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Assessing cognitive impairments in individuals previously infected with COVID-19: A meta-analytic approach

Faculdade de Ciências Humanas e Sociais

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Trabalho efetuado sob a orientação do Professor Doutor Luís Faísca

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Declaração de Autoria do Trabalho

Declaro ser o autor deste trabalho, que é original e inédito. Autores e trabalhos consultados estão devidamente citados no texto e constam na listagem de referências incluídas.

Assinatura

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(Nicole Pereira Amem)

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Abstrato

A Síndrome Respiratória Aguda Grave 2 (SARS-CoV-2) conhecida como novo coronavírus, é o agente responsável pela Doença por Coronavírus 2019 (COVID-19). Esta doença foi inicialmente identificada em dezembro de 2019 na China, mais especificamente, na cidade de Wuhan, da província de Hubei. Apesar desta infeção aguda ser frequentemente reportada como uma doença respiratória, está associada com o envolvimento de múltiplos órgãos. Apesar de os sintomas mais frequentemente associados à COVID-19 serem caracterizados como febre, tosse e dificuldades respiratórias, um espetro de sintomas, entre os quais défices a nível cognitivo têm sido reportados. Comumente referidos como "*COVID brain fog*", esta síndrome relacionada com a infeção SARS-CoV-2 é caracterizada um conjunto de sintomas como dificuldades de concentração, foco e manutenção da atenção, estando associada a dificuldades no quotidiano. Frequentemente, estas dificuldades prolongam-se durante longos períodos, persistindo até vários meses após a infeção inicial, independente do nível de severidade de doença. A etiologia destes sintomas ainda não é totalmente compreendida, tendo em conta a própria complexidade da estrutura cerebral, o percurso incerto pelo qual o vírus SARS-CoV-2 potencialmente invade o Sistema Nervoso Central, bem como o espetro de possíveis mecanismos de resposta do corpo ao vírus.

A presente meta-análise tem como objetivo explorar quais os potenciais domínios cognitivos afetados pelo COVID-19. Foram utilizadas as bases de dados PsycINFO, PubMed e Web of Science durante o percurso de investigação, tendo sido utilizados termos relacionados com cognição e COVID-19, como: *[(COVID-19 OR coronavirus OR Sars-cov-2) AND (cognition OR cognitive impairment)]*. Foram selecionados inicialmente 3833 artigos no total. Para serem incluídos, os estudos deveriam incluir: um grupo de indivíduos previamente infetados com SARS-CoV-2 sem histórico prévio de disfunção cognitiva, dados normativos ou grupo de controlo sem histórico de infeção por SARS-CoV-2, resultados neuropsicológicos objetivos após COVID-19, apresentar informação necessária para o cálculo dos *effect sizes* e estar escrito em inglês, português ou espanhol. Foi utilizado o *sofwtare "Comprehensive Meta-Analysis"* para a análise dos dados deste estudo. De modo a estimar os *effect sizes*, recorreu-se a um *random effects approach.*

Foram considerados os domínios: funcionamento executivo, velocidade de processamento, memória verbal, memória de trabalho verbal, funcionamento global,

memória visual, linguagem, viso-construção, atenção, memória de trabalho visual, raciocínio, imagética visual, viso-perceção, orientação espacial e temporal, e memória global.

A meta-análise abrangeu 43 estudos com 5546 indivíduos previamente infetados com SARS-COV-2 e 3647 indivíduos saudáveis sem histórico de COVID-19. A idade média dos pacientes com COVID foi 48,82 anos, e nos controlos foi 46,24 anos. A proporção média de mulheres nos grupos foi de 53% e 57%, respetivamente. A média de anos de educação foi 14,33 para o grupo COVID e 14,74 para o controlo. Quanto ao tempo desde a infeção, a média foi de 154 dias. Em relação à severidade da doença, 42,59% da amostra foi classificada como de nível misto (vários níveis de severidade incluídos na mesma amostra), 14.81% como ligeiro, 11,11% moderadas, 14,81% severo e 16,67% não relataram esta medida. Quanto à região geográfica, a maioria dos estudos incluídos eram da Europa (62.79%), de seguida América (18.60%), Ásia (11.63%), e África (2.33%), sendo que 4.65% não estavam atribuídos a uma região. A maioria dos estudos incluídos tinha dois grupos, sendo estes 31 no total, e os restantes 12 estudos incluíam um grupo. Em relação ao tipo de avaliação utilizado, 37 estudos implementaram avaliações presenciais, enquanto 6 estudos implementaram avaliações remotas.

Os *effect sizes* observados variaram entre pequena a moderada magnitude, sendo predominantemente significativos. Os resultados do presente estudo sugerem uma influência negativa do COVID-19 sobre o funcionamento cognitivo global. Inclusive, mais especificamente, foram encontrados resultados significativos no funcionamento executivo, na velocidade de processamento, na memória verbal, na memória de trabalho verbal, na memória visual, na linguagem, na atenção, na memória de trabalho visual e na viso-perceção.

Foram inclusive identificados efeitos de moderação significativos, sendo estes a idade, o sexo, o tempo após COVID-19, o ponto de início reportado, a diferença de anos de educação entre o grupo COVID e o grupo de controlo, os sintomas de depressão, os sintomas de ansiedade, a severidade da doença e a região geográfica onde o estudo foi realizado. Os resultados apresentados sugerem que a idade poderá intensificar o fraco nível de desempenho em tarefas de funcionamento executivo e atenção, no entanto, indivíduos com mais idade apresentam menor comprometimento a nível da velocidade de processamento. O sexo feminino foi associado a um pior desempenho em tarefas de funcionamento global, bem como funcionamento executivo, velocidade de

processamento, atenção e raciocínio. O tempo deste a infeção demonstrou uma associação com melhorias a nível do funcionamento executivo. Diferenças em anos na educação entre grupos afetaram a memória verbal. O ponto de início reportado nos estudos incluídos teve influência sobre a velocidade de processamento, a memória de trabalho verbal, o raciocínio e a atenção. Relativamente a fatores psicopatológicos, sintomas de depressão apresentaram uma influência significativa sobre memória verbal, e sintomas de ansiedade sobre linguagem. O nível de severidade de doença teve efeito sobre o raciocínio e viso-construção. O tipo de avaliação apresentou um efeito sobre a atenção. Por fim, a região geográfica onde o estudo foi realizado exerceu um efeito significativo sobre a linguagem.

É importante salientar que a investigação disponível sobre os défices cognitivos perante a COVID-19 é heterogénea devido à contribuição de diversos fatores. A proliferação acelerada de estudos empenhados em compreender os mecanismos do SARS-CoV-2, bem como as consequências associadas, tais como défices cognitivos, embora notável e necessária, pode apresentar desafios aos padrões científicos. Vários estudos não incluíram grupos de controlo saudáveis para comparação. A situação pandémica global, durante a maior parte da realização e publicação da pesquisa, foi marcada por medidas de restrição de mobilidade, resultando na utilização de diferentes métodos de avaliação, alternando entre avaliações presenciais limitadas e avaliações remotas.

Os resultados da presente meta-análise suportam a ideia de que existe uma associação entre o COVID-19 e défices cognitivos. Deste modo, especificam a ideia do potencial padrão de sintomas associados à doença. Tendo em conta as proporções que a pandemia já atingiu, com um número de infeções alarmante, é importante ter em conta a implementação de avaliações neuropsicológicas em indivíduos previamente infetados com SARS-CoV-2.

Palavras-chave: COVID-19, *SARS-CoV*-2, coronavírus, teste neuropsicológico, cognição, défices cognitivos

Abstract

The new coronavirus named *Severe Acute Respiratory Syndrome Coronavirus-2* (*SARS-CoV-2*) is responsible for the Coronavirus disease 2019 (COVID-19). COVID-19 was initially identified in December 2019 in Wuhan, Hubei province of China. Although this acute infectious disease is often reported as a respiratory disease, it is associated with the involvement of multiple organs. A spectrum of symptoms resulting from SARS-CoV-2 has been described. Among these, cognitive impairment has consistently been reported, often being associated to a significant burden on the daily lives of previously infected individuals.

The current meta-analysis aimed to explore the potential specific cognitive domains affected by COVID-19. In the course of investigation, a literature search was conducted in PsycINFO, PubMed and Web of Science, retrieving a total of 43 studies.

Our findings indicate impaired results in executive functioning, processing speed, verbal memory, verbal working memory, global functioning, visual memory, language, attention, visual working memory and visual perception. Although in-depth investigation regarding the influence of COVID-19 on cognitive functioning is still necessary, this study provides evidence suggesting an association between COVID-19 and cognitive impairment.

Keywords: COVID-19, *SARS-CoV*-2, coronavirus, neuropsychological test, cognition, cognitive impairment.

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Introduction

Coronavirus disease 2019 (COVID-19) was originally identified in Wuhan, Hubei province of China in December 2019 (Zhou et al., 2020a). On March 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic caused by *Severe Acute Respiratory Syndrome Coronavirus-2* (*SARS-CoV-2*) (World Health Organization, 2021). As of 21 September 2023, there have been 770 million confirmed COVID-19 cases and 6 million deaths globally (https://covid19.who.int). *SARS-COV-2* is a type of virus that comprises a single-stranded *ribonucleic acid* (RNA) and binds to *angiotensin converting enzyme 2* (ACE-2) receptor in order to commence a replication cycle in its host cells (Alnefeesi et al., 2021; Zhou et al., 2020a).

The primary symptoms frequently associated with COVID-19 are fever, cough and shortness of breath (Li et al., 2020). While COVID-19 is predominantly characterized by its effects on the respiratory system, it has been acknowledged that it can also affect various other organs, being a multi-organ pathology that results in a broad variety of symptoms (Gupta et al., 2020; Gavriatopoulou et al., 2020). Colloquially termed as "COVID brain fog", this common syndrome related to SARS-CoV-2 infection is characterized by a variety of neurocognitive symptoms encompassing issues such as difficulty in focusing, concentrating and maintaining attention (Becker et al., 2021; Nasserie et al., 2021). These symptoms may persist several months after acute illness in previously infected individuals, regardless of the severity of the initially presented symptoms, commonly referred to as long COVID (or post-COVID condition) (Dagan et al., 2021).

Brain sequelae has been a matter of concern, as neurological symptoms that vary in extent are common in infected individuals, being smell and taste dysfunction the most prevalent (Butowt & Bartheld, 2020). Neuroimaging findings have provided an insight into brain damage in COVID-19 patients, evidencing cerebrovascular events, hypoxic alterations, metabolic modifications of astrocytes, microglial activation, neuro-axonal damage, as well as neuronal loss (Xu et al., 2023). Neuropathological findings have also contributed to the understanding of the possible extent damage related to *SARS-COV-2* in the brain, evidencing hypoxic and ischemic abnormalities, infarcts and microglial activation (Thakur et al., 2021). These findings go accordingly to a significant proportion of infected individuals that have been reported to exhibit psychological, neurological and cognitive changes, which may manifest during acute stage of illness and post-illness

(Schou et al., 2021, Ceban et al., 2022). A systematic review and meta-analysis performed by Ceban et al (2022), in which the proportion of cognitive impairment in individuals evaluated 12 or more weeks after Sars-Cov-2 infection diagnosis was quantified, revealed that over 20% of the collected sample experienced cognitive consequences after acute COVID-19. Earlier research indicates that cognitive impairment is a consequence commonly found in COVID-19 patients which can be manifested through wide range of symptoms. Although research examining cognitive functioning often reports a high prevalence and pattern of cognitive impairments, especially concerning executive functioning, attention and memory (Bungenberg et al., 2022; Costas-Carrera et al., 2022; Crivelli et al., 2022; Jaywant et al., 2021; Krishnan et al., 2022; Lopez-Leon et al., 2021; Mazza et al., 2021; Miskowiak et al., 2021; Miskowiak et al., 2023), results are still inconsistent, as studies have also found insignificant or minor cognitive decline in COVID-19 patients (Mattioli et al., 2021; Whiteside et al., 2022; Francis et al., 2023; Rennison et al., 2023). Some reviews highlight particular domains of cognitive impairment after COVID-19 infection, including executive functioning, attention and memory (Bertuccelli et al., 2022; Biagianti et al., 2022; Crivelli et al., 2022; Tavares-Júnior et al., 2022).

The etiology of these symptoms as well as the mechanisms involved in potential long-lasting impairments are still not completely understood, given a variety of factors such as the complexity of brain structure and function, the unclear course of central virus invasion, as well as the spectrum of possible responses to the virus (Xu et al., 2023). However, the varied symptomatology suggests multiple pathogenic pathways related to the central nervous system (CNS). It has been proposed that these mechanisms may be involved in the etiology of cognitive dysfunction in COVID-19 patients (Heneka et al., 2020). Several hypotheses have been suggested, including possible direct effects of the virus in the brain or indirect effects through local and systemic responses against *SARS-COV-2* (Pattanaik et al., 2023). Direct invasion of the nervous system has been hypothesized to eventuate via olfactory nerves, as ACE-2 receptors seem to be present in the *olfactory mucosa* as well as in the *epithelial sustentacular cells*, this being a possible route of entry into the CNS. Traces of the virus have been found in the olfactory mucosa of post-mortem infected individuals. Other cranial nerves including the *vagus*, *glossopharyngeal* and the *trigeminal* nerves could also serve as a pathway, as they get exposed to the virus during infection (Pattanaik et al., 2023). Regarding possible indirect

invasion of nervous system, immune-mediated mechanisms appear to have a substantial impact, as infection causing systemic inflammatory responses that trigger an excessive production of proinflammatory cytokines such as *interleukins* (*IL-6, IL-2, IL-12 and IL-15*) as well as *tumor necrosis factor alpha* (*TNF-α*) may cause the activation of *microglial cells*. These cytokines may reach the cerebrospinal fluid spaces of the brain and spinal cord by disrupting and crossing the *blood brain barrier* (*BBB*) (Pattanaik et al., 2023). A systemic reduction of lymphocyte cells as a consequence of virus destruction given their ACE2 expression, decreases the body's defense, which may trigger neural and neuroendocrine dysregulation. A coagulation cascade, resulting in a pathological hypercoagulation state that consequently prompts endothelial injury, is another cause of concern as it provokes pathological brain changes (Xu et al., 2023). The brain capillary endothelium that forms the neurovascular element of the BBB is another potential route for CNS infection (Pattanaik et al., 2023). Another possible mechanism of CNS damage is hypoxia, as it might trigger a hypercoagulable condition conductive to micro thrombotic brain vessel occlusion, as well as ischemic damage (Consentino et al., 2021).

