

ARTICLE



Selective visuoconstructional impairment following mild COVID-19 with inflammatory and neuroimaging correlation findings

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People recovered from COVID-19 may still present complications including respiratory and neurological sequelae. In other viral infections, cognitive impairment occurs due to brain damage or dysfunction caused by vascular lesions and inflammatory processes. Persistent cognitive impairment compromises daily activities and psychosocial adaptation. Some level of neurological and psychiatric consequences were expected and described in severe cases of COVID-19. However, it is debatable whether neuropsychiatric complications are related to COVID-19 or to unfoldings from a severe infection. Nevertheless, the majority of cases recorded worldwide were mild to moderate self-limited illness in non-hospitalized people. Thus, it is important to understand what are the implications of mild COVID-19, which is the largest and understudied pool of COVID-19 cases. We aimed to investigate adults at least four months after recovering from mild COVID-19, which were assessed by neuropsychological, ocular and neurological tests, immune markers assay, and by structural MRI and ¹⁸FDG-PET neuroimaging to shed light on putative brain changes and clinical correlations. In approximately one-quarter of mild-COVID-19 individuals, we detected a specific visuoconstructive deficit, which was associated with changes in molecular and structural brain imaging, and correlated with upregulation of peripheral immune markers. Our findings provide evidence of neuroinflammatory burden causing cognitive deficit, in an already large and growing fraction of the world population. While living with a multitude of mild COVID-19 cases, action is required for a more comprehensive assessment and follow-up of the cognitive impairment, allowing to better understand symptom persistence and the necessity of rehabilitation of the affected individuals.

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INTRODUCTION

The majority of worldwide cases of SARS-CoV-2 infection were mild to moderate, self-limited illness in non-hospitalized people. In the beginning of the pandemic, the WHO–China Joint Mission on COVID-19 reported 80% of the 55 924 patients with laboratory-confirmed COVID-19 in China to Feb 20 (2020), had mild-to-moderate disease, while 13.8% developed severe disease and 6.1% evolved to critical stage requiring intensive care [1]. As of

February 10th, 2022, there has been estimated more than 402 million confirmed cases of COVID-19 reported to WHO. It is expected that more than 320 million (80%) had mild to moderate COVID-19. Now, more than 24 months after the start of the events that overturned the health systems across the world, new worries are emerging.

Vaccine distribution worldwide is heterogeneous, so the emergence of new variants has been the new status quo. These

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new variants were more transmissible, leading to a sharp increase in cases in shorter periods and infecting a larger number of people with less severe presentations [2]. However, mild COVID-19 has been much less studied than the moderate and severe forms.

An increasing concern is the long-lasting presentation of COVID-19 which has been identified in about 5% of COVID-19 infected individuals a month after infection, and in up to 2% after four months [3]. Symptoms include fatigue, headache, cognitive compromise, dyspnea, and anosmia [3]. The association with higher number of symptoms [4] and the slow decrease of people having lasting symptoms [5] suggests that the pathophysiological drivers underlying the presence of symptoms might be transient, such as inflammatory response. However, recent data shows that mild COVID-19 is related to important long-lasting symptoms, including neurological and psychiatric manifestations, and persistent sequelae, in about 30% of those patients, with increasing prevalence in aged individuals [6]. In England, a modeling of health economic impact of the long-COVID symptoms estimated the government willingness-to-pay cost could reach more than 32 billion pounds to avoid the potential 557,764 QALY's loss in population [7].

Undoubtedly, beyond the COVID-19 pandemic obvious consequences, it also carries a significant psychological stressor with a tremendous impact on individuals and society. Death and insecurity about the future are powerful psychological stressors and social isolation results in loss of educational activities, structured work, and mental health problems [8]. Historical records suggest that previous influenza pandemics of the XVIII and XIX centuries were marked by increased incidence of neuropsychiatric syndromes, such as insomnia, anxiety, depression, mania, psychosis, suicide, delirium [9, 10], and neuromuscular or demyelinating processes. These usually appear during the acute viral phase or at subsequent periods after infection, in recovered patients. As an example, lethargic encephalitis had a surge in cases following the Spanish flu of 1918 [11]. In the XXI century, there were reports of neuropsychiatric sequelae, such as narcolepsy, convulsions, encephalitis, encephalopathy, Guillain-Barre syndrome (GBS) and other neuromuscular and demyelinating processes, associated with SARS-CoV-1, H1N1 and MERS-CoV, virus from the same genus of the actual SARS-CoV-2 [12–14]. Thus, there were plenty of reasons to assume long-lasting neuropsychiatric symptoms associated with COVID-19.

Magnetic resonance imaging data in patients with severe or mild forms of COVID-19 demonstrated brain lesions [15, 16]. A multimodal study including neuropsychological evaluation, MRI and PET-CT imaging in 29 hospitalized patients observed frontoparietal damage with a distinctive pattern of lesions from sepsis, without attentional and processing speed worsening and with persistent changes in language and visual testes up to a month of discharge [17]. Individuals who recovered from suspected or confirmed COVID-19 had a worse performance on cognitive tests in multiple domains when matched with non-COVID-19 subjects, showing evident deficits even amongst those without severe disease [18]. In a preliminary study, we demonstrated important deficits in the visuospatial processing in around 25% of mild (not requiring hospitalization) COVID-19 patients [19]. Here, we report results of the baseline of a prospective observational cohort study of individuals with mild COVID-19 cases. They were investigated using neuropsychological tests, PET-CT and MRI neuroimaging, and immune markers analysis aiming to shed light on the mechanisms of long standing symptoms and related findings.

METHODS

Research design and procedures

Initially, we assessed clinical status, mental health and history of neurological symptoms with online questionnaires and scales, using the

REDCap platform. All included individuals had positive RT-PCR for SARS-CoV-2 and mild COVID-19 presentation. After answering the questions, participants were assigned to subsequent procedures in two different visits. On the first one, neuropsychological assessment, neurological examination and brain structural magnetic resonance imaging (MRI) were performed. On the second visit, blood was collected and 18-FDG-PET brain imaging was performed. Overall research design is shown in Fig. 1.

