 2 Bar chart representing proportion of studies reporting cognitive (a), psychiatric (b), and general (c) symptoms. GI, gastrointestinal.

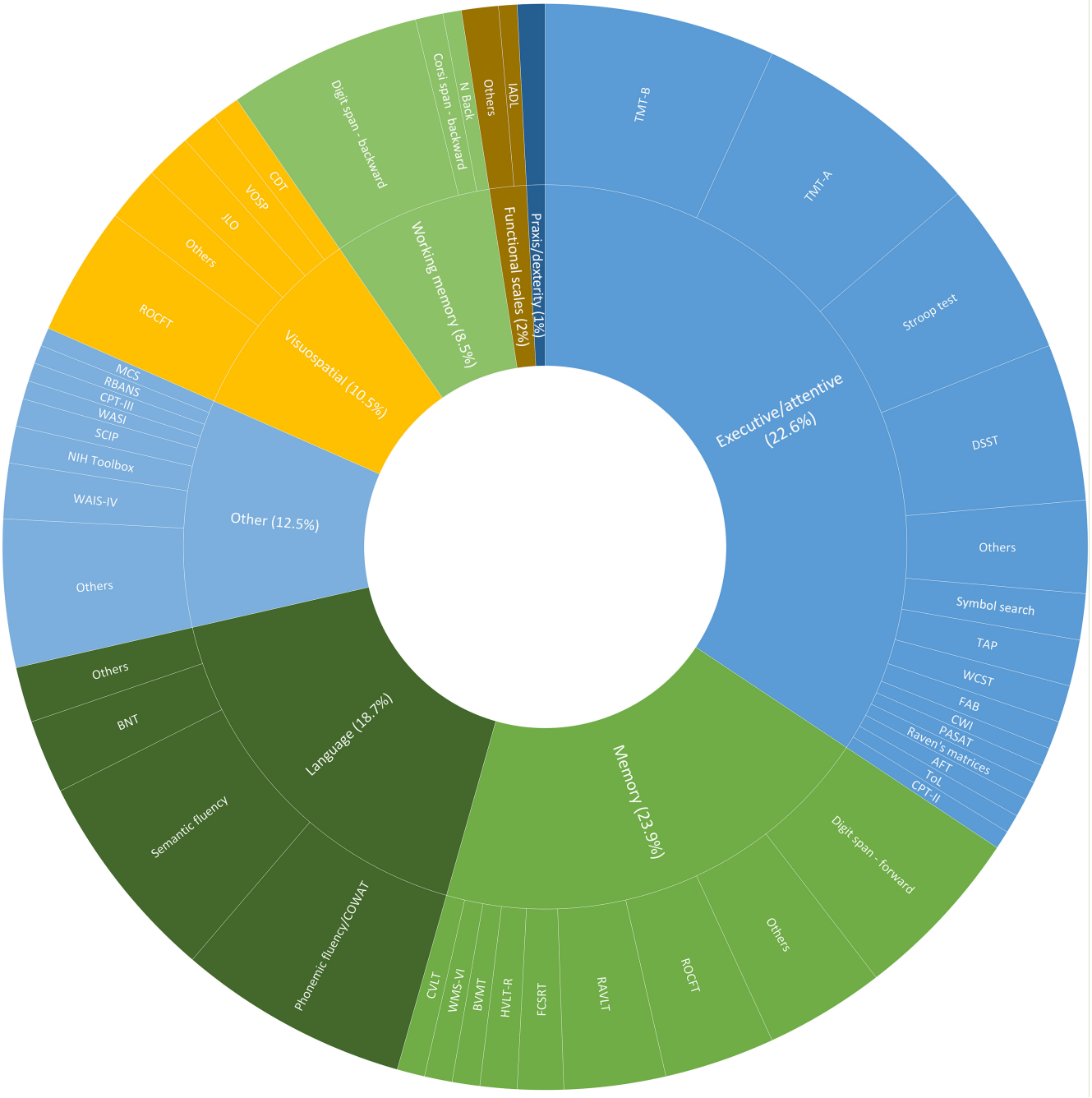

FIGURE 3 Neuropsychological domains evaluated along with specific neuropsychological tests employed (area is proportional to the frequency of employment for each test). AFT, Alternate Fluency Test; BNT, Boston Naming Test; BVMT, Brief Visuospatial Memory Test; CDT, Clock Drawing Test; COWAT, Controlled Oral Word Association Test; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; CWI, Color Word Interference; DSST, Digit Symbol Substitution Test; FAB, Frontal Assessment Battery; FCSRT, Free and Cue Selective Reminding Test; HVLT-R, Hopkins Verbal Learning Test–Revised; IADL, Instrumental Activities of Daily Living; JLO, Judgment of Line Orientation; MCS, Memory Complaint Scale; NIH, National Institute of Health; PASAT, Paced Auditory Serial Addition Test; RAVLT, Rey Auditory Verbal Learning test; RBANS, Repeatable Battery for the Assessment of Neurophysiological Status; ROCFT, Rey–Osterrieth complex figure; SCIP, Subtest Screen for Cognitive Impairment in Psychiatry; TAP, Test of Attentional Performance; TMT, Trail Making Test; ToL, Tower Of London; VOSP, Visual Object and Space Perception Battery; WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition; WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test; WMS-VI, Wechsler Memory Scale, 6th edition.

Notably, in the absence of a shared and fixed meaning for the aforementioned labels, even the same term may acquire different nuances between diverse studies, ultimately referring to slightly different syndromes. Our results are consistent with the findings of Stefanou et al. [15], stating the absence of an agreed or unique definition/label for the prolonged symptoms that may occur after COVID-19. A certain evolution of the use of terminology should, however, be mentioned, because some labels more recently