Other factors might also have an impact on cognitive and psychological functioning. Critical care and sedation have been associated with a range of holistic long-term consequences, including the acquisition or exacerbation of cognitive and psychological impairments (Yuan et al., 2020). These consequences have also been studied specifically in COVID-19 survivors, considering the impact of clinical and inflammatory indicators, as well as psychological stressors (such as distress and traumatic recollections related to illness, stigma, isolation from social networks and concern of transmitting virus to others), revealing substantial proportions of depression, anxiety, obsessive compulsive disorder, *post-traumatic stress disorder (*PTSD) and insomnia (Mazza et al., 2020).

As research into the impact of COVID-19 on cognitive functioning is still ongoing, it is crucial to determine whether this relationship varies based on clinical factors and participant characteristics, in order to comprehend potential intervening variables beyond the disease's impact on cognition.

Several sociodemographic factors, linked to the escalation of COVID-19 symptomatology, may affect the its association with changes in cognitive functioning. Examining sex as a moderating factor to gain insights into its influence on cognitive function in relation to COVID-19 is essential due to previously documented sex-based

disparities regarding overall symptomatology. Male sex has been reported to exhibit tendency for more severe symptoms and a higher mortality rate in contrast to females. Nevertheless, females have been associated with worse outcome changes, being more prone to self-report enduring symptoms beyond the acute phase of illness (Jacobs et al., 2023; Vasilevskaya et al., 2023).

Analyzing the geographical region in which the assessment occurred and where individuals reside is crucial for comprehending whether cognitive impairment linked to COVID-19 is connected to a myriad of intricate environmental and societal elements, as well as possible differences in norms and standards of assessment tied to the specific study location (Jain et al., 2020).

Investigating age as moderator is important in order to detect potential distinction among diverse age groups. Current research finding suggest that COVID-19 has a disproportionate impact on the elderly population, who face a higher likelihood of hospitalization and are associated with elevated mortality rates. Advancing in age has also been linked to increased severity of symptomatology, as well as a reduced quality of life after acute illness (De Biase et al., 2020; Ceban et al., 2021).

The level of education is an important variable to consider as a moderator, as it has previously been reported as a protective factor against the onset of cognitive decline. It has been suggested to have a role in reducing the influence of pathological factors on the clinical presentation of dementia symptomatology (Ott et al., 1995; Liu et al., 2021).

The concept of disease severity denotes the hierarchy of COVID-19 symptomatology (Marshal et al., 2020). Establishing if severity of illness has an impact on cognitive outcomes is a valuable moderator variable, having in mind that previous research has presented conflicting results regarding the impact of severity on cognitive functioning. It has been reported that individuals previously infected with COVID-19 exhibit a worsening of cognitive functioning, whether the severity of their disease refers to as severe or non-severe (Birberg Thornberg et al., 2023; Crivelli et al., 2022). In contrast, other studies have reported that severity is associated with poor cognitive performance, with severe symptoms often being associated to worse cognitive outcomes (Ollilla et al. 2022; Cechetti et al., 2022; Guo et al., 2022; Ceban et al., 2021; Liu et al., 2021).

It is important to consider psychopathology as a moderator when analyzing the impact of COVID-19 on cognitive functioning, as COVID-19 patients have been reported to exhibit a notable occurrence of emergence of psychiatric consequences, including a high incidence of PTSD, major depression and anxiety. These disorders and their clinical symptoms have been linked to increased vulnerability in cognitive processing (Mazza et al., 2020; Büttiker et al., 2022).

Given the heterogeneity in methodologies employed across the existing literature exploring the impact of COVID-19 on cognitive functioning, we intentionally incorporated both one-group and two-group study designs. This deliberate inclusion recognizes the diverse approaches within the field, reflecting the complexity and multifaceted nature of cognitive assessments in the context of COVID-19. Anticipating that such diversity in study designs could influence findings across cognitive domains, we introduced the number of groups as a moderator in our analysis. This strategic choice allows us to systematically assess whether the variation in the number of groups impacts the observed cognitive outcomes, thereby providing a nuanced understanding of the potential moderating effects associated with study design.

Incorporating a temporal dimension into the current analysis was crucial to understand the potential trajectory of cognitive changes over time, as previous studies have reported different cognitive patterns in different phases of the post-COVID condition (Lamontagne et al., 2021; Poletti et al., 2022). This allows us to capture the influence of different time periods in the context of previous SARS-CoV-2 infection, providing a more comprehensive understanding of the aftermath of the condition.

The COVID-19 pandemic precipitated an abrupt and widespread shift in psychological assessment methodologies, leading to a surge in the popularity of remote assessments (Zanin et al., 2021). Recognizing that this increased popularity of remote assessments has resulted in a higher diversity of methodologies, it is crucial to analyze its effects on the considered outcomes.

Lastly, different studies report varied criteria to refer to the beginning of COVID-related events, often referring to temporal starting points such as diagnosis of the SARS-CoV-2 infection, hospital discharge date or disease onset. Therefore, it is important to consider the potential effect of this variability in cognitive outcomes.

The impact of COVID-19 on cognitive functioning has been addressed in a growing number of systematic reviews and some meta-analysis. We encountered three meta-analyses that assessed the cognitive performance of post-COVID individuals in comparison to control groups. Crivelli et al. (2022) focused on Montreal Cognitive Assessment (MoCA) results, a cognitive screening tool found to be reliable in the detection of mild cognitive deficits. Their research included five studies and indicated that individuals with COVID-19 (assessed between the acute phase of illness and 6 months after infection) exhibited a worse overall cognitive performance in comparison to healthy control individuals (*mean difference* = −0.94). Houben et al. (2022) reported multiple cognitive domains extracted from five studies. Their overall results indicated that COVID-19 patients exhibited a significant decrease not only in overall cognitive functioning, but also in specific cognitive domains: attention including three studies (*SMD* = -0.54), executive functioning including four studies (*SMD* = -0.31), fluency including three studies (*SMD* = -0.36), processing speed including two studies (*SMD* = -0.56), verbal memory including one study (*SMD* = -0.98), visuospatial ability including two studies (*SMD* = -0.11) and working memory including five studies (*SMD* = -0.29). Velichkovsky et al. (2023) focused on second-level assessment measures, reporting multiple cognitive functions. Regarding verbal long-term memory, findings from three studies indicated that there were no statistically significant differences between individuals with COVID-19 and healthy controls (*d* = -0.16). Similarly, in visual long-term memory, the inclusion of two studies revealed non-significant results (*d* = -0.67), suggesting comparable performance between individuals with COVID-19 and healthy controls in this cognitive domain. The investigation of visual spatial attention involved two facets: reaction time scores from two studies and accuracy scores from four studies. For reaction time scores, no significant differences were found (*d* = 0.623), indicating a similarity in the speed of visual spatial attention between the two groups. Additionally, for accuracy scores, results across four studies were not significant (*d* = -0.276), suggesting comparable levels of precision in visual spatial attention. Turning to working memory, which was evaluated across five studies, the analysis did not reveal any statistically significant differences between individuals with COVID-19 and healthy controls (*d* = -0.059). In the domain of verbal short-term memory, findings from five studies indicated a small but statistically significant effect (*d* = -0.27). This result suggests that participants with COVID-19 exhibited worse performance in verbal short-term memory compared to healthy controls.

These previous meta-analyses have provided valuable insights into the impact of COVID-19 on cognition. However, it is important to note that these earlier studies were constrained by a limited pool of available studies at the time. In this phase, a broader extent of new studies is available. Therefore, our analysis builds upon this foundational work by incorporating a substantially larger number of studies, thus allowing a more comprehensive and robust analysis of the COVID-19 and cognition literature. This expanded dataset not only enhances the statistical power of our findings, as it also provides a more nuanced understanding of the topic.

In this meta-analysis, we examine the consequences of COVID-19 on cognition using an unrestricted collection of objective neuropsychological tests. Our aim is to analyze if COVID-19 affects cognitive functioning, across different cognitive domains.

Methods

Study selection and inclusion criteria

The studies included in the meta-analysis were identified through three databases: PsycINFO, PubMed and Web of Science. The terms used for the search were related to COVID-19 and cognition [(COVID-19 OR coronavirus OR Sars-cov-2) AND (cognition OR cognitive impairment)]. Regarding the language of the studies, only studies in English were included, plus one in Spanish. The search covered the title, abstract and keywords of all the studies available in the previously mentioned databases until August 2023, identifying 3826 documents. Reference lists of prior meta-analysis and systematic reviews were also screened in order to identify further relevant studies, therefore including 7 additional studies.

In order to be included, studies had to meet the following criteria: (a) clinical group must include adults without previous history of cognitive impairment and with history of COVID-19; (b) if a control group is included, must comprise healthy adults without previous history of COVID-19 or similar infection; (c) report objective neuropsychological outcomes following COVID-19 infection; (d) enclose sufficient information to compute effect sizes; (d) written in English, Spanish or Portuguese.

Regarding longitudinal studies, the data was collected from the first time point available. As for intervention studies, only data prior to the intervention was considered.

When studies were published by the same authors, they were examined for overlapping samples. In this situation, the article that had a larger sample would be included.

Out of the 3833 initial articles, only 43 articles were eligible according to the inclusion criteria (Figure 1).

Recorded variables

For each study, a set of sample characteristics was collected for the COVID and the control groups. This included the following data: sample size, mean age, number of females, mean years of education, geographical region, symptomatology of depression measure (mean results from Patient Health Questionnaire-9 - PHQ-9), symptomatology of anxiety measure (mean results from Hospital Anxiety and Depression Scale – HADS) and type of neuropsychological assessment (remote or in-person). For the COVID group, days post COVID and severity of infection were also included. Disease severity was classified according to WHO, including the levels: mild, moderate and severe. Mixed category was also created in order to include samples that integrated multiple severity levels and therefore could not be attributed to a specific one.

The cognitive domains included were: executive functioning, processing speed, verbal memory, verbal working memory, global functioning, visual memory, language, visual construction, attention, visual working memory, reasoning, visual imagery, visual perception, temporal and spatial orientation and global memory. The measures extracted for each cognitive domain are presented in supplemental table A.

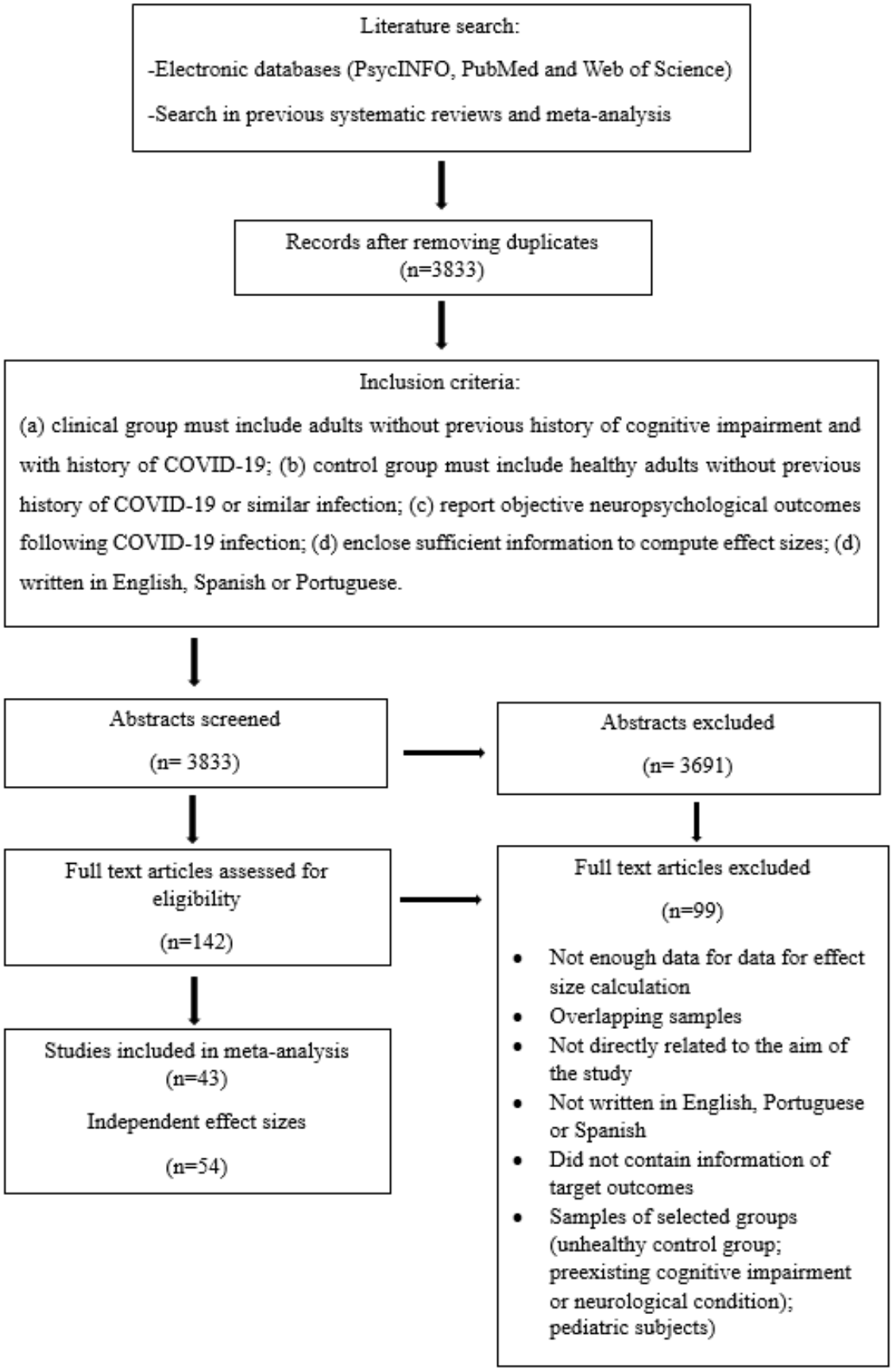

Figure 1 Flow diagram of the screening and selection of articles

Meta analytic procedures

Effect size estimates

Regarding effect sizes that involved group comparisons between COVID groups and control groups, we calculated Cohen's *d*. As for effect sizes that only included a clinical group (COVID group), we considered the normative group as the control group, and used the reported standardized scores, converting all means and standard deviations into *Z-scores*, in order to calculate Cohen's *d* values.