Participants

The study was approved by the IRB of Universidade Federal de Minas Gerais (UFMG) (CAAE3768820.1.0000.5149). Written informed consent was provided by all participants. COVID-19 disease severity 1 and 2 according to the WHO clinical ordinal scale was referred to as mild COVID-19 [20]. Initial data collection was conducted using the Research Electronic Data Capture Platform (REDCap) and followed data protection regulation [21]. Volunteers were recruited through the NUPAD of Faculdade de Medicina-UFMG (FM-UFMG). We contacted a total of 338 patients with RT-PCR confirmed diagnosis of COVID-19. The average time between RT-PCR confirmation and inclusion was 4.35 (\pm 2.45) months. Recruiting and sample details are described in the Supplementary Methods and Supplementary Tables 1 and 2.

Psychiatric assessment. Two questions at the REDCap online form were the initial screening used as exclusion criteria: "Have you ever been diagnosed with a mental disorder" and if the answer is positive, "Does this disorder persist to this day?". Even if the participant did not report previous or current mental disorder we adopted two other screening measures to document possible psychiatric symptoms. The DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure-Adult [22] and Self Reporting Questionnaire - SRQ-20 [23].

Cognitive assessment. We adopted standardized psychometric measures previously validated for the Brazilian population. To assess the subjective perception of cognitive change (worsening) we adopted the AD8 scale [24]. Although usually adopted in cases of Alzheimer's disease, we adopted the test for self-report and its original instructions, asking the participant to report cognitive changes after the recovery of COVID-19.

Following the more commonly adopted guidelines regarding cognitive impairment we adopted the -1.5 standard-deviation below demographically adjusted normative values as indicative criteria of deficits. The cutoff score 1 ("normal")/2 ("impairment") was adopted for the classification of our participants. The summed score was also used. This is usually the recommended threshold for minor neurocognitive disorders (APA, 2013) or mild cognitive impairment [25]. In our neuropsychological assessment protocol we classified the observed impairment regarding main cognitive functions assessed by each test: language (verbal fluency), visuoconstructive (Rey-Osterrieth Complex Figure Test (ROCF) Copy) [26], memory (Logical Memory and ROCF recall) [26, 27], attention (Trail Making Test) [28], executive functions (Verbal Fluency Switching and Five Point Test) [29, 30] and working memory (Digit Span) [31].

Neurologic and ophthalmological exams. Neurological evaluation was performed by two neurologists (STC and HO), encompassing mental status, cranial nerves, motor and sensory function, tendon reflexes, coordination, gait and stance. A routine ophthalmological examination was performed by an ophthalmologist (LCM) to rule out possible ocular conditions that could interfere with the assessments: refraction, eye alignment and motility, pupil, visual confrontation field, examination of the external eye, attachments, previous and posterior segments.

Neuroimaging

Magnetic resonance imaging (MRI). Brain imaging acquisitions were performed for every patient on a 3.0T MRI system (Skyra; Siemens, Erlangen, Germany) with a 20-channel receive head coil. The protocol included isotropic three-dimensional (3D) T1, T2 and T2-FLAIR sequences, performed at Hermes Pardini Institute. T1-weighted spin-echo sequence, isotropic 3D T2-WI turbo spin-echo (SPACE), isotropic 3D fluid-attenuated inversion recovery (FLAIR), diffusion-weighted MRI (DW-MRI), and susceptibility-WI imaging (SWI). Gadolinium-contrast was not administered.

PET/CT. Resting-state 18F-FDG PET/CT brain images were acquired in a GE D690 (GE Healthcare, Milwaukee, WI, USA) PET/CT scanner. Blood glucose level was checked and only patients with <140 mg/dl were injected with 0.09 mCi/kg of 18F-FDG. After 50 min in a quiet and dark room with

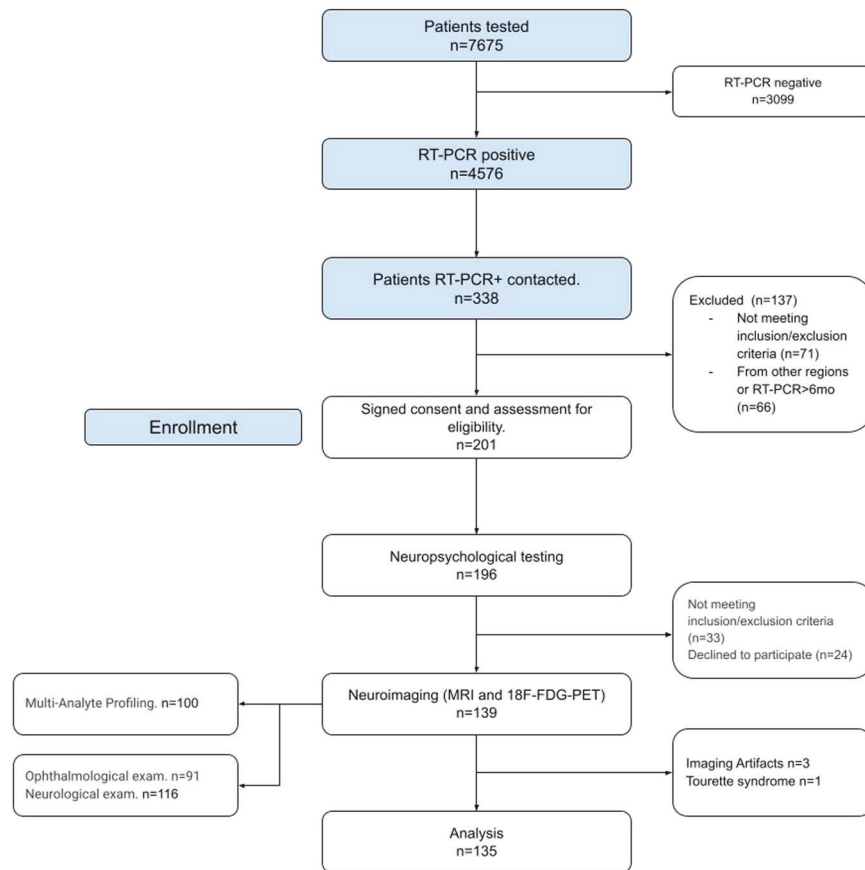


Fig. 1 Research design and subsamples for each research procedure. Neuropsychological tests were available for 191 participants (one patient was unable to perform the tests due to anxiety symptoms). Neuroimaging data was available for 166 participants—excluding five as previously mentioned—other 26 images were excluded due to technical problems during data acquisition (6 MRI datasets and 20 FDG-PET datasets), which led to a final subsample of neuroimage data of 135 participants. Lastly, immunological data was acquired for 100 participants which had both neuropsychological and neuroimaging data.

minimum stimuli, PET brain images were acquired for 10 min, and reconstructed using the OSEM (Ordered Subsets Expectation Maximization) algorithm. Attenuation correction was performed using the CT image.