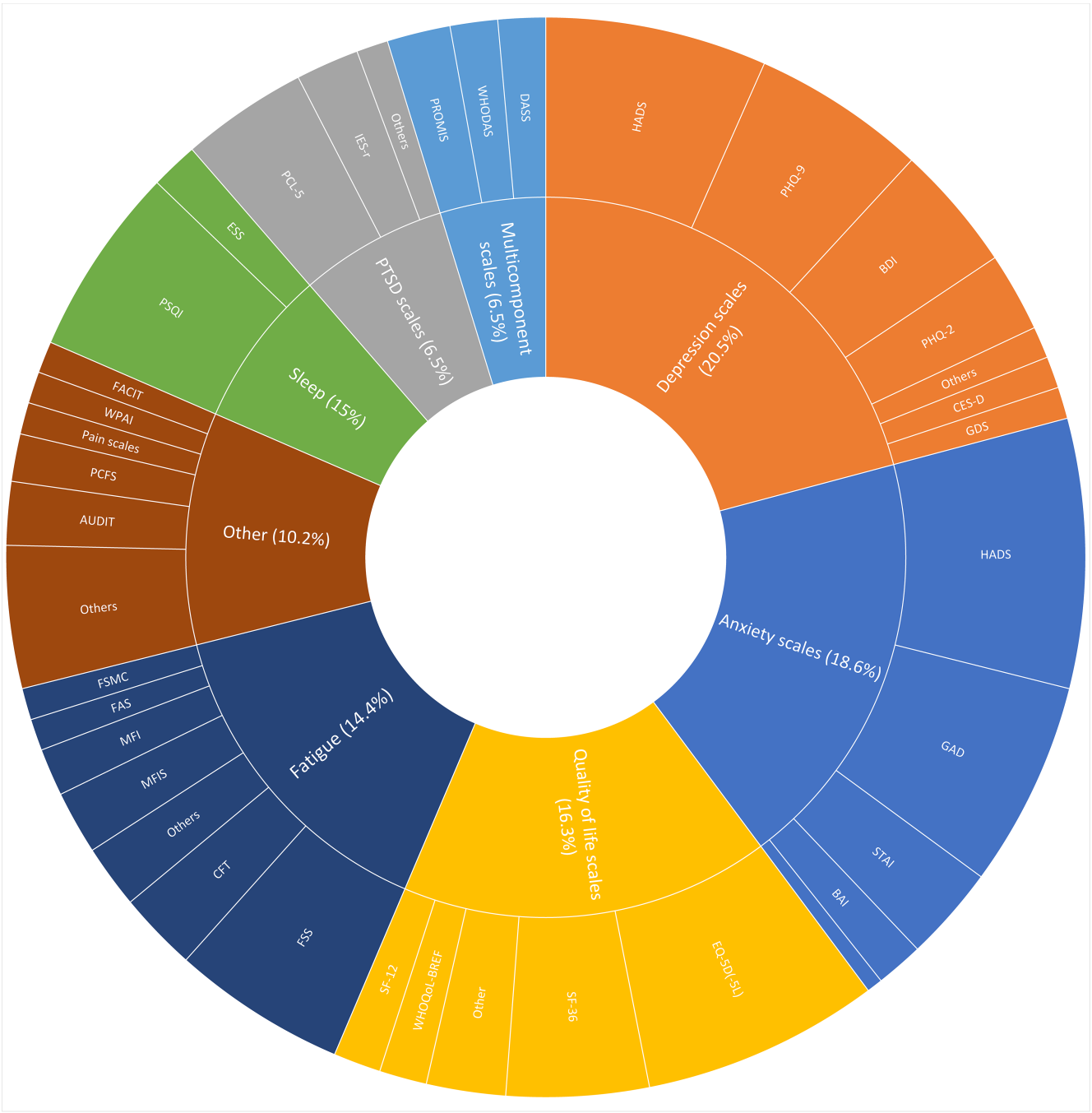

FIGURE 4 Psychiatric symptoms domains evaluated by psychiatric scales along with specific scales employed for each domain (area is proportional to relative frequency of employment for each scale). AUDIT, Alcohol Use Disorder Identification Test; BAI, Back Anxiety Inventory; BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies–Depression; DASS, Depression Anxiety Stress Scale; EQ-5D(-5L), EuroQol five-dimension five-level scale; ESS, Epworth Sleepiness Scale; FACIT, Functional Assessment of Chronic Illness Therapy; FAS, Fatigue Assessment Scale; FSMC, Fatigue Scale for Motor and Cognitive Function; FSS, Fatigue Severity Scale; GAD, General Anxiety Disorder; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; IES-r, Impact of Event Scale–Revised; MFI, Multidimensional Fatigue Inventory; MFIS, Modified Fatigue Impact Scale; PCFS, Post-COVID-19 Functional Status; PCL-5, PTSD Checklist for DSM-5; PHQ, Patient Health Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; PSQI, Pittsburgh Sleep Quality Index; PTSD, Posttraumatic Stress Disorder; SF-12, 12-Item Short Form Survey; SF-36, 36-Item Short Form Survey; STAI, State–Trait Anxiety Inventory Questionnaire; WHODAS, World Health Organization Disability Assessment Schedule; WHOQoL-BREF, World Health Organization Quality-of-Life Scale; WPAI, Work Productivity and Activity Impairment Questionnaire.

proposed, for example, post-COVID-19 syndrome/condition (with cognitive/neuropsychiatric features) and PASC/PACS (and variations thereof), are becoming frequently used.

Moreover, and particularly in older studies, we found a lack of standardization of the temporal relationship between the appearance of the cognitive syndrome and the infection, both in terms of