A positive *d* value reports a higher mean by the control group. As recommended by Cohen's (1988) guidelines, effect sizes were interpreted as small ($d = 0.2$), moderate ($d = 0.5$), and large ($d = 0.8$).

To perform data analysis, Comprehensive Meta-Analysis software (Borenstein, Hedges, Higgins, & Rothstein, 2005) was used.

Analysis of effect sizes

A random effects model approach was applied for the estimation of the overall effect sizes, based on the calculation of a weighted average of individual effect sizes (Rosenthal, 1991).

A set of calculations were performed for each meta-analysis: predictions were based on a 95% confidence interval (CI), Z significance test for null effects and its *p* value (<.05), within group heterogeneity (Qwithin) as well as the percentage of variation across studies due to heterogeneity rather than sampling error (I^2).

In order to test the categorical moderator effects, a subgroup analysis with the mixed-effects between groups heterogeneity statistics (Qbetween) was used.

Concerning the continuous moderator effects, a meta-regression based on the random effect sized model was used to calculate variations in effect sizes across studies that included this type of moderator variables, using the percentage of between-study variance explained (R^2) as a measure.

To detect potential outliers and analyze the distributions of effect sizes, forests plots were examined. Sensitivity analysis were also conducted, estimating an overall effect size after the removal of studies one by one, in order to determine the impact of potential outliers on the overall range of means.

To detect the presence of publication bias and possible missing studies, funnel plots for random effects models were analyzed and the "trim and fill" method for random effects models was used (Duval & Tweedie, 2000).

Results

The current meta-analysis included 43 studies (involving a total of 54 samples), with 5546 COVID patients and 3647 healthy controls. The mean age of the individuals in the COVID group was 48.82 years (ranging from 20.50 years to 68.65 years), and in the control group was 46.24 years (ranging from 20.60 years to 68.90 years). The mean proportion of females in the COVID group was 53% (ranging from 5% to 88%), and in the control group was 57% (ranging from 33% to 77%). The mean education years in the COVID group was 14.33 years (ranging from 12 to 17 years), and in the control group was 14.74 years (ranging from 12 to 17 years), however, only 29 samples were reported for the COVID group, and 20 samples for the control group. Regarding the time since COVID infection, 43 samples reported this measure, with a mean of 154 days (ranging from 20 to 365 days). As for the severity of disease, 14.81% (8 samples) were classified as mild, 42.59% (23 samples) as mixed, 11.11% (6 samples) as moderate, 14.81% (8 samples) as severe and 16.67% (9 samples) did not report this data. Regarding the geographical region of assessment, 2.33% (1 study) of the reported studies was from Africa, 18.60%, (8 studies) were from America, 11.63% (5 studies) were from Asia, 62.79% (27 studies) were from Europe and 4.65% (2 studies) were not attributed to a continent. In context of the number of groups, 31 of the included studies had two groups (clinical group and healthy control group) and the remaining 12 studies had one group (clinical group). Lastly, as for the type of assessment, 37 studies implemented in-person assessments and 6 studies implemented remote assessments.

Overall, most of the effect sizes in analysis presented small to moderate significant results. Each cognitive domain is separately analyzed in text below, and presented in table 1.

Cognitive domains

Table 1 Effect sizes with 95% confidence intervals and heterogeneity statistics comparing individuals previously infected with SARS-CoV-2 with healthy controls and normative data.

	k	Effect Size		Z	*p* value	Heterogeneity		
		d	95% CI			I^2	*Q*Within	*p* value
Executive Functioning	44	0.335	0.240-0.431	6.875	<0.001	67.330	131.619	<0.001
Processing Speed	39	0.400	0.302-0.498	7.989	<0.001	69.357	124.008	<0.001
Verbal Memory	33	0.326	0.199-0.453	5.032	<0.001	79.965	159.720	<0.001
Verbal Working Memory	29	0.251	0.110-0.391	3.500	<0.001	78.760	131.824	<0.001
Global Functioning	26	0.540	0.407-0.673	7.946	<0.001	81.830	137.589	<0.001
Visual Memory	16	0.228	0.088-0.368	3.192	0.001	68.321	47.349	<0.001
Language	14	0.245	0.108-0.382	3.501	<0.001	60.557	32.959	0.002
Visual Construction	11	-0.019	-0.485-0.448	-0.078	0.938	95.265	211.206	<0.001
Attention	8	0.294	0.159-0.429	4.262	<0.001	43.025	12.286	0.092
Visual Working Memory	6	0.239	0.071-0.407	2.792	0.005	61.673	13.046	0.023
Reasoning	6	0.376	-0.019-0.770	1.865	0.062	86.580	37.259	<0.001
Visual Imagery	4	0.163	-0.103-0.428	1.199	0.231	65.433	8.679	0.034
Visual Perception	4	0.502	0.229-0.774	3.602	<0.001	51.252	6.154	0.104
Orientation	3	-0.067	-0.246-0.111	-0.738	0.461	0.000	0.393	0.822
Global Memory	3	-0.215	-0.826-0.395	-0.692	0.489	82.027	11.128	0.004

Executive functioning

Forty-four independent effect sizes were computed to assess executive functioning measures in subjects who had previously been infected with SARS-CoV-2. Analysis of the effect size indicated that individuals post-COVID-19 infection performed worse compared to both healthy controls and normative data in the assessed executive functioning measures ($d = 0.335$, 95% CI [0.240, 0.431], $p < 0.001$). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of 0.321 (95% CI [0.227, 0.415]) to 0.355 (95% CI [0.265, 0.445]). In the trim and fill analysis 7 studies were imputed to the left side of the mean, with an adjusted overall mean of 0.258 (95% CI [0.157, 0.358]). Regarding the heterogeneity test, it was

significant, QWithin (43) = 131.619, p <0.001, and more than 67% of the observed variance was not accounted for by sampling error only (I^2 = 67.330).

Processing speed

Thirty-nine independent effect sizes were computed to assess processing speed measures in adults who had previously been infected with COVID-19. Analysis of the effect size indicated that individuals post-COVID-19 infection performed worse compared to both healthy controls and normative data in the assessed processing speed measures, being small and significant (d = 0.400, 95% CI [0.302, 0.498], p <0.001). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of 0.373 (95% CI [0.284, 0.462]) to 0.421 (95% CI [0.327, 0.514]). In the trim and fill analysis 8 studies were imputed to the left side of the mean, with an adjusted overall mean of 0.293 (95% CI [0.185, 0.401]). Regarding the heterogeneity test, it was significant, QWithin (38) = 124.008, p <0.001, and more than 69% of the observed variance was not accounted for by sampling error only (I^2 = 69.357).

Verbal memory

Thirty-three independent effect sizes compared verbal memory measures. The overall effect size revealed that COVID-19 subjects performed worse when compared to healthy controls and normative data, being small and significant (d = 0.326, 95% CI [0.199, 0.453], p <0.001). A sensitivity analysis showed that after the removal of potential outliers, the general effect size would be in range of 0.279 (95% CI [0.170, 0.388]) to 0.349 (95% CI [0.227, 0.471]). In the trim and fill analysis 6 studies were imputed to the right side of the mean, with an adjusted overall mean of 0.427 (95% CI [0.294, 0.560]). As for the heterogeneity test, it was significant, QWithin (32) = 159.720, p <0.001, with more than 79% of the observed variance not being accounted for by sampling error only (I^2 = 79.965).

Verbal working memory

Twenty-nine independent effect sizes were computed to assess verbal working measures. The overall effect size indicated that COVID-19 subjects performed worse in comparison to controls and normative data, being small and significant (d = 0.251, 95%

CI [0.110, 0.391], p <0.001). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of 0.225 (95% CI [0.087, 0.363]) to 0.289 (95% CI [0.172, 0.406]). The trim and fill analysis suggested absence of any publication bias, as no studies were imputed in this case. Regarding the heterogeneity test, it was significant, QWithin (28) = 131.824, p <0.001, and over than 78% of the observed variance was not accounted for by sampling error only (I^2 = 78.760).

Global functioning

Twenty-six independent effect sizes were computed for global functioning measures. The overall effect size indicated that COVID-19 subjects performed worse in comparison to controls and normative data, being medium and significant (d = 0.540, 95% CI [0.407, 0.673], p <0.001). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of 0.511 (95% CI [0.385, 0.636]) to 0.564 (95% CI [0.427, 0.700]). In the trim and fill analysis, no studies were imputed to either side of the mean, as no publication bias was suggested. Regarding the heterogeneity test, it was significant, QWithin (25) = 137.589, p <0.001, and over than 81% of the observed variance was not accounted for by sampling error only (I^2 = 81.830).

Visual memory

Sixteen independent effect sizes compared visual memory measures. The overall effect size was small and significant. This indicated that, when compared to healthy controls and normative data, COVID-19 subjects perform slightly worse (d = 0.228, 95% CI [0.088, 0.368], p =0.001). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of 0.201 (95% CI [0.061, 0.342]) to 0.285 (95% CI [0.205, 0.364]). In the trim and fill analysis 6 studies were imputed to the left side of the mean, with an adjusted overall mean of 0.096 (95% CI [-0.042, 0.235]). Regarding the heterogeneity test, it was significant, QWithin (15) = 47.349, p <0.001, and more than 68% of the observed variance was not accounted for by sampling error only (I^2 = 68.321).

Language

Fourteen independent effect sizes compared language measures. The overall effect size revealed that COVID-19 subjects performed worse when compared to healthy controls and normative data, being small and significant (d = 0.245, 95% CI [0.108, 0.382], p <0.001). A sensitivity analysis showed that after the removal of potential outliers, the general effect size would be in range of 0.198 (95% CI [0.089, 0.308]) to 0.277 (95% CI [0.145, 0.410]). In the trim and fill analysis 1 study was imputed to the left side of the mean, with an adjusted overall mean of 0.196 (95% CI [0.040, 0.353]). As for the heterogeneity test, it was significant, QWithin (13) = 32.959, p =0.002, with over than 60% of the observed variance not being accounted for by sampling error only (I^2 = 60.557).

Visual construction

Eleven independent effect sizes compared visual construction. The overall effect size was small and not significant, not indicating a difference in performance regarding this domain (d = -0.019, 95% CI [-0.485, 0.448], p = 0.938). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of -0.170 (95% CI [-0.621, 0.281]) to 0.129 (95% CI [-0.275, 0.533]). In the trim and fill analysis no studies were imputed, as no publication bias were suggested. Regarding the heterogeneity test, it was significant, QWithin (10) = 211.206, p <0.001, and over than 95% of the observed variance was not accounted for by sampling error only (I^2 = 95.265).

Attention

Eight independent effect sizes compared attention measures. The overall effect size indicated that COVID-19 subjects performed worse in comparison to controls and normative data, being small and significant (d = 0.294, 95% CI [0.159, 0.429], p <0.001). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of 0.257 (95% CI [0.130, 0.384]) to 0.352 (95% CI [0.223, 0.481]). In the trim and fill analysis 3 studies were imputed to the left side of the mean, with an adjusted overall mean of 0.214 (95% CI [0.085, 0.343]). Regarding the heterogeneity test, it was not significant, QWithin (7) = 12.286, p = 0.092, and over than 43% of the observed variance was not accounted for by sampling error only (I^2 = 43.025).

Visual working memory

Six independent effect sizes compared visual working memory measures. The overall effect size indicated that COVID-19 subjects performed worse in comparison to controls and normative data, being small and significant (d = 0.239, 95% CI [0.071, 0.407], p = 0.005). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of 0.198 (95% CI [0.048, 0.347]) to 0.287 (95% CI [0.157, 0.418]). In the trim and fill analysis 3 studies were imputed to the left side of the mean, with an adjusted overall mean of 0.148 (95% CI [-0.002, 0.298]). Regarding the heterogeneity test, it was significant, QWithin (5) = 13.046, p = 0.023, and over than 61% of the observed variance was not accounted for by sampling error only (I^2 = 61.673).

Reasoning

Six independent effect sizes compared reasoning measures. The overall effect size was small and not significant, indicating no relevant differences in performances (d = 0.376, 95% CI [-0.019, 0.770], p = 0.062). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of 0.235 (95% CI [-0.092, 0.562]) to 0.527 (95% CI [0.231, 0.822]). In the trim and fill analysis 2 studies were imputed to the right side of the mean, with an adjusted overall mean of 0.548 (95% CI [0.157, 1.011]). Regarding the heterogeneity test, it was significant, QWithin (5) = 37.259, p <0.001, and more than 86% of the observed variance was not accounted for by sampling error only (I^2 = 86.580).

Visual perception

Four independent effect sizes compared visual perception measures. The overall effect size was medium and significant. This indicated that, when compared to healthy controls and normative data, COVID-19 subjects perform worse (d = 0.502, 95% CI [0.229, 0.774], p <0.001). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of 0.394 (95% CI [0.122, 0.667]) to 0.620 (95% CI [0.380, 0.860]). In the trim and fill analysis 1 study was imputed to the right side of the mean, with an adjusted overall mean of 0.544 (95% CI [0.293, 0.795]). Regarding the heterogeneity test, it was not significant, QWithin (3) = 6.154, p = 0.104, and more than 51% of the observed variance was not accounted for by sampling error only (I^2 = 51.252).

Visual imagery

Four independent effect sizes compared visual imagery measures. The overall effect size indicated that COVID-19 subjects did not exhibit a difference in performance when compared to controls and normative data, being small and not significant (d = 0.163, 95% CI [-0.103, 0.428], p = 0.231). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of 0.024 (95% CI [-0.141, 0.188]) to 0.260 (95% CI [-0.030, 0.551]). The trim and fill analysis suggested absence of any publication bias, as no studies were imputed in this situation. Regarding the heterogeneity test, it was significant, QWithin (3) = 8.679, p = 0.034, and over than 65% of the observed variance was not accounted for by sampling error only (I^2 = 65.433).

Global Memory

Three independent effect sizes compared global memory measures. The overall effect size revealed that COVID-19 subjects, healthy controls and normative data did not have differences in performance, being small and not significant (d = -0.215, 95% CI [-0.826, 0.395], p = 0.489). A sensitivity analysis showed that after the removal of potential outliers, the general effect size would be in range of -0.447 (95% CI [-1.177, 0.282]) to 0.086 (95% CI [-0.225, 0.397]). The trim and fill analysis suggested absence of any publication bias, as no studies were imputed in this situation. As for the heterogeneity test, it was significant, QWithin (2) = 11.128, p = 0.004, with over than 82% of the observed variance not being accounted for by sampling error only (I^2 = 82.027).