LUMINEX immunoassay. Peripheral blood samples were obtained in EDTA vacuum tubes. Plasma samples were prepared by centrifugation of venous blood (3000 g for 15 min at 4 °C), divided in aliquots and stored at −80 °C until analysis. Biomarkers including chemokines, inflammatory cytokines, regulatory cytokines and growth factors were analyzed at Instituto René Rachou–Fiocruz using the MultiPlex kit 45-Plex Human ProcartaPlex™ (Thermo Fisher Scientific, USA, EPXR450-12171-901) according to the manufacturer's instructions (the full list of markers can be found in the Supplementary Material). The biomarker concentrations were determined according to standard curves using a 5-parameter logistic fit and the results were expressed as pg/mL.

Statistical analyses

A detailed description of the statistical analysis is provided in Supplementary Information.

RESULTS

Sociodemographic data and report of COVID-19 symptoms

Our sample ($n = 192$) was predominantly female ($n = 71\%$), relatively young (on average 38.17 ± 9.82 years), highly educated (66% with a college degree or post graduation) and average socioeconomic status according to Brazilian standards (62%). Regarding the COVID-19 infection 6% were referred to hospitalization during the acute phase of the disease. The most reported symptoms were headache (77%), myalgia (68%) and anosmia (64%).

Mental health, ophthalmologic and neurological symptoms

About 8% of our sample has a history of mental disorders ($n = 15$), mostly depression and anxiety disorders. According to the SRQ-20 screening 91 participants (48%) showed non-psychotic psychiatric symptoms. Similar results were seen in the self-reported DSM-5 screening where a relatively similar number of participants showed signs of depression (49%), anxiety (53%), anger (47%) and sleep disorders (50%). Other symptoms are shown in Supplementary Table 3. Although these values are considerably high they do not refer to mental disorders per se, but a higher number of symptoms when compared to the general population. Isolated and nonspecific neurological findings were encountered, such as optokinetic nystagmus, absence of ankle reflexes, indifferent plantar responses, decreased pinprick sensitivity on distal extremity of toes, global tendon hyperreflexia, unsustained ankle clonus, postural tremor and intention tremor.

Regarding cognitive changes, 51% of our sample reported subjective daily problems with thinking/or memory, 39% problems with judgment and 34% in remembering appointments.

Neuropsychological assessment results

The frequency of cognitive impairment is shown on Table 1. We did not find significant differences in most of the neuropsychological tests, with frequencies of impairment around 8% (the expected for the criterion −1.5 standard-deviations below normative data). However, we found an atypically high rate of impairment in the copy ROCFT (26%). Matched controls showed about 6% of impairment in the same task.

Table 1. Neuropsychological impairment in COVID-19 patients ($n = 191$).

Test	Impairment ^a		Patients ^b M(SD)	Controls ^b M(SD)	t-test ^c	
	n	%			p	d
Verbal Fluency (animals)	16	8%	19.35 (5.59)	19.76 (4.79)	0.699	-0.08
Verbal Fluency (fruits)	5	3%	17.00 (4.14)	16.24 (3.88)	0.354	0.19
Switching fluency (pairs)	5	3%	17.00 (4.14)	8.84 (1.68)	0.820	-0.05
ROCFT - Copy	48	24%	34.14 (2.95)	29.22 (4.41)	0.001	1.31
ROCFT - Immediate Recall ^d	9	5%	20.61 (6.19)	17.22 (5.42)	0.003	0.58
ROCFT - Delayed Recall ^d	14	7%	21.04 (5.98)	16.41 (5.28)	0.001	0.82
Logical Memory - Immediate Recall	17	9%	10.69 (3.55)	11.76 (2.26)	0.184	-0.27
Logical Memory - Delayed Recall	10	5%	9.82 (3.92)	10.27 (4.10)	0.581	-0.11
Digit Span Forward	0	0%	51.16 (22.88)	50.22 (26.42)	0.851	0.04
Digit Span Backward	0	0%	24.82 (16.45)	28.51 (15.09)	0.250	-0.23
Five Point Test (unique)	0	0%	29.08 (11.6)	27.45 (12.47)	0.505	-0.23
Trail Making Test A	21	11%	37.45 (14.08)	39.41 (14.46)	0.498	-0.23
Trail Making Test B	19	10%	96.37 (54.78)	85.67 (43.38)	0.263	-0.23

M mean, SD standard-deviation, ROCFT Rey-Osterrieth Complex Figure Test.

^aCompared to Brazilian normative data.

^bMatched by age, education and sex ($n = 49$ for each group).

^cIndependent samples *t*-tests and effect size calculated by the Cohens's *d* equation.

^dThis differences were not significant after controlling for the copy impairment in an analysis of covariance (ANCOVA) model.

When compared to the matched control sample we observed significant differences in this test. The copy trial was the most affected ($t = 6.40$, $p < 0.001$, $d = 1.31$), while the immediate ($t = 2.88$, $p = 0.003$, $d = 0.58$) and delayed recalls ($t = 4.06$, $p = 0.001$, $d = 0.82$) showed less prominent differences. No other statistically significant difference was observed between patients and matched controls (p values ranged from 0.184 to 0.870). We compared patients and controls in both memory trials using analysis of covariance (ANCOVA) controlling for the copy score, to investigate if the memory difficulties in the task were secondary to the visuospatial impairment. The analysis showed no differences in immediate ($F = 0.474$, $p = 0.506$) or delayed recall ($F = 0.219$, $p = 0.650$) after controlling for the copy score, which suggests a more specific impairment in the visuoconstructional processes of COVID-19 patients. Some examples of abnormal ROCFT copies are shown in Supplementary Fig. 1.