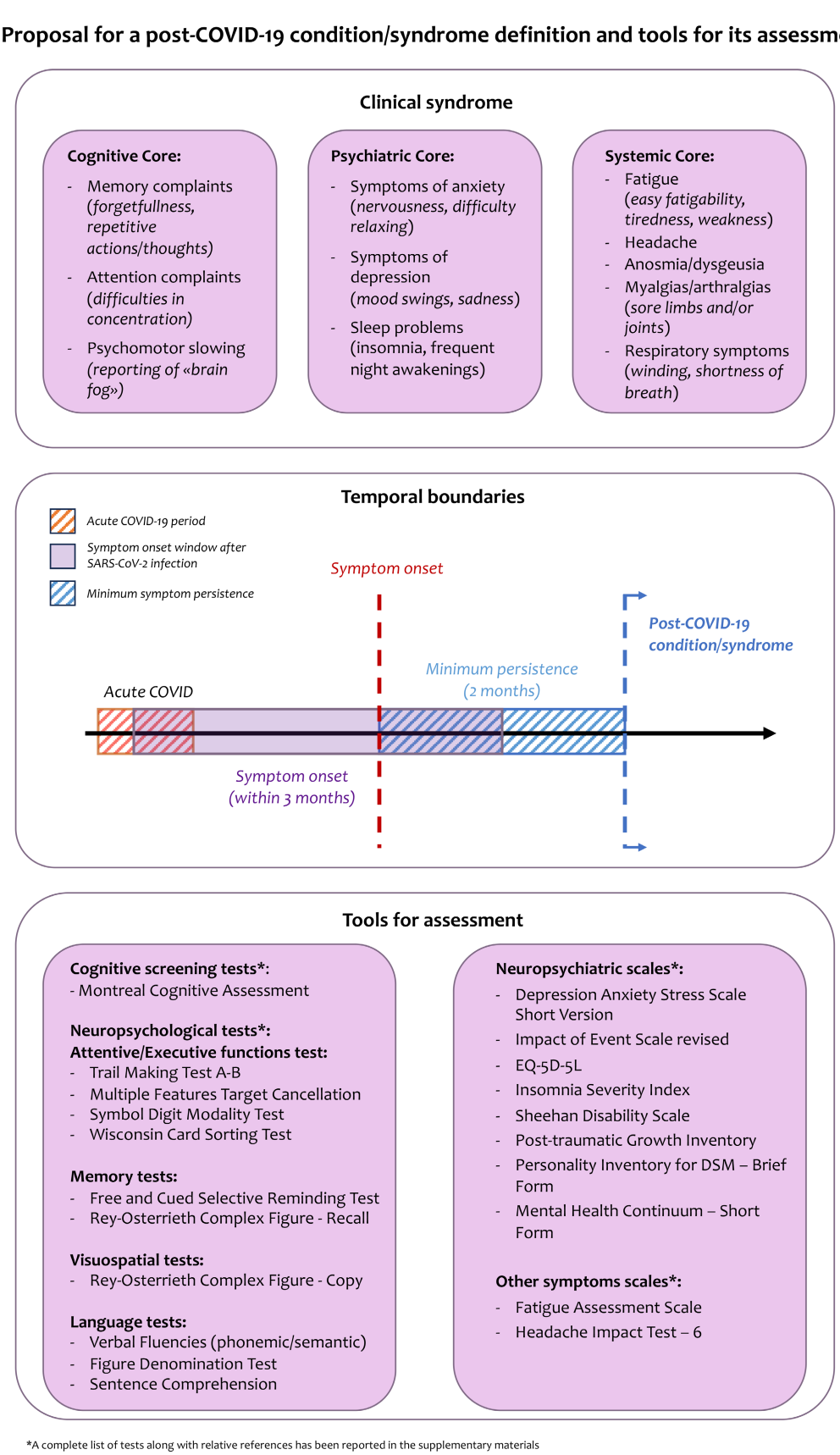

FIGURE 5 Graphical summary of post-COVID condition/syndrome with cognitive/neuropsychiatric symptoms. Clinical characteristics, temporal limits, and an example of neuropsychological battery together with neuropsychiatric and other tools useful for its clinical testing are reported. A complete list of tests along with respective references for the cited instruments is provided in the supplementary materials. DSM, Diagnostic and Statistical Manual of Mental Disorders; EQ-5D-5L, EuroQol five-dimension five-level scale.

persistence of symptoms after their onset and, importantly, in terms of onset after COVID-19.

The UK NICE proposed defining post-COVID-19 syndrome as "an unrestricted cluster of often overlapping signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis" [11]. Similarly, the WHO [10], by expert consensus, has fixed temporal boundaries for post-COVID-19 condition, that is, beginning within 3 months of acute COVID-19 and lasting for at least 2 months from its onset.

Both definitions, however, lack phenomenological specificity, lacking a description of features that may be characteristic of this condition. Moreover, the proposed temporal boundaries, although reasonable, seem somewhat artificial [9] and need further validation of their true biological meaning, because manifestations of long COVID syndrome/post-COVID-19 condition often begin in the immediate postacute period and persist well after 2–3 months [6, 16], as shown in our review. This notwithstanding, this standardization effort by the scientific community is reflected in patients' enrollment criteria reported in most recent works, which show a gradual and growing incorporation of these guidelines.

Despite the plethora of symptoms sometimes ascribed to long COVID [12], our review shows that cognitive manifestations of long COVID are quite consistent, particularly memory (reported in 82% of studies) and attentional complaints (reported in 69%). Our review also shows that cognitive symptoms are often accompanied by other noncognitive disturbances such as anxiety (77%) and depressive (78%) symptoms, and fatigue (85%). However, reported symptoms lack, once more, standardization of the tools employed for their objective assessment [17].