Orientation (temporal and spatial)

Three independent effect sizes compared temporal and spatial orientation. The overall effect size indicated that COVID-19 subjects and controls did not have a difference in performance, being small and not significant (d = -0.067, 95% CI [-0.246, 0.111], p = 0.461). A sensitivity analysis indicated that after the removal of potential outliers, the general effect size would be in range of -0.113 (95% CI [-0.344, 0.188]) to -0.034 (95% CI [-0.256, 0.187]). The trim and fill analysis suggested absence of any publication bias, as no studies were imputed in this situation. Regarding the heterogeneity test, it was not significant, QWithin (2) = 0.393, p = 0.822, and none of the observed variance was accounted for by sampling error only (I^2 = 0.000).

Categorical Moderators Analysis

Executive functioning

The effect of disease severity was not significant, as indicated by a non-significant Q-between test (Qbetween(3) = 2.428, p = 0.488), suggesting that executive functioning remains consistent across different levels of severity. The effect of geographical region of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(2) = 1.232, p = 0.540), suggesting that executive functioning remains consistent across different geographical regions. The effect of the type of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 3.425, p = 0.064), suggesting that executive functioning remained consistent whether the evaluation was performed in-person or remote. The effect of the starting point to assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(2) = 5.102, p = 0.078), proposing that executive functioning remained unaffected regardless of the diagnosis, the discharge or the disease onset being the starting point considered in the studies. Lastly, the effect of the group configuration was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 1.572, p = 0.210), suggesting that executive functioning remains consistent whether studies included one group (clinical sample) or two groups (clinical sample and control sample).

Processing speed

The effect of disease severity was not significant, as indicated by a non-significant Q-between test (Qbetween(3) = 0.810, p = 0.847), suggesting that processing speed remains consistent across different levels of severity. The effect of geographical region of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween (2) = 0.210, p = 0.900), suggesting that processing speed remains consistent across different geographical regions. The effect of the type of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 2.646, p = 0.104), suggesting that processing speed remained consistent whether the evaluation was performed in-person or remote. The effect of the starting point to assessment was significant, as indicated by a significant Q-between test (Qbetween(2) = 11.785, p = 0.003), suggesting that the starting point considered in the studies included, this being the

diagnosis, the discharge or the disease onset, had an effect on processing speed. Lastly, the effect of the group configuration was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 0.936, p = 0.333), suggesting that processing speed remains consistent whether studies included one group (clinical sample) or two groups (clinical sample and control sample).

Verbal memory

The effect of disease severity was not significant, as indicated by a non-significant Q-between test (Qbetween(3) = 3.385, p = 0.336), suggesting that verbal memory remains consistent across different levels of severity. The effect of geographical region of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween (3) = 4.709, p = 0.194), suggesting that verbal memory remains consistent across different geographical regions. The effect of the type of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 1.635, p = 0.201), suggesting that verbal memory remained consistent whether the evaluation was performed in-person or remote. The effect of the starting point to assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(2) = 0.935, p = 0.627), suggesting that the starting point considered in the studies included, this being the diagnosis, the discharge or the disease onset, did not have an effect on verbal memory. Lastly, the effect of the group configuration was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 2.564, p = 0.109), suggesting that verbal memory remains consistent whether studies included one group (clinical sample) or two groups (clinical sample and control sample).

Verbal working memory

The effect of disease severity was not significant, as indicated by a non-significant Q-between test (Qbetween(3) = 6.288, p = 0.098), suggesting that verbal working memory remains consistent across different levels of severity. The effect of geographical region of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween (2) = 0.508, p = 0.776), suggesting that verbal working memory remains consistent across different geographical regions. The effect of the type of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 0.542,

p = 0.462), suggesting that verbal working memory remained consistent whether the evaluation was performed in-person or remote. The effect of the starting point to assessment was significant, as indicated by a significant Q-between test (Qbetween(2) = 6.804, p = 0.033), suggesting that the starting point considered in the studies included, this being the diagnosis, the discharge or the disease onset, did have an effect on verbal working memory. Lastly, the effect of the group configuration was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 2.314, p = 0.128), suggesting that verbal memory remains consistent whether studies included one group (clinical sample) or two groups (clinical sample and control sample).

Global Functioning

The effect of disease severity was not significant, as indicated by a non-significant Q-between test (Qbetween(3) = 2.199, p = 0.532), suggesting that global functioning remains consistent across different levels of severity. The effect of geographical region of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween (2) = 5.607, p = 0.061), suggesting that global functioning remains consistent across different geographical regions. The effect of the type of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 1.868, p = 0.172), suggesting that global functioning remained consistent whether the evaluation was performed in-person or remote. The effect of the starting point to assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(2) = 3.316, p = 0.191), suggesting that the starting point considered in the studies included, this being the diagnosis, the discharge or the disease onset, did not have an effect on global functioning. Lastly, the effect of the group configuration was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 3.281, p = 0.070), suggesting that global functioning remains consistent whether studies included one group (clinical sample) or two groups (clinical sample and control sample).

Visual memory

The effect of disease severity was significant, as indicated by a significant Q-between test (Qbetween(3) = 7.792, p = 0.051), suggesting that visual memory is affected by the level of severity of the infection. Subsequent subgroup analyses revealed that the 'mild'

(Qwithin(1) = 11.261, p = 0.001) level presented significance, indicating that mild severity of infection has an effect on visual memory. However, only two studies assessed visual memory using samples classified as mild. The effect of geographical region of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween (2) = 5.090, p = 0.078), suggesting that visual memory remains consistent across different geographical regions. The effect of the type of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 0.407, p = 0.523), suggesting that visual memory remained consistent whether the evaluation was performed in-person or remote. The effect of the starting point to assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(2) = 4.291, p = 0.117), suggesting that the starting point considered in the studies included, this being the diagnosis, the discharge or the disease onset, did not have an effect on visual memory. Lastly, the effect of the group configuration was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 0.784, p = 0.376), suggesting that visual memory remains consistent whether studies included one group (clinical sample) or two groups (clinical sample and control sample).

Language

The effect of disease severity was not significant, as indicated by a non-significant Q-between test (Qbetween(3) = 0.706, p = 0.872), suggesting that language remains consistent across different levels of severity. The effect of geographical region of assessment was significant, as indicated by a significant Q-between test (Qbetween (3) = 17.687, p = 0.001), suggesting that the geographical region of assessment influences language. However, subsequent group analyses did not reveal any significant differences. This might be explained by the discrepancy of studies attributed to each geographical region, as Africa only included 1 study, America included 2 studies and Asia included 1 study, whilst Europe included 10 studies. The effect of the type of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 1.173, p = 0.279), suggesting that language remained consistent whether the evaluation was performed in-person or remote. The effect of the starting point to assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(2) = 1.995, p = 0.369), suggesting that the starting point considered in the studies included, this being the diagnosis, the discharge or the disease onset, did not have an effect on language. Lastly,

the effect of the group configuration was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 0.065, p = 0.799), suggesting that language remains consistent whether studies included one group (clinical sample) or two groups (clinical sample and control sample).

Visual construction

The effect of disease severity was significant, as indicated by a significant Q-between test (Qbetween(3) = 8.857, p = 0.031), suggesting that visual construction is affected by different levels of severity. Subsequent subgroup analyses revealed that the 'mild' (Qwithin(1) = 5.601, p = 0.018) and 'mixed' (Qwithin(6) = 94.805, p <0.001) levels presented significant differences, indicating that visual construction does not remain consistent across these levels. However, the mild severity only included 2 studies, meanwhile, the mixed severities included seven. The effect of geographical region of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween (2) = 2.637, p = 0.268), suggesting that visual construction remains consistent across different geographical regions. The effect of the type of assessment was not considered, as not enough studies were available to perform this analysis. The effect of the starting point to assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(2) = 5.127, p = 0.077), suggesting that the starting point considered in the studies included, this being the diagnosis, the discharge or the disease onset, did not have an effect on visual construction. Lastly, the effect of the group configuration was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 0.174, p = 0.677), suggesting that visual construction remains consistent whether studies included one group (clinical sample) or two groups (clinical sample and control sample).

Attention

The effect of disease severity was not significant, as indicated by a non-significant Q-between test (Qbetween(3) = 5.646, p = 0.130), suggesting that attention is affected by different levels of severity. The effect of geographical region of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween (1) = 0.520, p = 0.471), suggesting that attention remains consistent across different geographical regions.

The effect of the type of assessment was significant, as indicated by a significant Q-between test (Qbetween(1) = 6.768, p = 0.009), suggesting that attention was influenced by the type of assessment. However, subsequent group analyses did not reveal any significant differences. This might be due to the fact that seven studies reported in-person assessment of attention, while only one assessed attention remotely. The effect of the starting point to assessment was significant, as indicated by a significant Q-between test (Qbetween(2) = 11.230, p = 0.004), suggesting that the starting point considered in the studies included, this being the diagnosis, the discharge or the disease onset, did have an effect on attention. Lastly, the effect of the group configuration was significant, as indicated by a significant Q-between test (Qbetween(1) = 7.280, p = 0.007), suggesting that attention does not remain consistent whether studies included one group (clinical sample) or two groups (clinical sample and control sample). However, these results might be explained by six studies reported measures of attention using one clinical group as a sample, while only two studies reported measures of attention using two groups, including a clinical group and a control group.

Visual working memory

The effect of disease severity was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 2.700, p = 0.100), suggesting that visual working memory remains consistent across different levels of severity. The effect of geographical region of assessment was not considered, as not enough studies were available to perform the analysis. The effect of the type of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 1.344, p = 0.246), suggesting that visual working memory remained consistent whether the evaluation was performed in-person or remote. The effect of the starting point to assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 1.645, p = 0.200), suggesting that the starting point considered in the studies included, this being the diagnosis, the discharge or the disease onset, did not have an effect on visual working memory. Lastly, the effect of the group configuration was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 1.344, p = 0.246), suggesting that visual working memory remains consistent whether studies included one group (clinical sample) or two groups (clinical sample and control sample).

Reasoning

The effect of disease severity was significant, as indicated by a significant Q-between test (Qbetween(3) = 35.815, p <0.001), suggesting that reasoning remains consistent across different levels of severity. The effect of geographical region of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween (3) = 2.111, p = 0.550), suggesting that reasoning remains consistent across different geographical regions. The effect of the type of assessment was not significant, as indicated by a non-significant Q-between test (Qbetween(1) = 0.092, p = 0.762), suggesting that reasoning remained consistent whether the evaluation was performed in-person or remote. The effect of the starting point to assessment was significant, as indicated by a significant Q-between test (Qbetween(2) = 11.201, p = 0.004), suggesting that the starting point considered in the studies included, this being the diagnosis, the discharge or the disease onset, had an effect on results. The effect of group configuration was not considered, as not enough studies were available to perform this analysis.

Regression analysis

A meta-regression analysis was conducted to assess whether these variables are predictive of the observed impairments: age of the COVID group, age difference between groups, proportion of females in COVID group, difference of proportion of females between groups, education years in COVID group, difference of education years between groups, days post COVID, symptomatology of depression (PHQ-9) and symptomatology of anxiety (HADS).

Executive functioning

According to metaregression analysis, the age of the COVID group emerged as a significant predictor of the obtained effect size (β = 0.011, p = 0.018, k = 41, R^2 = 0.12). Age difference between groups also had an impact on effect size (β = -0.828, p = 0.024, k = 30, R^2 = 0.18). The proportion of females in COVID group significantly predicted the effect sizes obtained (β = -0.689, p = 0.004, k = 44, R^2 = 0.19). The difference of proportion of females was also a significant predictor for the obtained effect size (β = -0.679, p = 0.053, k = 30, R^2 = 0.14). Education years in COVID group did not reveal to be a significant predictor of the obtained effect size (β = -0.017, p = 0.688, k = 29, R^2 =

0.00), neither did the difference of education years between groups (β = 0.008, p = 0.922, k = 16, R^2 = 0.00). Days post COVID was significant in predicting the effect size observed (β = -0.001, p = 0.011, k = 37, R^2 = 0.18). Symptomatology of depression was not significant in predicting the effect size observed (β = 0.004, p = 0.937, k = 10, R^2 = 0.00), neither was symptomatology of anxiety (β = 0.027, p = 0.251, k = 10, R^2 = 0.31).

Processing speed

The age of the COVID group was a significant predictor of the effect size (β = 0.011, p = 0.023, k = 37, R^2 = 0.18). The age difference between groups, however, was not a significant predictor of the effect size (β = 0.004, p = 0.766, k = 23, R^2 = 0.00). The proportion of females in COVID group was significantly predictive of the effect size obtained (β = -0.677, p = 0.004, k = 39, R^2 = 0.21), the difference of proportion of females between groups, however, was not a significant predictor (β = -0.286, p = 0.371, k = 25, R^2 = 0.00). Education years in COVID group was not significant predictor of the obtained effect size (β = -0.004, p = 0.922, k = 24, R^2 = 0.00), neither was the difference of education years between groups (β = 0.048, p = 0.459, k = 14, R^2 = 0.00). Days post COVID was also not significant in predicting the effect size observed (β = -0.001, p = 0.126, k = 31, R^2 = 0.00). Symptomatology of depression was not significant in predicting the effect size observed (β = -0.085, p = 0.102, k = 8, R^2 = 0.18), neither was symptomatology of anxiety (β = -0.029, p = 0.366, k = 10, R^2 = 0.00).

Verbal memory

The age of the COVID group did not have a significant impact as a predictor of the obtained effect size (β = 0.013, p = 0.093, k = 30, R^2 = 0.00), neither did the age difference between groups (β = -0.007, p = 0.750, k = 18, R^2 = 0.00). The proportion of females in COVID group was not a significant predictor of the obtained effect size (β = 0.147, p = 0.689, k = 33, R^2 = 0.00), neither was the difference of proportion of females between groups (β = 0.129, p = 0.834, k = 19, R^2 = 0.00). Education years in COVID group did not prove to be a significant predictor of the obtained effect size (β = 0.022, p = 0.780, k = 19, R^2 = 0.00). However, the difference of education years between groups was a significant predictor (β = 0.137, p = 0.005, k = 8, R^2 = 1.00). Days post COVID did not have a significant predictive value for the observed effect size (β = 0.000, p = 0.797, k =

29, R^2 = 0.00). Symptomatology of depression was significant in predicting the effect size observed (β = -0.086, p = 0.018, k = 7, R^2 = 0.95), however, symptomatology of anxiety (β = 0.583, p = 0.583, k = 10, R^2 = 0.00) was not.