In order to test if the cognitive deficits were restricted to the visuoconstructional processes or explained by symptoms of mental disorders or sociodemographic factors, we computed spearman rank-order correlations between neuropsychological tests Z-scores between these factors (Supplementary Fig. 2). Most correlations were not statistically significant but we found a weak positive association of socioeconomic status and test performance ($\rho = 0.290$, $p < 0.01$). However, this coefficient was relatively similar in most neuropsychological tests, and did not seem a factor specifically related to the visuoconstructional measure. Even when patients and matched-controls were compared covarying socioeconomic status the difference remained significant ($p < 0.001$).

The neuropsychological profile of the COVID-19 showed a specific pattern of impairment in visuoconstructional processes, measured by the ROCF, in about 26% of the patients. To further investigate this deficit and its neurobiological correlates we stratified our sample in patients with and without impairment.

Luminex multiplex assay findings

Eleven biomarkers, namely LIF Interleukin 6 Family Cytokine (LIF), C-X-C motif chemokine ligand 10 (CXCL10), chemokine (C-C-motif) ligand 2 (CCL2), C-type lectin domain containing 11 A (CLEC11A), C-C motif chemokine ligand 11 (CCL11), granulocyte-macrophage colony-stimulating factor (CSF), hepatocyte growth factor (HGF),

interleukin 31 (IL31), interleukin 1 receptor antagonist (IL1RN), interleukin 10 (IL10) and nerve growth factor (NGF) were upregulated in the plasma of individuals with COVID-19 that showed visuoconstructional impairment in the copy of the ROCF test when compared to patients without this deficit. Figure 2A shows the multiplex results.

Individuals were grouped based on the expression levels of 11 plasma biomarkers upregulated in those with visuoconstructive deficit when compared with those without deficit. In the hierarchical clustering, individuals were segregated in two main groups, one with low frequency of visuoconstructive deficit and relatively low levels of the 11 plasma biomarkers, the other with high incidence of deficit and higher levels of these proteins. This result suggests that lower expression of the 11 biomarkers is associated with protection against cognitive impairment (Fig. 2B). Among the individuals with visuoconstructive deficit, at least four clusters were found (Fig. 2C), indicating that the highly expressed 11 plasma biomarkers associated with cognitive impairment can be present at distinct combinatorial patterns. Individuals with visuoconstructive deficit from clusters 1 and 4 performed poorly at the ROCF test (Fig. 2D).

Significant correlation was observed between the lowest values of the ROCF test and the highest plasma levels of SCF ($c = 0.39$, $p = 0.048$), CSF ($c = 0.46$, $p = 0.020$), HGF ($c = 0.40$, $p = 0.041$) and IL1RA ($c = 0.59$, $p = 0.001$), which was not observed in the group of individuals without visuoconstructive deficit ($p \geq 0.30$ for all). The ROCF test values did not correlate with the age and the gender of the subjects as well as with the levels of the biomarkers ($p \geq 0.31$ for all), but CCL11 increased plasma levels correlated with increasing age ($c = 0.41$, $r = 0.001$).

Neuroimaging findings

We observed no structural changes in the MRI (no signs of thromboembolism, atrophy, acute encephalitis or leptomenigeal enhancement) in any of the 135 patients. The VBM-based analysis of GM images showed no voxel clusters of significant positive or negative correlations with scores on the ROCF test, at the threshold of $p < 0.0005$ and 10 contiguous voxels.

The analysis of WM images also showed no voxel clusters of significant positive correlation with scores on the ROCF test.