Many studies incorporated cognitive measures within their assessment protocol; some considered it sufficient to use a cognitive screening test alone, whereas an extensive neuropsychological battery was used in less than half of the studies. Nevertheless, employed neuropsychological batteries differed significantly in explored cognitive domains, even if a clear prevalence of attentive–executive, memory, and language functions can be observed. In studies also surveying psychiatric symptoms, self-administered scales were frequently used, even though with much heterogeneity of tools.

Overall, the reported subjective complaints are only seldom systematically followed by formal neuropsychological testing or psychiatric testing/evaluation, making substantiation of post-COVID-19 syndromes difficult. Furthermore, cognitive domains and psychiatric symptoms are rarely investigated and reported together (only in 20% of studies), making it difficult to draw a complete picture of this complex and often varied syndrome.

Finally, studies that reported the outcomes of neuropsychological testing have shown that attention and executive functions were affected in almost all cases, often together with memory, but the association with reported symptoms seems quite loose. This may suggest that the picture is even more complex, with partial disentanglement between cognitive and neuropsychiatric symptoms manifested by these patients and cognitive sequelae found at formal testing, a concept that has been already postulated in several previous works [18, 19].

Because inhomogeneity in diagnostic criteria and methods for investigation have profound implications in both clinical and research practice (e.g., to correctly diagnose patients and hence to enroll them in clinical studies that investigate post-COVID sequelae and their treatment), a greater effort is needed in developing a shared framework to describe and assess post-COVID sequelae.

Considering the findings of our review, we postulate that cognitive complaints within long COVID/post-COVID-19 syndrome are part of a larger syndrome in which we recognize three main symptom cores (i.e., cognitive, psychiatric, and systemic) and that, within these cores, symptoms most consistently reported are difficulties in memory and attention, depression and anxiety, and fatigue, together with headache, anosmia/dysgeusia, myalgias, and respiratory complaints.

Short of a temporal definition rooted into prolonged patients' observation, it seems reasonable to assess these manifestations within the temporal framework set by the NICE guidelines and WHO for "post-COVID-19 condition" (i.e., symptoms beginning within 12 weeks/3 months since acute COVID-19, with 2 months persistence from onset or at least persisting beyond 12 weeks after acute infection itself).

Standardization of batteries or establishment of a consensus on which cognitive domains should be investigated, and by which tools, together with appropriate psychiatric testing, appears desirable in this context. In line with the results of our review, we propose that cognitive evaluation should include at least a thorough assessment of attentive/executive, memory, and language functions, whereas psychiatric testing should be directed toward the investigation of depressive, anxiety, and adjustment disorder symptoms. A summary of syndrome characteristics as well as a proposal for neuropsychological and neuropsychiatric tools for their assessment is reported in Figure 5.

Our review has some limitations. First and foremost, we decided to focus primarily on cognitive symptoms after COVID-19; this may have limited our ability to screen studies reporting other kinds of symptoms (e.g., psychiatric, and other general symptoms). Although this may be true, the relative similarity in proportion of studies reporting neurological and psychiatric symptoms found in our review seems to suggest that these symptoms are tightly associated. Moreover, we limited our search to one database (PubMed). Finally, the short duration of most of the observational studies so far performed may have limited the ability to catch the full picture of post-COVID-19 syndrome. In this regard, results of larger observational cohort studies with longer longitudinal follow-up are needed to further clarify the characteristics of the syndrome along with its natural history.

AUTHOR CONTRIBUTIONS

Alessia Nicotra: Conceptualization; methodology; writing – original draft; data curation; formal analysis. **Federico Masserini:** Conceptualization; methodology; data curation; formal analysis; writing – original draft. **Francesca Calcaterra:** Writing – review & editing. **Clara Di Vito:** Writing – review & editing. **Pietro Emiliano Doneddu:** Writing – review & editing. **Simone Pomati:** Supervision; writing – review &

editing. **Eduardo Nobile-Orazio:** Writing – review & editing. **Agostino Riva:** Writing – review & editing. **Domenico Mavilio:** Writing – review & editing. **Leonardo Pantoni:** Supervision; conceptualization; methodology; writing – review & editing.

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CONFLICT OF INTEREST STATEMENT

A.N. has been partially supported by a liberal donation from PIAM Pharmaceutics Italy to the Neuroscience Research Center, Department of Biomedical and Clinical Sciences, University of Milan.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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