Verbal working memory

The age of the COVID group did not have a significant impact as a predictor of the obtained effect size (β = 0.006, p = 0.409, k = 27, R^2 = 0.00), nor did the age difference between groups (β = 0.098, p = 0.859, k = 17, R^2 = 0.00). The proportion of females in COVID group was not a significant predictor of the obtained effect size effect size (β = -0.172, p = 0.660, k = 29, R^2 = 0.00), neither was the proportion of females between groups (β = 0.098, p = 0.859, k = 17, R^2 = 0.00). Education years in COVID group did not have a significant predictive value for the observed effect size (β = 0.042, p = 0.462, k = 20, R^2 = 0.00), but the difference of education years between groups did (β = 0.142, p = 0.034, k = 9, R^2 = 0.55). Days post COVID did not have a significant predictive value for the observed effect size (β = -0.001, p = 0.250, k = 24, R^2 = 0.00). Symptomatology of depression was not significant in predicting the effect size observed (β = 0.007, p = 0.870, k = 6, R^2 = 0.00), neither was symptomatology of anxiety (β = 0.097, p = 0.092, k = 9, R^2 = 0.19).

Global Functioning

The effect size obtained did not show a significant association with the age of individuals in the COVID group (β = 0.013, p = 0.112, k = 24, R^2 = 0.03), neither did the age difference between groups (β = -0.446, p = 0.341, k = 22, R^2 = 0.18). The proportion of females in COVID group revealed to be a significant predictor of the obtained effect size (β = -0.883, p = 0.024, k = 26, R^2 = 0.32), however the proportion of females between groups was not significant (β = -0.446, p = 0.341, k = 22, R^2 = 0.18).

Education years in COVID group did not exhibit significant predictive power for the observed effect size (β = 0.039, p = 0.445, k = 14, R^2 = 0.22), nor did the difference of education years between groups (β = 0.066, p = 0.445, k = 10, R^2 = 0.00). Days post COVID also did not have a significant predictive value for the observed effect size (β = -0.001, p = 0.419, k = 22, R^2 = 0.00). Symptomatology of depression was not significant in predicting the effect size observed (β = -0.024, p = 0.554, k = 7, R^2 = 0.00). It was not

possible to conduct analysis regarding symptomatology of anxiety between groups, as not enough studies reported the necessary data for this variable (k = 3).

Visual memory

The age of the COVID group did not have a significant impact as predictor of the obtained effect (β = 0.010, p = 0.253, k = 15, R^2 = 0.12). Age differences between groups also did not reach significance (β = -0.055, p = 0.430, k = 6, R^2 = 0.00). The proportion of females in COVID group was not a significant predictor of the obtained effect size (β = -0.557, p = 0.248, k = 16, R^2 = 0.09), neither was the proportion of females between groups (β = 0.533, p = 0.742, k = 8, R^2 = 0.00). Education years in COVID group was not significant predictor of the obtained effect size (β = 0.068, p = 0.176, k = 8, R^2 = 0.00). It was not possible to conduct analysis regarding the difference of education between groups, as not enough studies reported the necessary data for this variable (k = 2). Days post COVID did not have a significant predictive value for the observed effect size (β = 0.000, p = 0.944, k = 14, R^2 = 0.00). It was not possible to conduct analysis regarding symptomatology of depression between groups, as no studies reported the necessary data for this variable (k = 0). Symptomatology of anxiety was not significant in predicting the effect size observed (β = 0.038, p = 0.704, k = 7, R^2 = 0.00).

Language

The age of the COVID group did not prove to be a significant predictor of the effect size (β = -0.011, p = 0.113, k = 14, R^2 = 0.30), neither did the age difference between groups (β = -0.116, p = 0.890, k = 7, R^2 = 0.00). The proportion of females in COVID group was not significantly predictive of the effect size obtained (β = -0.048, p = 0.957, k = 14, R^2 = 0.00), nor was the difference of proportion of females between groups (β = -0.116, p = 0.890, k = 7, R^2 = 0.00). Education years in COVID group was not a significant predictor of the obtained effect size (β = -0.135, p = 0.053, k = 10, R^2 = 1.00), neither was the difference of education years between groups (β = -0.143, p = 0.067, k = 4, R^2 = 1.00). Days post COVID was also not significant in predicting the effect size observed (β = -0.001, p = 0.254, k = 11, R^2 = 0.12). Symptomatology of depression was not significant in predicting the effect size observed (β = 0.006, p = 0.910, k = 4, R^2 = 0.00), however, symptomatology of anxiety (β = 0.124, p = 0.011, k = 7, R^2 = 1.00) was.

Visual construction

The effect size obtained did not indicate a significant association with the age of individuals in the COVID group (β = 0.044, p = 0.072, k = 11, R^2 = 0.23), neither did the age difference between groups (β = 0.100, p = 0.608, k = 4, R^2 = 0.00). The proportion of females in COVID group was not significantly predictive of the effect size obtained (β = -0.463, p = 0.797, k = 11, R^2 = 0.00), nor was the difference of proportion of females between groups (β = -7.331, p = 0.295, k = 4, R^2 = 0.00). Education years in COVID group did not exhibit significant predictive power for the observed effect size (β = 0.051, p = 0.596, k = 7, R^2 = 0.00). It was not possible to conduct analysis regarding the difference of education between groups, as not enough studies reported the necessary data for this variable (k = 1). Days post COVID also did not have a significant predictive value for the observed effect size (β = 0.005, p = 0.141, k = 9, R^2 = 0.08). It was not possible to conduct analysis regarding symptomatology of depression between groups, as not enough studies reported the necessary data for this variable (k = 1). Symptomatology of anxiety was not significant in predicting the effect size observed (β = -0.033, p = 0.915, k = 7, R^2 = 0.00).

Attention

The age of the COVID group was a significant predictor of the effect size (β = 0.040, p = 0.007, k = 8, R^2 = 1.00). However, it was not possible to conduct analysis regarding the age difference between groups, as not enough studies reported the necessary data for this variable (k = 2). The proportion of females in COVID group was a significant predictor of the obtained effect size (β = -0.826, p = 0.003, k = 8, R^2 = 1.00). It was not possible to conduct analysis regarding the difference of proportion of females between groups, as not enough studies reported the necessary data for this variable (k = 2). Education years in COVID group was not significant a predictor of the obtained effect size (β = -0.012, p = 0.910, k = 6, R^2 = 0.00). The difference of education years was not accounted for analysis, as not enough studies reported the necessary data for the analysis regarding this variable (k = 1). Days post COVID was significant in predicting the effect size observed (β = -0.005, p = 0.002, k = 5, R^2 = 1.00). It was not possible to conduct analysis regarding symptomatology of depression between groups, as not enough studies reported the necessary data for this variable (k = 2). Symptomology of anxiety was not significant in predicting the effect size observed (β = 0.058, p = 0.739, k = 5, R^2 = 0.00).

Visual working memory

The effect size obtained did not show a significant association with the age of individuals in the COVID group (β = 0.004, p = 0.748, k = 6, R^2 = 0.00), nor did age difference between groups (β = 0.060, p = 0.090, k = 4, R^2 = 0.00). The proportion of females in COVID group was not significantly predictive of the effect size obtained (β = -0.062, p = 0.925, k = 6, R^2 = 0.00), neither was the difference of proportion of females between groups (β = -0.432, p = 0.855, k = 5, R^2 = 0.00). It was not possible to conduct analysis regarding the education years in COVID group neither the difference of education between groups, as no studies reported the necessary data for these variables (k = 0). Days post COVID was also not significant in predicting the effect size observed (β = 0.001, p = 0.191, k = 5, R^2 = 0.53). It was not possible to conduct analysis regarding symptomatology of depression, neither symptomatology of anxiety between groups, as not enough studies reported the necessary data for these variables (k = 1).

Reasoning

The age of the COVID group did not prove to be a significant predictor of the effect size (β = 0.015, p = 0.384, k = 6, R^2 = 0.12), however, the age difference between groups did (β = 0.117, p = 0.001, k = 6, R^2 = 0.84). The proportion of females in COVID group was not significantly predictive of the effect size obtained (β = 0.884, p = 0.574, k = 6, R^2 = 0.00), nor was the difference of proportion of females between groups (β = 5.198, p = 0.131, k = 6, R^2 = 0.35). It was not possible to conduct analysis regarding education years in COVID group (k = 2), nor the difference of education years between groups (k = 1), as not enough studies reported the necessary data for these variables. Days post COVID was also not significant in predicting the effect size observed (β = 0.001, p = 0.683, k = 5, R^2 = 0.00). It was not possible to conduct analysis regarding symptomatology of depression, nor symptomatology of anxiety between groups, as not enough studies reported the necessary data for these variables (k = 1).

Discussion

COVID-19 does not only affect the respiratory system, but also has impact on other systems, either directly from the beginning of the contamination or through consequence of the respiratory infection. The wide range of symptoms that may persist after acute

illness, as well as the different systems involved in these symptoms, have been the reason for the growing concept of COVID-19 as a systemic pathology (Munjal et al., 2020).

Cognitive impairment has been a continuous subjective report in patients previously infected with SARS-COV-2, and objective measures have also been consistently used to assess cognitive functioning, often evidencing poor results (Schild et al., 2023).

This study was conducted in order to examine whether COVID-19 has an influence on cognitive functioning. We synthesized the findings from 43 studies investigating the consequences of SARS-COV-2 infection on cognition. To address our aim, measures of multiple domains were extracted: executive functioning, processing speed, verbal memory, verbal working memory, global functioning, visual memory, language, visual construction, attention, visual working memory, reasoning, visual imagery, visual perception, global memory and orientation (temporal and spatial). Our analysis revealed multiple statistically significant, small to moderate overall effect sizes regarding different cognitive domains, suggesting that individuals who were previously infected with SARS-COV-2 might experience impaired cognitive functioning.

Regarding executive functioning, our analysis revealed a small, statistically significant overall effect size (d = 0.335), indicating that individuals previously infected with SARS-COV-2 might present a worse performance in executive functioning measures, when compared to healthy control individuals and normative data. These results go in agreement with the results reported in Houben et al.'s meta-analysis (2022), that also reported a worse performance of the COVID-19 subjects in executive functioning measures. This effect, however, was not estimated in the other previous meta-analysis. Considering that the olfactory system establishes connections to areas such as the orbitofrontal cortex and hippocampus, it has also been hypothesized that SARS-COV-2 might indirectly influence higher-level cognitive functions. Neuroimaging reports of frontal hypometabolism seem to support this hypothesis (le Guennec et al., 2020). A study conducted by Hosp et al. (2022) revealed a correlation between neurological symptomatology and executive impairment with frontoparietal hypometabolism in fluorodeoxyglucose (FDG)-positron emission tomography (PET). Douaud et al. (2022) reported that the thickness of the gray matter and tissue contrast in the orbitofrontal cortex, which are lined to executive functioning, showed a significant reduction in COVID-19 patients when compared to a control group.

Concerning processing speed, this analysis revealed an almost medium, statistically significant overall effect size (d = 0.400), suggesting that COVID-19 subjects exhibit poorer performance in processing speed measures when compared to healthy controls. These findings align with the outcomes reported in a previous meta-analysis by Houben et al. (2022), that also reported a worsening performance of individuals previously infected with SARS-CoV-2 in processing speed measures. However, no other earlier meta-analysis reported this effect. The processing speed impairment often observed in individuals after COVID-19 appears to be linked to changes in complex brain networks rather than isolated dysfunctions (Ariza et al., 2023). These results are consistent with the previous study by Hosp et al. (2021), which detected reduced metabolic activity in frontoparietal systems during the subacute phase following SARS-CoV-2 infection. The state of white matter integrity has been linked not only to intellectual capacity, but more specifically, to processing speed (Dhont et al., 2020; Brugulat-Serrat et al., 2020). Radnis et al. (2020) reported the connection between white matter intensities and hypoxic-ischemic brain injury in cases of acute respiratory distress syndrome (ARDS) related to COVID-19. In a more recent investigation, effects on the white matter are reported one year post SARS-CoV-2 infection, particularly in areas such as the corona radiata, corpus callosum and superior longitudinal fasciculus. This effect is particularly noticeable in patients who have undergone intensive care unit (ICU) treatment (Huang et al., 2022). Several mechanisms have been proposed as potential mediators for these injuries besides hypoxia, such as indirect viral infection (Paniz-Mondolfi et al., 2020), systemic inflammatory responses (Liddelow et al., 2017) or coagulopathy (Wang et al., 2020).

In the context of verbal memory domain, our analysis indicated a small, statistically significant overall effect size (d = 0.326), indicating that individuals who were infected with SARS-CoV-2 demonstrated poorer results in comparison to healthy controls and normative data. These results are consistent with the findings reported in Houben et al.'s meta-analysis (2022), that reported a worse performance of this population in verbal memory measures, however, Velichkovsky et al.'s meta-analysis (2023) found no significant differences for this cognitive domain. This difference in results could possibly be due to the difference of sample sizes. Our analysis regarding visual memory revealed a statistically small, significant overall effect size (d =0.228), which is suggestive that individuals previously infected with SARS-COV-2 exhibit diminished performance in this domain. Our results do not align with the results reported in the previous meta-

analysis by Velichkovsky et al. (2023), as no significant differences were identified regarding this cognitive domain. However, these differences might be due to a discrepancy in the number of studies included. The analysis regarding global memory did not indicate a statistically significant overall effect size (d = -0.215), suggesting the absence of differences in performance between groups. However, only three measures were extracted from the same study (Ollilla et al., 2022) for this domain, as these were memory indexes and did not fit in the verbal memory nor the visual memory domains, since they contained tasks measuring both domains. Poor results in memory after COVID-19 could partially be explained by an unrestrained release of pro-inflammatory cytokines, namely interleukins (IL-6, IL-2, IL-12, IL-15 and IL-1β) and tumor necrosis factor (TNF-α), that may potentially induce a state of systemic inflammation. These cytokines are able to breach through the blood brain barrier (BBB) and trigger their own release. This condition of neuroinflammation has the potential to activate microglia, inducing them to release additional molecules, thereby exacerbating neuroinflammation. Activation of cytokine receptors on neurons can potentially set off a cascade of events that ultimately leads to neuronal damage or cell death (Pattanaik et al., 2023). The hippocampus is particularly susceptible to these pro-inflammatory cytokines due to the high concentration of IL-1β receptors in its neuronal compartments (Zorzo et al., 2023). The elevated levels of cytokines also have an adverse effect on neurogenesis, as neuroinflammation interferes with this critical process (Stepien et al., 2023). The potential damage of hippocampus functioning leaves cognitive functions such as attention processes, working memory and long-term memory at a high risk (Alnefeesi et al., 2021). Hypoxia could also play a role in cognitive dysfunction in COVID-19 patients. The hippocampus is also highly susceptible to hypoxia-induced neuronal damage. This process elicits signals in neurons to stimulate microglia, leading to phagocytosis. Hypoxic respiratory failure can potentially induce a hypercoagulable condition favorable to thrombotic brain vessel occlusion. Consequently, this could result in ischemic damage, leading to modifications in brain functions and cognitive impairment (Consentino et al, 2021; Thakur et al, 2021; Zorzo et al, 2023). Dondaine et al. (2022) compared COVID-19 patients divided in a group of outpatients who did not suffer pulmonary complications and a group of inpatients with hypoxemic pneumonia that received oxygen therapy, finding that in the latter group the memory impairment was greater, especially regarding the cue efficiency index and the total recall in Free and Cue Selective Reminding Test (FCSRT), considered to possibly be indicative of hippocampal damage. Lu et al. (2020) also highlighted the

possibility of memory impairment linked to hippocampus damage at 3 months post-COVID. A study investigating COVID-19 patients presenting persistent pulmonary dysfunction found cognitive impairment, namely verbal memory, to be correlated to higher d-dimer levels, an indicator of thrombosis or pulmonary coagulation disorder, what could imply potential cerebral vascular complications such as hypoxia (Miskowiak et al., 2021).