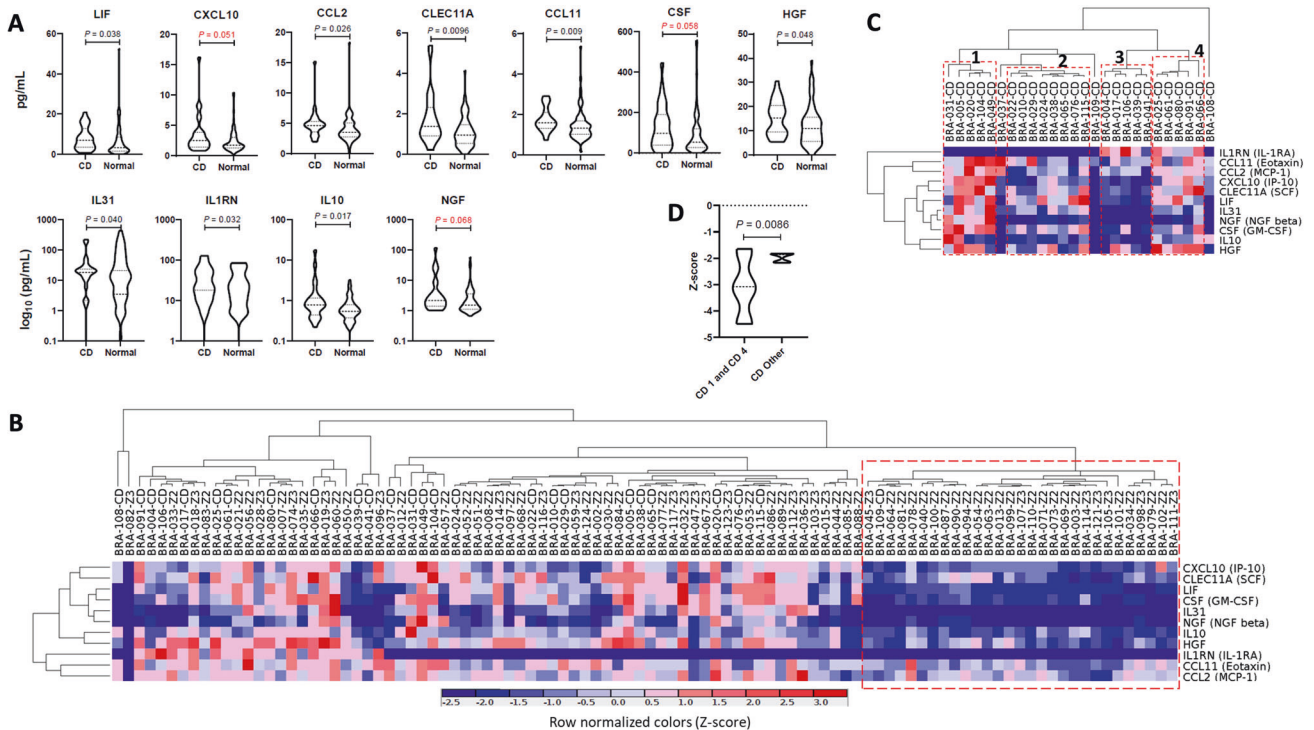


Fig. 2 Plasma Biomarkers and Hierarchical clustering of individuals with visuoconstructive deficit or normal outcome after mild COVID-19 and the differentially expressed plasma biomarkers. **A** Differentially expressed plasma biomarkers associated with visuoconstructive deficit after mild COVID-19. Dashed lines = medians; dotted lines = quartiles. CD = visuoconstructive deficit. N for CD = 26; N for normal = 74. **B** Hierarchical clustering of individuals with visuoconstructive deficit or normal outcome after mild COVID-19 and the differentially expressed plasma biomarkers. **C** Hierarchical clustering of individuals with visuoconstructive deficit after mild COVID-19 and their upregulated plasma biomarkers. **D** Comparison of Z-scores at the Rey–Osterrieth Complex Figure (ROCF) test compared with Kolmogorov–Smirnov statistical test (interquartile).

Conversely, there was a large number of voxels ($n = 1,848$) in which there were significant negative correlations between regional volumes and Z-scores on the ROCF test, indicating a widespread pattern of inverse relationship between test performance and WM volumes (see Fig. 3). These voxels were aggregated in nine clusters (Table 2), the largest of which ($n = 1426$ voxels) encompassing the subgenual portion of the corpus callosum and the cingulum on both hemispheres (Fig. 3). The additional clusters involved WM portions of the inferior frontal gyrus and the fronto-occipital fasciculus bilaterally, as well as the right fusiform gyrus and the bilateral lingual gyri (Table 2).

FDG-PET images indicated nine clusters of voxels displaying significant correlations with Z-scores on the ROCF test (see Fig. 3 and Table 2). Two of those were clusters of significant positive correlation, involving the left inferior temporal gyrus and the left inferior occipital gyrus (Table 2). The six clusters of significant negative correlation encompassed frontal (right dorsal anterior cingulate, Rolandic operculum and ventrolateral frontal cortices, and left superior lateral frontal cortex) and occipital regions (bilateral inferior occipital cortex, and left calcarine/lingual gyri (Table 2).

DISCUSSION

Cognitive deficits following COVID-19 infection have been documented across studies of patients with different ages, disease severity and recovery time [32]. A smaller number of studies analyzed more specific cognitive functions, such as episodic memory, executive functions, verbal fluency [17] and sustained attention [33]. On the other hand, Mattioli and colleagues [34] reported no significant differences between patients and controls in neuropsychological tests, four months after the infection. However, there are inconsistencies regarding affected cognitive

functions and severity of deficits [35]. We observed significant cognitive impairment only in the ROCF, a drawing task test used to assess visuospatial abilities, executive functions and memory. The deficits observed in the ROCF could not be explained by socio-demographic factors, ophthalmologic deficits or psychiatric symptoms, suggesting cognitive deficit secondary to SARS-CoV-2 infection. Other factors which may influence performance, such as motor coordination, spatial neglect, visual attention, semantic knowledge, intelligence and executive functions were not likely to explain the observed difficulties, since we did not find any significant differences in other non-verbal (Trail Making Test and Five Points Test) and verbal tests (verbal fluency, digit span) also related to these processes.

Visuoconstructive deficits are usually defined as an atypical difficulty in using visual and spatial information to guide complex behaviors like drawing, assembling objects or organizing multiple pieces of a more sophisticated stimuli. In drawing a complex figure, as in the ROCF, the patient must organize visual and spatial information in a planned manner to execute the drawing per se, a processes that demand several more specific cognitive abilities related to perceiving, processing, storing and recalling visuospatial information, both regarding shape and position, as well the planning and execution of the drawing per se.

These processes involve multiple brain regions, including the occipito-parietal regions, the dorsal and ventral streams and connections with the cingulate, medial temporal and frontal cortices, integrating the perception and interpretation of the visual information with memory and executive systems [36, 37]. Drawing tasks have been getting attention lately for their sensitivity to study visuospatial deficits, which were shown to be early biomarkers of neurodegenerative disorders, such as Alzheimer’s and Parkinson’s disease [38–40].

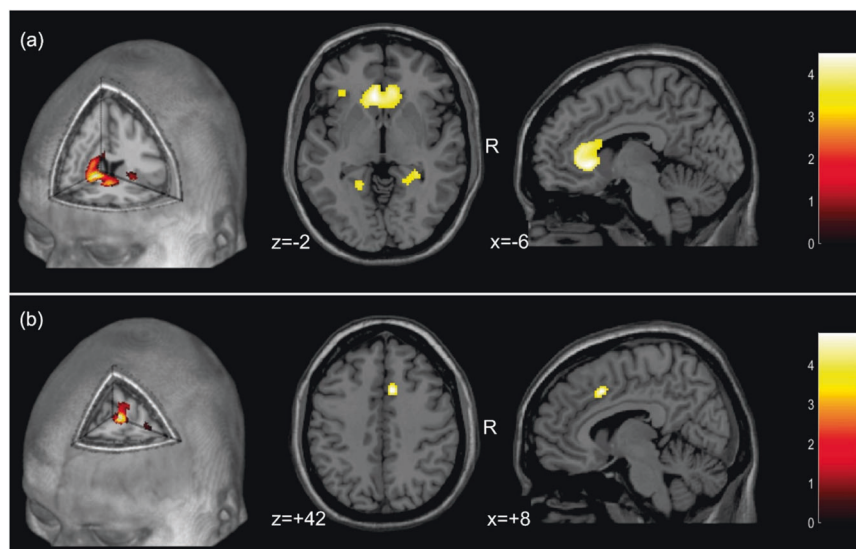


Fig. 3 Brain correlates of visuoconstructional performance in mild COVID-19 patients. **a** Findings of negative correlation between performance on the Rey-Osterrieth Complex Figure (ROCF) test and white matter volume (filtered at the $Z > 3.29$ threshold). The foci show the peak of the greatest significance within the cluster (highlighted in yellow), located in the left and right genu of the corpus callosum, extending to the cingulum bundle; **b** Findings of negative correlation between performance on the ROCF test and glucose metabolism (filtered at the $Z > 3.29$ threshold). The foci show the peak of the greatest significance within the cluster (highlighted in yellow), located in the right dorsal anterior cingulate gyrus. The colored bar represents the T value. Foci of significance were overlaid on axial brain slices spatially normalized into an approximation to the Talairach and Tournoux stereotactic atlas (Talairach and Tournoux, 1988). Abbreviations: R right. Statistical details are provided in Table 2.