The current analysis regarding verbal working memory revealed a small, statistically significant overall effect size ($d = 0.251$), which is suggestive that individuals previously infected with SARS-COV-2 exhibit worse performance in verbal working memory measures when compared to healthy controls and normative data. These results align with the findings reported in a previous meta-analysis by Houben et al. (2022), that also reported deficits in working memory measures, but do not align with Velichkovsky et al.'s meta-analysis (2023) which reported no significant differences regarding this cognitive domain. As mentioned before, these differences in results might be due to a discrepancy in the number of included studies. Our analysis regarding the visual working memory domain revealed a small, statistically significant overall effect size ($d = 0.239$), indicating that COVID-19 subjects exhibit poor performances in visual working memory measures. Our results coincide with the findings reported in Houben et al.'s analysis (2022), however, another previous meta-analysis by Velichkovsky et al. (2023) reported no significant differences regarding this cognitive domain, which could potentially be explained by a discrepancy in the number of included studies. The potential brain damage caused by COVID-19 may result in subsequent dysfunction in working memory among affected patients (Shan et al., 2022). As previously mentioned, the hippocampus has been highlighted as being particularly vulnerable to the elevated levels of cytokines associated with SARS-CoV-2 infection (Zorzo et al, 2023). The state of neuroinflammation state has been linked to a heightened risk of working memory impairment (Alnefeesi et al, 2021). This association is particularly noteworthy because the hippocampus plays a crucial role in supporting memory during brief delays, as assessed in tests of working memory (Borders et al., 2022). The proper functioning of fronto-parietal regions is vital for this function, and these areas are highly susceptible to COVID infection, particularly in the early post-infection phase (Chai et al., 2018; Assem et al., 2020; Egbert et al., 2020; Douaud et al., 2022; Zalpoor et al., 2022).

Our analysis regarding the language domain revealed a small, statistically significant overall effect size (d = 0.245). This is suggestive that COVID-19 subjects perform poorly in language measures when compared to healthy controls and normative data. This effect has not yet been explored in earlier meta-analysis. García-Sánchez et al. (2022) evaluated COVID-19 patients during acute illness and found a strong association between ferritin levels and language impairment, suggesting that hyper inflammation in neuronal damage may potentially have impact on the performance of language-related tasks.

The analysis regarding reasoning did not indicate a statistically significant overall effect size (d = 0.376), suggesting that COVID-19 participants did not differ from controls and normative data in terms of reasoning performance. Previous meta-analysis did not explore did effect. Triana et al. (2020) related the observed poor results in the Abstraction domain of MoCA with the profile found in hypoxemic patients with Chronic Obstructive Pulmonary Disease (COPD), suggesting that hypoxic states might potentially play a role in reasoning impairment (Liesker et al., 2004).

Attention domain presented a small, significant overall effect size (d = 0.294), suggesting that COVID-19 participants perform worse in attention measures in comparison to healthy population. An earlier meta-analysis by Houben et al. (2022) reported attention deficits in this population as well. Velichkovsky et al. (2023) reported in their meta-analysis the results of visual-spatial attention domains divided into reaction time and accuracy scores, both of which did not reach significance. Zhou and colleagues (2020b) conducted an assessment of individuals with COVID-19 though digital methods, revealing a noteworthy impairment in attention. The evidenced impairment in attention was found to be significantly associated with elevated inflammatory markers. This finding is particularly interesting, in light of previous evidence suggesting a potential connection between microglial inflammation and the subsequent onset of Alzheimer's disease (Madrekar et al., 2010) Attentional processes play a critical role in the encoding of information into memory and are vulnerable to hippocampal damage as previously mentioned risk (Alnefeesi et al, 2021). This area has been referred to as highly susceptible in the context of SARS-CoV-2 infection (Zorzo et al, 2023).

Visuospatial capacity has been previously considered a broad term that includes a range of cognitive processes related to visual and spatial processing. This capacity refers to the ability to perceive, process and manipulate information in visual and/or spatial

forms. Cognitive domains such as visual construction, visual imagery and visual perception have been considered crucial components of visuospatial capacity (Trojano & Conson, 2008). Hellgren et al. (2021) reported that individuals with abnormalities found on magnetic resonance imaging (MRI) exhibited lower scores on tasks evaluating visuospatial functioning. These abnormalities consisted in the presence of multiple white matter lesions, mainly distributed in frontal and parietal areas. The potential damage of the parietal area raises concern in the context of visuospatial processing, given that numerous neural pathways essential for this cognitive process traverse this lobe and also bilateral activation of this area has been associated with visuospatial functioning (Kravitz et al., 2011; Seydell-Greenwald et al., 2017). An earlier meta-analysis by Houben et al. (2022) reported significant decrease in visuospatial abilities in comparison to healthy individuals.

A recent study involving participants who suffered a mild infection, reported an atypically high rate of impairment (26%) in the copy version of the Rey Complex Figure Task (RCFT), which was inversely correlated to white matter volumes in specific areas of the brain such as the subgenual portion of the corpus callosum and cingulum on both hemispheres (De Paula et al., 2023). However, the current analysis indicated an insignificant overall effect size (d = -0.019). This suggests that individuals who recovered from COVID-19 did not differ from healthy individuals regarding this cognitive domain.

The current analysis regarding visual imagery did not indicate a statistically significant overall effect size (d = 0.163), indicating that COVID-19 subjects did not differ from control subjects and normative data in terms of visual imagery performance.

Regarding visual perception, our analysis indicated a medium, statistically significant overall effect size (d =0.502), indicating that individuals previously infected with SARS-COV-2 demonstrate a poor performance in visual perception measures.

Relatively to temporal and spatial orientation, in our analysis, overall effect size did not reveal to be statically significant (d = -0.067), indicating that groups do not perform differently in this measure.

Regarding global functioning, our analysis indicated a medium, statistically significant overall effect size (d = 0.540), suggesting that individuals who previously contracted SARS-COV-2 exhibit an impaired general cognitive functioning. These results are consistent with the reported results in the earlier meta-analysis by Crivelli et al.

(2022), that suggested a worse general cognitive functioning of COVID subjects when compared to healthy controls. In a study conducted in 2022, a total of 20 COVID-19 inpatients presenting neurological symptomatology were evaluated using MoCA, finding that 70% of the observed sample scored below the established cut-off value (<26/30 points). The evidenced cognitive impairment was associated with volume changes in white matter, especially in the frontal and parietal lobes (Rau et al., 2022). Furthermore, ischemic stroke has been reported as the prevailing neurological complication observed in COVID-19 cases, often presenting as small diffuse lesions in both cortical and sub-cortical areas, being a possible cause for multiple cognitive impairments presented in COVID-19 patients (Ghannam et al., 2020). Despite the ongoing uncertainty about the specific pathological mechanisms behind potential cognitive impairment associated with COVID-19, various hypotheses have been proposed. These encompass direct consequences of cellular damage caused by viral invasion, secondary inflammatory responses, diminished angiotensin-converting enzyme 2 (ACE2) activity, hypoxia, sepsis, multi-organ damage, or oxidative stress (Bandala et al., 2021).

Earlier meta-analyses presented valuable results, however the current meta-analysis highlights important points. The inclusion of a comprehensive examination of several cognitive domains, which allows for a more nuanced understanding of the impact of COVID-19 on cognitive functioning in comparison to some earlier meta-analyses. Also, the incorporation of a larger body of recent research compared to earlier meta-analyses is highly valuable in the understanding of this evolving field.

As we consider the current findings, it becomes imperative to consider the potential moderating factors that might influence the observed outcomes. Age demonstrated impact on various cognitive domains, including executive functioning, attention and processing speed. The results indicated that older individuals with a prior history of SARS-CoV-2 infection exhibited poorer performance in executive functioning and attention measures. Conversely, findings suggested that older individuals who recovered from COVID-19 presented lower levels of impairment in processing speed measures. Furthermore, a greater age difference between the COVID group and the healthy control group was associated with higher levels of impairment in the executive functioning domain. These results suggest that age might exacerbate the risks associated with the COVID-19 related cognitive impairments in attention and executive functioning.

Previous research reporting cognitive impairment has been associated with older age (Vasilevskaya et al., 2023; Liu et al., 2021).

The current findings suggest a significant influence of sex on the performance across various cognitive domains, including executive functioning, processing speed, attention, global functioning and reasoning. Specifically within the COVID group, a higher percentage of females was associated with diminished performance in executive functioning, processing speed, attention and global functioning measures. Additionally, a greater difference of percentage of females between the COVID group and the healthy control group was linked to poorer results in executive functioning and reasoning measures. Accordingly, Vasilevskaya and colleagues (2023) have reported an association between female sex and cognitive impairment, more specifically to executive dysfunction. Female sex has previously been associated with a susceptibility for higher burden of persistent symptoms after SARS-CoV-2 infection (Vasilevskaya et al., 2023). Reasons for this difference between female and male sex remain unclear, however, it has been hypothesized that enhanced immune responses and physiological differences in females might potentially contribute to a prolongation of the disease manifestation (Yong, 2021; Michelen et al., 2021).

Cognitive impairment has been observed up to a year post-illness (Lamontagne et al., 2021). Nonetheless, there are reports suggesting potential improvement within 3 to 6 months following the initial illness (Poletti et al., 2022). In our study, an extended time period after COVID-19 was correlated with an increase in executive functioning measures.

According to the current results, the considered starting point demonstrated influence on processing speed, verbal working memory, reasoning and attention. Notably, all considered starting points (diagnosis, discharge and disease onset) significantly affected processing speed results. Verbal working memory, on the other hand, was specifically influenced by the discharge starting point. Regarding processing speed, all the considered starting points (diagnosis, discharge and disease onset) had a significant effect on the presented results. Verbal working memory results were specifically influenced by discharge. Reasoning and attention, however, were not specifically influenced by any of the starting points, which could potentially be explained by the uneven distribution of studies across the different variables.

While education did not demonstrate a significant effect on any cognitive domain, the difference of years of education between the COVID group and the healthy control group had an effect on verbal memory and verbal working memory. Specifically, as this difference increases, a higher level of impairment is observed. It is important, however, to interpret the relationship between the difference in years of education and verbal working memory with caution, as only a small portion of the studies (9 out of 20) in this domain reported this measure.

In terms of psychopathology symptomatology, elevated depression symptoms were linked to greater impairment in verbal memory measures, while increased anxiety symptoms were associated with higher impairment in language measures. It is important to interpret these results cautiously, given their limitation due to a small number of studies in each cognitive domain, which may not fully represent the entire sample. Psychopathological factors such as anxiety, depression and PTSD, which present either as disorders or symptoms at a high prevalence in this clinical group, have been previously reported to play a role in in cognitive impairment. Extended periods of stress, often associated to anxiety and PTSD, are linked to an increase in cortisol levels that have been correlated with both short-term and long-term memory deficits (Wolf, 2008; Cenat et al., 2021; Nikolin et al., 2021).

The severity of infection exerted influence on the results of visual memory, reasoning and visual construction. Specifically, mild severity significantly impacted visual memory, while both mild and mixed severity had a significant effect on visual construction. However, none of the severity levels were found to be significant for reasoning. It is crucial to note that all these domains faced the limitation of a discrepancy in the number of studies across severity levels, potentially influencing the findings.

The geographical region as a moderator demonstrated a significant effect on language while the number of groups and the type of assessment showed effects on attention. Nevertheless, it is important to approach these results with caution due to the limitation arising from the discrepancy in the number of studies across variables.

It should be noted that the available research regarding cognitive impairment is heterogeneous due to the contribution of different factors. The accelerated proliferation of research striving to understand the mechanisms of SARS-CoV-2 and its associated consequences (such as cognitive impairment), although remarkable, may pose potential

challenges to scientific standard codes (Ioannidis et al., 2020). Several studies did not present healthy control groups for comparison, as a considerable number opted to contrast the results of individuals previously infected with SARS-COV-2 with the standardized mean score of the employed test in the general population. The worldwide pandemic situation at which the time most of the research was conducted and published, was characterized by mobility restriction measures, resulting in different assessment methods to be employed, alternating between limited in-person assessments and increasingly common remote and online assessments.

Conclusion

In conclusion, the present meta-analysis supports the idea that there is a link between COVID-19 and cognitive impairment. Effect sizes were generally significant and small across most cognitive domains, indicating that cognitive deficits were, for the most part, of a small magnitude. These results indicate that COVID-19 potentially has influence on cognitive functioning, more specifically in executive functioning, processing speed, verbal memory, verbal working memory, global functioning, visual memory, language, attention, visual working memory and visual perception.

Considering the increasing number of individuals affected by COVID-19 presenting these deficits, the implementation of a complete neuropsychological assessments including cognitive screenings and second level tests is highly valuable for clinical practice in this population.

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Anexos

Anexo A

Supplemental Table A

Supplemental table A Measures included in the selected studies.