The COVID-19 individuals investigated herein were often unable to produce a proper copy of Rey's figure, and had difficulties in memory. Immediate and delayed recall seems to be secondary to the copy impairment. The lack of ability to assemble or organize parts into a whole object or figure is considered constructional apraxia, a neuropsychological syndrome which results in inability to accurately reproduce two-dimensional or three-dimensional visual models [41]. Constructional apraxia might follow acquired brain lesions or aging-related neurodegenerative diseases which affect the parietal or frontal lobes, but it is very uncommon in younger patients as the ones in our study, with a mean age of 38 years. Constructional apraxia is a sign of a divergence between the intended action and the actual performance, which may be seen in tests of free drawing or standardized tests of copy, including the ROCF. The performance on visuoconstruction and memory tests, such as the ROCF, are associated with different aspects of everyday life, including the capacity to learn, problem-solving skills, and activities of daily living [42]. A more comprehensive assessment and follow-up of the visuoconstructive impairment should allow better understanding of symptom persistence and the need of rehabilitation.

HCoVs have molecular structure and mode of replication similar to neuro-invasive animal coronaviruses [43], which can reach the CNS and induce different types of neuropathology. MHV is the best known coronavirus involved in short- and long-term neurological disorders [44]. It is plausible to consider their involvement in neuropsychiatric symptoms and possible post-viral sequelae. The angiotensin-converting enzyme 2 (ACE2 or Ace2) has been identified as a primary entry receptor for SARS-CoV-2, indicating that SARS-CoV-2 may be able to infect the brain and result in CNS symptoms in patients with COVID-19 [45].

In other viral infections, such as HTLV-1, a correlation between the proviral load in peripheral blood mononuclear cells was observed with brain white matter lesions, and deficits in tasks requiring integrity of subcortical activation, including constructive praxis [46]. Persistent neuroinflammation was considered a possible explanation for white matter lesion and cognitive impairment in HTLV-1-infected patients [46]. The disruption of

cytokines and chemokines signaling in the CNS can contribute to the dysfunctional host-viral immune function and pathogenesis that occurs in inflammatory diseases such as HTLV-1 infection [47]. In infections with influenza A virus (IAV), neuropsychiatric complications were reported after infection with either neurotropic or non-neurotropic variants [48], suggesting that viral infections can provoke neuroinflammation via peripherally-produced cytokines.

Cytokines produced by the peripheral innate immune system can trigger a secondary neuroinflammatory response in the CNS, depicted by activation of microglia and production of proinflammatory cytokines (IL-1 beta, IL-6, and TNF-alpha) [49–51]. IL-6 and IL-1 beta are typical features from the innate immune response. IL-6 acts as a major proinflammatory mediator for the induction of the acute phase response and IL-1 beta was identified as a severity marker of the COVID-19 progress. We did not find significant differences between participants with/without visuoconstructional impairment, regarding these markers. However, after recovery from the acute phase high levels of IL-6 or IL-1 beta are not expected, especially in individuals with mild COVID-19 at post-acute phase (at least after 4 months) such as in our sample.

Neuroinflammation was shown to severely affect cognition and behavior in animal models [48, 52, 53]. It is mediated by the increase of cytokines and chemokines, reactive oxygen species (ROS) and second lipid messengers produced by astrocytes and microglia, endothelial and peripheral immune cells [54]. Chronic neuroinflammation implies persistent activation of microglia and other immune cells in the CNS with potential damage [55, 56], such as neuropathological changes and psychiatric complications, such as depression and cognitive deficits [53, 57, 58].

Among the 11 upregulated plasma biomarkers in individuals with visuoconstructional deficit, 10 composed a functional interaction network where they up- or downregulate each other (Fig. 4). These interactions are represented by the broken edges of the network connecting the nodes, which, in turn, represent the protein biomarkers. Four biomarkers are components of the canonical "Neuroinflammation Signaling Pathway" and four of the "IL-17 Signaling pathway". Furthermore, six of the 10 biomarkers in

Table 2. Significant correlations between performance on the Rey–Osterrieth Complex Figure Test and neuroimaging measurements of gray and white matter volumes (MRI) and glucose metabolism (FDG-PET).

Brain region ^a	Direction of significant correlation	Cluster size ^b	Coordinates ^c			Peak Z-score ^d
			x	y	z	
Gray matter volume						
No significant correlations.	–	–	–	–	–	–
White matter volume						
Left and right genu of the corpus callosum, extending to the cingulum bundle	Negative	1426	–6	26	–2	4.32
Right fusiform gyrus	Negative	93	32	–22	–26	4.01
Right lingual gyrus	Negative	127	30	–44	–8	3.84
Right inferior frontal gyrus	Negative	98	40	6	16	3.76
Left lingual gyrus	Negative	41	–18	–52	2	3.73
Left inferior frontal gyrus	Negative	20	–34	30	–2	3.48
Left inferior fronto-occipital fasciculus	Negative	15	–24	4	–8	3.47
Left inferior fronto-occipital fasciculus	Negative	15	–32	–10	–8	3.44
Right inferior fronto-occipital fasciculus	Negative	13	32	–10	–8	3.43
Glucose metabolism (FDG-PET)						
Left inferior temporal gyrus	Positive	34	–56	–46	–22	3.96
Left inferior occipital gyrus (superior portion)	Positive	53	–48	–68	–16	3.92
Right dorsal anterior cingulate gyrus	Negative	69	8	16	42	4.61
Right Rolandic operculum and opercular part of the inferior frontal gyrus	Negative	57	52	8	12	4.48
Right inferior occipital gyrus	Negative	62	38	–74	–6	4.15
Left calcarine and lingual gyri	Negative	66	–14	–92	–8	3.88
Left superior frontal gyrus	Negative	50	–16	60	–8	3.75
Left inferior occipital gyrus (inferior portion)	Negative	19	–30	–82	–8	3.46
Right medial frontal and orbital frontal gyri	Negative	20	18	54	–4	3.43

^aFor the analysis of white matter volumes, the brain regions where voxel clusters were located were identified according to the MRI Atlas of Human White Matter (Oishi et al., 2010). For the analysis of glucose metabolism, brain regions were identified according to the Automatic Anatomical Labeling Toolbox for SPM12 (Rolls et al., 2015).