Cognitive domain	Measure	Variable in evaluation	Authors
1. Executive functioning	1.1. Attention Network Test (ANT) – Incongruent flankers, all types of cues	Time taken to perform task.	Lamontagne et al. (2021).
	1.2. Clock Drawing Test (CDT)	Sum of correct answers.	Akinci et al. (2022), Cian et al. (2021), Crivelli et al. (2021).
	1.3. Color Word Interference Test - Composite Score (Delis-Kaplan Executive Function System)	Total score.	Birberg Thornberg et al. (2022).
	1.4. Color Word Interference Test – Inhibition/Switching Score (Delis-Kaplan Executive Function System)	Total score.	Birberg Thornberg et al. (2022).
	1.5. Color Word Interference Test – Inhibition Score (Delis-Kaplan Executive Function System)	Total score.	Birberg Thornberg et al. (2022).
	1.6. Executive Functioning Index	Sum of scores from: Trail Making Test-B, Stroop (interference score), Frontal Assessment Battery.	Ollila et al. (2022).
	1.7.Executive Functioning Task (MoCA Basic)	Point if correct.	Amalakanti et al. (2021).
	1.8. Frontal Assessment Battery	Total score (sum of scores from: Similarities Test, Verbal Fluency Test, Luria Motor Sequences, Conflicting Instructions, Go-no-go, Prehension Behavior).	Ortelli et al. (2021), Rubega et al. (2022).
	1.9. Five Points Test	Sum of correct answers.	De Paula et al. (2023).

1.10. Inhibition errors (Vienna Test System)	Sum of errors.	Delgado-Alonso et al. (2022).
1.11. Navon Task	Time taken to perform task. Percentage of errors.	Ortelli et al. (2021), Ortelli et al. (2022a).
1.12. Prototypes (CogLab)	Time taken to perform task.	Francis et al. (2023).
1.13. Simon Task (Incongruent Measure)	Time taken to perform task. Sum of correct answers.	Francis et al. (2023), Hausswirth et al. (2023).
1.14. Spatial Planning	Time taken to perform task. Sum of correct answers.	Hampshire et al. (2022).
1.15. Stroop Test – Interference Measure	Time taken to perform task. Sum of incorrect answers. Sum of correct answers.	Akinci et al. (2023), Almeria et al. (2020), Almeria et al. (2023), Chang et al. (2023), Costas-Carrera et al. (2022), Dressing et al. (2021), Hosp et al. (2021), Ortelli et al. (2021), Ortelli et al. (2022a), Ortelli et al. (2022b).
1.16. Stroop Test – Interference Measure (Braincheck)	Time taken to perform task.	Henneghan et al. (2022).
1.17. Stroop Test – Word/Color Measure	Time taken to perform task. Sum of incorrect answers.	Ortelli et al. (2022a), Ortelli et al. (2022b), Rubega et al. (2022).
1.18. Target Detection	Time taken to perform task. Sum of correct answers.	Hampshire et al. (2022), Zhao et al. (2021).
1.19. Trail Making Test (Delis-Kaplan Executive Function System)	Time taken to perform task.	Rennison et al. (2023).
1.20. Trail Making Test-B	Time taken to perform task.	Akinci et al. (2023), Almeria et al. (2020), Almeria et al. (2023), Ariza et al. (2023), Chang et al. (2022), Crivelli et al. (2021), De Paula et al. (2023), Dressing et al. (2021), Vannorsdall et al. (2021).
1.21. Trail Making Test-B (Braincheck)	Time taken to perform task.	Henneghan et al. (2022), Hosp et al. (2021).

1.22. Trail Making Test-B (MyCognition)	Time taken to perform task. Sum of correct answers.	Vakani et al. (2023).
1.23. Trail Making Test-B (Vienna Test System)	Time taken to perform task.	Delgado-Alonso et al. (2022).
1.24. Trail Making Test- BA	Difference of time taken to perform TMT-A and TMT-B	Ariza et al. (2023), Cechetti et al. (2023), Rennison et al. (2023).
1.25. Tower of London	Sum of correct answers.	Zhao et al. (2021).
1.26. Tower of London (Brief Assessment of Cognition in Schizophrenia)	Sum of correct answers.	Poletti et al. (2021).
1.27. Tower of London (Vienna Test System)	Sum of correct answers.	Delgado-Alonso et al. (2022).
1.28. Verbal Fluency (Brief Assessment of Cognition in Schizophrenia)	Sum of correct answers.	Poletti et al. (2021).
1.29. Verbal Fluency (Screen for Cognitive Impairment in Psychiatry)	Sum of correct answers.	Miskowiak et al. (2021), Miskowiak et al. (2023).
1.30. Verbal Fluency - Alternate	Sum of correct answers.	Cian et al. (2022), De Paula et al. (2023).
1.31. Verbal Fluency - Categories	Sum of correct answers. Sum of repetitions. Sum of incorrect answers.	Akinci et al. (2023), Almeria et al. (2020), Almeria et al. (2023), Ariza et al. (2023), Birberg Thornberg et al. (2022), Cian et al. (2022), Costas-Carrera et al. (2022), Crivelli et al. (2021), De Paula et al. (2023), Guo et al. (2022), Hosp et al. (2021), Vannorsdall et al. (2021).
1.32. Verbal Fluency - Phonemic	Sum of correct answers.	Akinci et al. (2023), Almeria et al. (2020), Almeria et al. (2023), Ariza et al. (2023), Cian et al. (2022), Cechetti et al. (2022), Costas-Carrera et al. (2022), Crivelli et al. (2021),

			Dressing et al. (2021), Hosp et al. (2021), Vannorsdall et al. (2021).
	1.33. Wisconsin Card Sorting Test	Reaction time for correct answers, for perseverative errors and for non-perseverative errors. Sum of correct answers, of perseverative errors, non-perseverative errors and overall errors.	Crivelli et al. (2021), Guo et al. (2022), Rennison et al. (2023).
2. Processing speed	2.1. Attention Network Test (ANT) – Congruent and neutral flankers, all types of cues	Time taken to perform task.	Lamontagne et al. (2021).
	2.2. Attentional Blink	Difference in percentage detection regarding first and second targets.	Francis et al. (2023)
	2.3. Choice Reaction Time	Time taken to perform task. Sum of correct answers.	Vakani et al. (2023), Zhao et al. (2021).
	2.4. Choice Response Time	Time taken to perform task. Sum of correct answers.	Hausswirth et al. (2023).
	2.5. Coding Subtest (Repeatable Battery for Assessment of Neuropsychological Status)	Sum of correct answers.	Birberg Thornberg et al. (2022).
	2.6. Coding Symbol Subtest (Brief Assessment of Cognition in Schizophrenia)	Sum of correct answers.	Poletti et al. (2021).
	2.7. Crossmodal Divided Attention - Visual-Auditive Task (Vienna Test System)	Time taken to perform task.	Delgado-Alonso et al. (2022).

2.8. Digit Symbol Coding Subtest (Wechsler Adult Intelligence Scale-IV)	Sum of correct answers.	Ariza et al. (2023), Crivelli et al. (2021).
2.9. Digit Symbol Modalities Test	Sum of correct answers.	Rubega et al. (2022).
2.10. Determination Test S1 (Vienna Test System)	Time taken to perform task.	Delgado-Alonso et al. (2022).
2.11. Digit Symbol Substitution Test (Braincheck)	Sum of correct answers.	Henneghan et al. (2022).
2.12. Intrinsic Alertness – Visual Task (Vienna Test System)	Time taken to perform task.	Delgado-Alonso et al. (2022).
2.13. Motor Control Task	Time taken to perform task.	Zhao et al. (2021).
2.14. Processing Speed Composite Score	Sum of scores from subtests: Color-Word Reading Task, Color-Word Naming Task and Symbol Digit Modalities Test.	Dressing et al. (2021).
2.15. Processing Speed Composite Score (Cambridge Brain Sciences)	Sum of scores from all the included tasks in Cambridge Brain Sciences: Spatial Span, Monkey Ladder, Paired Associates, Token Search, Digit Span, Odd One Out, Rotations, Feature Match, Spatial Planning, Interlocking Polygons, Grammatical Reasoning, Double Trouble.	Wild et al. (2021)
2.16. Processing Speed Composite Score (Wechsler Adult Intelligence Scale-IV)	Sum of scores from subtests from Wechsler Adult Intelligence Scale-IV: Symbol Search, Coding.	Rennison et al. (2023).
2.17. Psychomotor Speed	Sum of correct answers.	Miskowiak et al. (2021), Miskowiak et al. (2023).
2.18. Reaction Time (Vienna Test System)	Time taken to perform task.	Delgado-Alonso et al. (2022).
2.19. Sign Coding Test (SCT)	Sum of correct answers.	Zhou et al. (2020).

2.20. Simon task (Congruent Measure)	Time taken to perform task. Sum of correct answers.	Hausswirth et al. (2023).
2.21. Simple Reaction Time Task	Time taken to perform task. Sum of correct answers.	Vakani et al. (2023), Zhao et al. (2021).
2.22. Smooth Pursuit Eye Movements	Time taken to perform task.	Delgado-Alonso et al. (2022).
2.23. Stroop – Color Naming	Time taken to perform task. Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023), Ariza et al. (2023),Costas-Carrera et al. (2022), Dressing et al. (2021), Hosp et al. (2021), Ortelli et al. (2022a), Ortelli et al. (2022b).
2.24. Stroop – Word Reading	Time taken to perform task. Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023), Ariza et al. (2023),Costas-Carrera et al. (2022), Dressing et al. (2021), Hosp et al. (2021), Ortelli et al. (2022a).
2.25. Sustained Attention Task	Time taken to perform task.	Ortelli et al. (2022a), Ortelli et al. (2022b).
2.26. Symbol Digit Modalities Test (SMDT)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023), Dressing et al. (2021), Hosp et al. (2021).
2.27. Trail Making Test-A	Time taken to perform task.	Akinci et al. (2023), Almeria et al. (2020), Almeria et al. (2023), Ariza et al. (2023), Cechetti et al. (2022), Chang et al. (2022), Costas-Carrera et al. (2022), Crivelli et al. (2021), De Paula et al. (2023), Delgado-Alonso et al. (2022), Dressing et al. (2021), Henneghan et al. (2022), Hosp et al. (2021), Rubega et al.

			(2022), Vannorsdall et all. (2021), Zhou et al. (2020).
	2.28. Unimodal Selective Attention – Visual Task (Vienna Test System)	Time taken to perform task.	Delgado-Alonso et al. (2022).
	2.29. Vigilance Task	Time taken to perform task. Percentage of errors. Percentage of accuracy.	Ortelli et al. (2021), Zhao et al. (2021).
	2.30. Visual Search (CogLab)	Time taken to perform task.	Francis et al. (2023).
	2.31. Visual Vigilance (Vienna Test System)	Time taken to perform task.	Delgado-Alonso et al. (2022).
3. Verbal Working Memory	3.1. Brown-Peterson Task (CogLab)	Percentage of correct answers.	Francis et al. (2023).
	3.2. Digit Span (MATRICS Consensus Cognitive Battery)	Sum of correct answers.	Zhou et al. (2020).
	3.3. Digit Span (Brief Assessment of Cognition in Schizophrenia)	Sum of correct answers.	Poletti et al. (2021).
	3.4. Digit Span (Wechsler Adult Intelligence Scale-IV)	Sum of correct answers.	Costas-Carrera et al. (2022).
	3.5. Digit Span (Repeatable Battery for Assessment of Neuropsychological Status)	Sum of correct answers.	Birberg-Thornberg et al. (2022).
	3.6.Digit Span (Screen for Cognitive Impairment in Psychiatry)	Sum of correct answers.	Miskowiak et al. (2021), Miskowiak et al. (2023).
	3.7. Digit Span Backward	Sum of correct answers.	Akinci et al. (2023), Almeria et al. (2020), Almeria et al. (2023), Ariza et al. (2023), Cechetti et al. (2022), Chang et al. (2022), Cian et al. (2022), Crivelli et

				al. (2021), De Paula et al. (2023), Dressing et al. (2021), Hosp et al. (2021), Rubega et al. (2022), Vannorsdall et al. (2021).
		3.8. Digit Span Forward	Sum of correct answers.	Akinci et al. (2023), Almeria et al. (2020), Almeria et al. (2023), Ariza et al. (2023), Cechetti et al. (2022), Chang et al. (2022), Cian et al. (2022), Crivelli et al. (2021), De Paula et al. (2023), Dressing et al. (2021), Hosp et al. (2021), Rubega et al. (2022), Vannorsdall et al. (2021).
		3.9. Memory Span (CogLab)	Sum of correct answers.	Francis et al. (2023).
		3.10. N Back Verbal (Vienna Test System)	Sum of incorrect answers.	Delgado-Alonso et al. (2022).
		3.11. Serial Position (CogLab)	Percentage of correct answers.	Francis et al. (2023).
		3.12. Subtraction Task	Sum of correct answers.	Giardini et al. (2022).
4.	Verbal Memory	4.1. Delayed Memory Index (Repeatable Battery for Assessment of Neuropsychological Status)	Sum of scores from tasks from Repeatable Battery for Assessment of Neuropsychological Status: List Recall, List Recognition, Story Recall, Figure Recall.	Birberg-Thornberg et al. (2022), Hellgren et al. (2021).
		4.2. Immediate Memory Index (Repeatable Battery for Assessment of Neuropsychological Status)	Sum of scores from tasks: List Learning, Story Memory.	Birberg-Thornberg et al. (2022), Hellgren et al. (2021).
		4.3. Logical Memory Delayed (Neuropsychological Assessment Battery)	Sum of correct answers.	Rennison et al. (2023).

4.4. Logical Memory Delayed (Repeatable Battery for Assessment of Neuropsychological Status)	Sum of correct answers.	Birberg-Thornberg et al. (2022).
4.5. Logical Memory Delayed (Wechsler Memory Scale)	Sum of correct answers.	De Paula et al. (2023).
4.6. Logical Memory Immediate (Neuropsychological Assessment Battery)	Sum of correct answers.	Rennison et al. (2023).
4.7. Logical Memory Immediate (Repeatable Battery for Assessment of Neuropsychological Status)	Sum of correct answers.	Birberg-Thornberg et al. (2022).
4.8. Logical Memory Immediate (Wechsler Memory Scale)	Sum of correct answers.	De Paula et al. (2023).
4.9.Verbal Learning (Brief Assessment of Cognition in Schizophrenia)	Sum of correct answers.	Poletti et al. (2021).
4.10. Verbal Learning (Hopkins Verbal Learning Test-Revised)	Sum of correct answers.	Dressing et al. (2021), Hosp et al. (2021).
4.11. Verbal Learning (Öktem Verbal Memory Processes Test)	Sum of correct answers.	Akinci et al. (2023).
4.12. Verbal Learning (Screen for Cognitive Impairment in Psychiatry Danish Version)	Sum of correct answers.	Miskowiak et al. (2021), Miskowiak et al. (2023).
4.13. Verbal Learning (Test de Aprendizaje Verbal Espana-Complutense)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023).
4.14. Verbal Learning (Rey Auditory Verbal Learning Test)	Sum of correct answers.	Vannorsdall et al. (2021).