^bNumber of contiguous voxels in each cluster that surpassed the initial cutoff of $p \leq 0.0005$.

^cMNI coordinates of the voxel of maximal statistical significance within each cluster.

^dZ-score for the voxel of maximal statistical significance in each region.

the network are related to hepatic necrosis and five to cardiac necrosis. The fact that 11 plasma biomarkers were associated with visuoconstructive deficit and 10 of them composed a functional network lend considerable support to the relevance of the immunological markers, which may act either in the protection or increasing risk to cognitive impairment. The association was not only by binary comparison, but also by comparing their levels and presence of visuoconstructive deficit.

Several upregulated biomarkers, identified in the present study, act on the central nervous system promoting protection or damage to the brain. HGF is a neuronal growth and survival factor capable of preventing neuronal death through its pro-angiogenic, anti-inflammatory and immunoregulatory activities and stimulating neuroregeneration by acting on neural stem cells and also promoting synaptogenesis [59]. Also part of the comprehensive multiplex assay, another relevant biomarker found in the present study was NGF, which has anti-inflammatory and homeostatic properties in the central nervous system [60]. However, NGF must be seen as a pleiotropic cytokine in contrast to other specialized cytokines, whose overall effects will be the result of signaling in the different systems expressing NGF receptors, in the CNS [60] or in the periphery, such as the respiratory system [61].

Other identified biomarkers act by promoting neuroinflammation. LIF is able to cross the blood-brain barrier and promote the induction of other pro-inflammatory cytokines in the central

nervous system [62]. CXCL10 acts as an mediator for the activation and influx of leukocytes, such as T cells and others, in various inflammatory diseases of the central nervous system [63]. CSF is essential for the pathogenesis of experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis, mediated by encephalitogenic T helper cells that produce IL-17 (Th17 cells) [64]. Cytokine C-C motif chemokine 11 (CCL11, also known as eotaxin-1) can limit neurogenesis and contribute to cognitive impairment [65]. Elevated CCL11 levels were also found in the plasma of long-COVID patients with cognitive deficits compared to those without cognitive symptoms [66]. Notably, in accordance with the study of Villeda et al. (2011), an age-related increased CCL11 in the plasma of the patients with visuoconstructive deficit was observed [65]. With the exception of HGF and IL1RN, all other markers identified in this study are components of the canonical pathways of IL-17 or neuroinflammation signaling (CCL2 participates in both). In addition to the well-established association between neuroinflammation and cognitive impairment, the role of Th17 cells in brain diseases associated with this condition, such as multiple sclerosis, cerebral ischemia and Alzheimer's disease, is also noteworthy. Th17 cells infiltrate the central nervous system where they induce direct brain cell damage or indirect effects mediated by disruption of the blood-brain barrier and neurovascular dysfunction [67]. In microglial cells, CCL2 decreases the activation of the protein GAD (aspartate

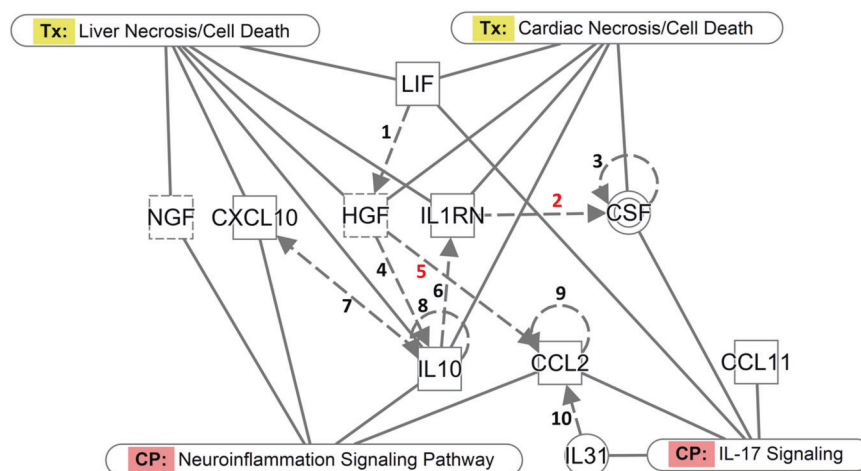


Fig. 4 Network of functional interactions between the differentially expressed plasma biomarkers (plain squares for cytokines or chemokines; dashed squares for growth factors, double circle for complex/group), canonical pathways (CP) and clinical pathology endpoints (Tx). (1) LIF protein increases expression of HGF mRNA [91]; (2) IL1RN protein decreases production of CSF protein [92]; (3) CSF protein increases its own dimerization [93]; (4) HGF increases secretion of IL10 protein [94]; (5) HGF protein decreases expression of CCL2 mRNA [95]; (6) IL10 protein increases expression of IL1RN mRNA [96]; (7) IL10 protein increases release of CXCL10 protein [97]; (8) IL10 protein increases expression of human IL10 mRNA [98]; (9) CCL2 mRNA is increased by CCL2 protein [99]; (10) IL31 protein increases expression of CCL2 mRNA [100, 101]).

1-decarboxylase) [68]. GAD, in turn, decreases the density of GABAergic neurons [68] and increased GABAergic function in the prefrontal cortex impairs working memory [69]. Versace et al. [70] reported that severe COVID-19 survivors had reduced GABAergic inhibition in the primary motor cortex associated with fatigue and dysexecutive syndrome [70].

CSF assessment might be helpful to identify signs of neuroinfection, neuronal injury and degeneration. However due to the mild nature of COVID-19 symptoms of our participants, we did not include lumbar puncture to collect CSF at the time of IRB approval.

With the exception of CCL2, CCL11 and IL31, the other found biomarkers are also upregulated in liver and heart injury, playing a protective and regenerative role. For example, IL1RN regulates cardiac remodeling by promoting the survival of cardiomyocytes in ischemic regions [71] and is also hepatoprotective [72]. We cannot rule out that individuals with visuoconstructive impairment post mild COVID-19 could also have some level of cardiac [73, 74] and/or hepatic damage [75]. COVID-19 has shown to be a multifactorial disease, which we are just starting to scratch the surface of. As no standard solution is yet available to solve this problem, new anti-inflammatory and immunomodulatory strategies will be necessary.

A recent study showed that mice mildly-infected with SARS-CoV-2 lost approximately one third of mature oligodendrocytes of the WM in the cingulum and corpus callosum, which was still present at 7-weeks post-infection [66]. WM-selective microglial reactivity was shown to inhibit neurogenesis, dysregulation of the oligodendrocytes and loss of myelin [76] in both mice and humans following SARS-CoV-2 infection [66]. Our main MRI finding was an inverse relationship between ROCF test copy performance and WM volumes encompassing the subgenual portion of the corpus callosum and the cingulum on both hemispheres. The crossing over characteristics and the corpus callosum findings might have an important role in understanding the correlation with constructive apraxia [77]. Visuoconstructive deficit is a common finding in callosal ischaemic lesions [78] and agenesis [79]. Although spatial abilities are expected to involve most prominently the right brain hemisphere, some tasks elicit bilateral brain activity [37]. Constructive apraxia has been associated with left- and right-hemisphere lesions, both in posterior and anterior regions, and their integration by white matter tracts. Involvement

of the right superior parietal lobe, angular gyrus, middle occipital gyrus have been previously associated with poorer performance in the ROCF copy task in pathological conditions, including vascular lesions [80], epilepsy [81], and traumatic brain lesions [82]. However, we found additional clusters involving WM portions of the inferior frontal gyrus and the fronto-occipital fasciculus bilaterally, as well as the right fusiform gyrus and the bilateral lingual gyri (Table 2).

Although increased volume seems paradoxical, since the correlation between brain volume and cognitive functioning is usually positive [83], there is evidence that COVID-19 patients might show an increased brain volume when compared to matched controls [84]. As reported by Lu and colleagues [85], recovered patients might show increased cerebral volume across different brain regions, including olfactory cortex, hippocampus, insula, left Rolandic operculum, left Heschl's gyrus and right cingulate gyrus. In diseases known to affect the white matter, such as multiple sclerosis, there are reports of transient increases in brain volume during periods of neuroinflammation relapse [86]. On the other hand, in a large imaging study, comparing brain scans from individuals before and after SARS-CoV-2 infection, it was found greater reduction in GM thickness in the orbitofrontal cortex and parahippocampal gyrus and greater reduction in global brain size [16]. As we lacked pre-COVID-19 imaging and all our participants had confirmed SARS-CoV-2 infection, we were not able to detect these reductions in GM or global brain size. Instead, we were able to identify changes correlated with a selective visuoconstructive impairment revealed by the ROCF test.

Brain metabolic changes have been documented across multiple studies of COVID-19 patients, although with inconsistent results [17, 87]. Patterns of hypo- or hypermetabolism across different cortical and subcortical symptoms are related to neuropsychiatric symptoms of the disease, including anosmia [88], fatigue [89] and cognitive impairment [17]. Concerning resting brain glucose metabolism measured with ^{18}F FDG-PET and copy-ROCF performance, we found the most significant cluster to have a negative correlation, located in the right dorsal anterior cingulate gyrus, but we also found clusters of significant positive correlation, involving the left inferior temporal gyrus and the left inferior occipital gyrus. Hosp and colleagues analyzed the pattern of covariance of PET-FDG brain images between COVID-19 patients

and controls and reported several regions of cortical hypometabolism in the frontal and parietal lobes, as well as the caudate nuclei, and hypermetabolism in the white matter, cerebellum, brainstem and the mesial temporal lobe, and this pattern was predictive of cognitive deficits [17].

There was not much attention directed to the large population affected by mild COVID-19, since they apparently had recovered well. More than two years into the pandemic, it is still underinvestigated. It was reported that home-isolated young adults (16–30 years old), with mild COVID-19, had persistent symptoms at 6 months, including fatigue, impaired concentration and memory problems [90]. As we observed roughly 25% of our mild COVID-19 patients presenting visuoconstructive impairment, we can expect millions of people worldwide potentially suffering from this kind of deficit. It is imperative to approach populational samples to better understand the extension, causes and persistence of the dysfunction. Why is that so worrying? Constructive apraxia might stay undiagnosed without specific visuospatial testing, which does not mean it has no functional implications in daily life. Visuospatial ability is key to several daily living activities, such as driving, planning, drawing, to locate oneself in a place, and several occupations rely on good visuospatial perception, such as artists, surgeons, designers, pilots, among others. The functional adaptability must be evaluated to plan rehabilitation strategies. Investigation of neuropsychiatric impacts and the pathophysiological drivers underlying the risk factors associated with COVID-19 are important in surveillance and in the development of evidence-based therapeutic strategies.

Factors affecting enrollment into our prospective cohort study would not be expected to introduce selection bias, however, as our findings occurred when establishing the baseline, we must consider the potential to have a selection bias, causing an overestimate, since included individuals were invited for a neuropsychiatric study. Nevertheless, our findings provide evidence of putative neuroinflammatory burden, in an already large and growing fraction of the world population with mild COVID-19, putatively afflicted by long COVID, which requires urgent confirmation, comprehension, and planning for mitigating actions.

DATA AVAILABILITY

To protect the data privacy of the study participants, the dataset cannot be made publicly available. Specific data needed for reproducing results is available from the corresponding author upon reasonable request.

CODE AVAILABILITY

Code needed for reproducing results is available from the corresponding author upon reasonable request.

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Study conception and/or design: JJP, DMM and MAR-S. Clinical assessment: JJP, RERPP, HSDT, STC, LCM. Data acquisition: JJP, NGSS, DVR, HMMV, NOC, JBS, MBS, DBO, CM, JNJ, LCS. Data analysis: JJP, RERPP, NGSS, FLSD, RSC, DSC, PRD, DMO, LCS, DMMQ, WMJr, GB, DMM, MAR-S. Manuscript writing and/or revision: JJP, RSC, LADM, CM, DMMQ, GB, DMM, MAR-S.

COMPETING INTERESTS

The authors declare no competing interests.

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