4.15. Verbal Learning (Repeatable Battery for Assessment of Neuropsychological Status)	Sum of correct answers.	Birberg-Thornberg et al. (2022).
4.16. Verbal Learning –Total Score (Test de Aprendizaje Verbal Espana-Complutense)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023).
4.17. Verbal Learning – Trial 1 (Test de Aprendizaje Verbal Espana-Complutense)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023).
4.18. Verbal Learning – Trial 5 (Test de Aprendizaje Verbal Espana-Complutense)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023).
4.19. Verbal Memory Index (Hopkins Verbal Learning Test-Revised)	Sum of scores from tasks from Hopkins Verbal Learning Test-Revised: Immediate Recall, Delayed Recall, Recognition.	Dressing et al. (2021).
4.20. Word List Delayed Recall (Braincheck)	Sum of correct answers.	Henneghan et al. (2022),
4.21. Word List Delayed Recall (Cognitron)	Time taken to perform task. Sum of correct answers.	Hampshire et al. (2022), Zhao et al. (2021).
4.22. Word List Delayed Recall (Free and Cued Selective Reminding Test)	Sum of correct answers.	Costas-Carrera et al. (2022).
4.23. Word List Delayed Recall (Hopkins Verbal Learning Test-Revised)	Sum of correct answers.	Dressing et al. (2021), Hosp et al. (2021).
4.24. Word List Delayed Recall (Montreal Cognitive Assessment)	Sum of correct answers.	Abdelghani et al. (2022), Triana et al. (2020).
4.25. Word List Delayed Recall (Montreal Cognitive Assessment - Basic)	Sum of correct answers.	Amalakanti et al. (2021).

4.26. Word List Delayed Recall (Öktem Verbal Memory Processes Test)	Sum of correct answers.	Akinci et al. (2023).
4.27. Word List Delayed Recall (Rey's auditory verbal Learning Test)	Sum of correct answers.	Ariza et al. (2023), Cechetti et al. (2022), Cian et al. (2022), Crivelli et al. (2021), Rubega et al. (2022), Vannorsdall et al. (2021).
4.28. Word List Delayed (Screen for Cognitive Impairment in Psychiatry Danish Version)	Sum of correct answers.	Miskowiak et al. (2021), Miskowiak et al. (2023).
4.29. Word List Delayed Recall (Test de Aprendizaje Verbal España-Complutense)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023).
4.30. Word List Delayed Recall - Semantic Cue (Test de Aprendizaje Verbal España-Complutense)	Sum of correct answers.	Almeria et al. (2023).
4.31. Word List Delayed Recall – Semantic Cue (Test de Aprendizaje Verbal España-Complutense)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023).
4.32. Word List Immediate Recall (Braincheck)	Sum of correct answers.	Henneghan et al. (2022),
4.33. Word List Immediate Recall (Cognitron)	Time taken to perform task. Sum of correct answers.	Hampshire et al. (2022), Zhao et al. (2021).
4.34. Word List Immediate Recall (Free and Cued Selective Reminding Test)	Sum of correct answers.	Costas-Carrera et al. (2022).

	4.35. Word List Immediate Recall (Rey's auditory verbal Learning Test)	Sum of correct answers.	Ariza et al. (2023).
	4.36. Word List Immediate Recall (Test de Aprendizaje Verbal España-Complutense)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023).
	4.37. Word List Delayed Recall (Hopkins Verbal Learning Test-Revised)	Sum of correct answers.	Dressing et al. (2021), Hosp et al. (2021).
	4.38. Word List Recognition (Öktem Verbal Memory Processes Test)	Sum of correct answers.	Akinci et al. (2023).
	4.39. Word List Recognition (Rey's auditory verbal Learning Test)	Sum of correct answers.	Ariza et al. (2023), Cian et al. (2022).
	4.40. Word List Recognition Memory Test	Time taken to perform task. Percentage of correct answers.	Guo et al. (2022).
	4.41. Word List Recognition (Rey's auditory verbal Learning Test)	Sum of correct answers across trials.	Ariza et al. (2023).
	4.42. Word List Recognition (Test de Aprendizaje Verbal España-Complutense)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023).
5. Global Functioning	5.1. Cambridge Brain Science (CBS) Global Composite Score	Sum of the scores from tasks from Cambridge Brain Science: Spatial Span, Visuospatial Working Memory, Self-ordered Search, Paired Associates, Spatial Planning, Spatial Rotation, Feature Match, Deductive Reasoning, Digit Span, Color Word Remapping, Interlocking Polygons, Verbal Reasoning.	Wild et al. (2021).

5.2. Cognitive Composite Score	Sum of the scores from tasks: Word List (RAVLT), TMT, Digit Span, Verbal Fluency.	Vannorsdall et al. (2021).
5.3. Global Accuracy Composite Score	Sum of the scores from tasks from Cognitron battery: 2D Mental Rotation, 3D Mental Rotation, Verbal Analogies, Spatial Span, Spatial Planning, Word List, Target Detection.	Hampshire et al. (2022).
5.4. Global Time Reaction Composite Score	Time taken to perform tasks across tasks from Cognitron battery: 2D Mental Rotation, 3D Mental Rotation, Verbal Analogies, Spatial Span, Spatial Planning, Word List, Target Detection.	Hampshire et al. (2022).
5.5. Mini Mental State Examination (MMSE)	Sum of scores from Orientation, Concentration, Attention, Verbal Memory, Naming and Visuospatial Ability tasks.	Cechetti et al. (2022), Cian et al. (2022), Giardini et al. (2022).
5.6. Montreal Cognitive Assessment (MoCA)	Sum of scores from Orientation, Attention, Abstraction, Language, Delayed recall, Naming and Visuospatial/Executive tasks.	Akinci et al. (2023), Ariza et al. (2023), Crivelli et al. (2021), Del Brutto et al. (2021), Ortelli et al. (2021), Ortelli et al. (2022a), Ortelli et al. (2022b), Raman et al. (2021), Rubega et al. (2022), Triana et al. (2020).
5.7. Montreal Cognitive Assessment – Basic Version (MoCA-B)	Sum of scores from Executive Function, Fluency, Calculation, Abstraction, Delayed Recall, Visual Perception, Naming and Attention tasks.	Amalakanti et al. (2021).
5.8. Repeatable Battery for Assessment of	Sum of the indices from the Repeatable Battery for Assessment of Neuropsychological Status: Immediate	Birberg-Thornberg et al. (2022), Hellgren et al. (2022).

	Neuropsychological Status (RBANS) Global cognition score	Memory, Delayed Memory, Attention, Language, Visuospatial/Constructional.	
	5.9. Screen for Cognitive Impairment in Psychiatry (SCIP) Total Score	Sum of scores from tasks from Screen for Cognitive Impairment in Psychiatry: Verbal Learning Test Immediate, Working Memory Test, Verbal Fluency Test, Verbal Learning Test Delayed, Processing Speed Test.	Miskowiak et al. (2021), Miskowiak et al. (2023).
	5.10. Telephone Interview for Cognitive Status (TICS-40)	Sum of scores from Orientation, Attention and Calculation, Naming, Verbal Memory, Category Fluency, Delayed Recall and Visuospatial tasks.	Liu et al. (2021).
6. Visual Memory	6.1. Delayed Free Recognition (Vienna Test System)	Sum of correct answers.	Delgado-Alonso et al. (2022).
	6.2. Delayed Matching to Sample (Cambridge Neuropsychological Test Automated Battery)	Percentage of correct answers.	Stavern et al. (2022).
	6.3. Figure Immediate Recall (Rey-Osterrieth Complex Figure)	Sum of correct answers.	Akinci et al. (2023), De Paula et al. (2023).
	6.4. Learning Test (Brief Visual Memory Test)	Sum of correct answers.	Dressing et al. (2021).
	6.5. Learning Total (Vienna Test System)	Sum of correct answers.	Delgado-Alonso et al. (2022).
	6.6. Object Delayed Memory Test	Time taken to perform task. Sum of correct answers.	Zhao et al. (2021).

	6.7. Object Immediate Memory Test	Time taken to perform task. Sum of correct answers.	Zhao et al. (2021).
	6.8. Pictorial Associative Memory	Time taken to perform task. Percentage of correct answers.	Guo et al. (2022).
	6.9. Recognition (Brief Visual Memory Test)	Sum of correct answers.	Dressing et al. (2021).
	6.10. Recognition (Vienna Test System)	Sum of correct answers.	Delgado-Alonso et al. (2022).
	6.11. Visual Memory Composite Score (Brief Visual Memory Test)	Sum of scores from tasks from Brief Visual Memory Test: Learning, Delayed Recall, Recognition.	Dressing et al. (2021).
	6.12. Visual Recognition Memory Task (MyCognition)	Sum of correct answers.	Vakani et al. (2023).
	6.13. Visual Reproduction (Wechsler Memory Scale-IV)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023).
7. Language	7.1. Naming (Boston Naming Test)	Sum of correct answers.	Almeria et al. (2020), Almeria et al. (2023), Ariza et al. (2023), Costas-Carrera et al. (2022).
	7.2. Naming (Montreal Cognitive Assessment)	Sum of correct answers.	Abdelghani et al. (2022), Triana et al. (2020).

	7.3. Naming (Montreal Cognitive Assessment - Basic)	Sum of correct answers.	Amalakanti et al. (2021).
	7.4. Naming (Neuropsychological Assessment Battery)	Sum of correct answers.	Rennison et al. (2023).
	7.5. Vocabulary Subtest (Wechsler Adult Intelligence Scale-III)	Sum of correct answers.	Costas-Carrera et al. (2022).
	7.6. Word Superiority (CogLab)	Time taken to perform task.	Francis et al. (2023).
8. Visual Construction	8.1. Figure Copy (Benson Figure Test)	Sum of correct answers.	Crivelli et al. (2021).
	8.2. Figure Copy (Rey Osterrieth Complex Figure Test)	Sum of correct answers.	Akinci et al. (2023), Almeria et al. (2020), Almeria et al. (2023), Cechetti et al. (2022), De Paula et al. (2023).
	8.3. Figure Copy (e Repeatable Battery for Assessment of 8.4.Neuropsychological Status)	Sum of correct answers.	Birberg-Thornberg et al. (2020).
	8.5. Block Design Subtest (Wechsler Adult Intelligence Scale-IV)	Sum of correct answers.	Rennison et al. (2023).
9. Visual Working Memory	9.1. 2-Back Task (MyCognition)	Sum of correct answers.	Vakani et al. (2023).

	9.2. Corsi Block-Tapping Task	Sum of correct answers.	Hausswirth et al. (2023).
	9.3. One Touch Stockings (Cambridge Neuropsychological Test Automated Battery)	Sum of correct answers.	Stavern et al. (2022).
	9.4. Rapid Visual Information Processing (Cambridge Neuropsychological Test Automated Battery)	Time taken to perform task.	Stavern et al. (2022).
	9.5. Spatial Span (Cognitron)	Time taken to perform task. Sum of correct answers.	Hampshire et al. (2022), Zhao et al. (2021).
	9.6. Spatial Span (Cambridge Brain Science)	Time taken to perform task. Sum of correct answers.	Wild et al. (2021).
	9.7. Spatial Working Memory (Cambridge Neuropsychological Test Automated Battery)	Sum of incorrect answers.	Stavern et al. (2022).
10. Reasoning	10.1. Abstraction (Montreal Cognitive Assessment)	Sum of correct answers.	Abdelghani et al. (2022), Triana et al. (2020).
	10.2. Abstraction (Montreal Cognitive Assessment - Basic)	Sum of correct answers.	Amalakanti et al. (2021).
	10.3. Raven's Progressive Matrices (RPM)	Sum of correct answers.	Cian et al. (2022).

	10.4. Verbal Analogies	Time taken to perform task. Sum of correct answers.	Hampshire et al. (2022), Zhao et al. (2021).
11. Visual Imagery	11.1. 2D Mental Rotation	Time taken to perform task. Sum of correct answers.	Hampshire et al. (2022), Zhao et al. (2021).
	11.2. 3D Mental Rotation	Time taken to perform task. Sum of correct answers.	Hampshire et al. (2022), Zhao et al. (2021).
	11.3. Mental Rotation Test	Time taken to perform task. Sum of correct answers.	Guo et al. (2022).
	11.4. Mental Rotation (CogLab)	Time taken to perform task.	Francis et al. (2023).
12. Visual Perception	12.1. Cognitrone S11 (Vienna Test System)	Sum of correct rejection.	Delgado-Alonso et al. (2022).
	12.2. Judgment of Line Orientation (JLO)	Sum of correct answers.	Costas-Carrera et al. (2022).
	12.3. Pattern Comparison	Time taken to perform task. Sum of correct answers.	Hausswirth et al. (2023).
	12.4. Visuoperception (Montreal Cognitive Assessment – Basic)	Sum of correct answers.	Amalakanti et al. (2021).
13. Spatial/Temporal Orientation	13.1. Spatial/Temporal Orientation (Montreal Cognitive Assessment)	Sum of correct answers.	Abdelghani et al. (2022), Triana et al. (2020).

	13.2. Spatial/Temporal Orientation (Montreal Cognitive Assessment - Basic)	Sum of correct answers.	Amalakanti et al. (2021).
14. Memory	14.1. Memory index	Sum of scores from tasks: Word List (WMS-III), Logical Memory Delayed (WMS-III), Figure Delayed Recall (ROFC).	Olilla et al. (2022).
15. Attention	15.1. Continuous Performance Test (CPT)	Time taken to perform task. Percentage of correct answers. Percentage of errors. Percentage of missing answers.	Zhou et al. (2020).
	15.2. Feature Match (Cambridge Brain Sciences)	Sum of correct answers.	Wild et al. (2021).