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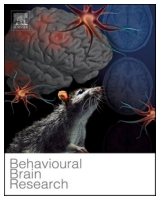

An immersive virtual reality-based object-location memory task reveals spatial long-term memory alterations in Long-COVID

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ABSTRACT

Object-location memory (OLM) is a type of declarative memory for spatial information and consists of the individual's ability to establish accurate associations between objects and their spatial locations. Long-COVID describes the long-term effects of the COVID-19 disease. Long-COVID patients show medial temporal lobe dysfunction and neuropsychological alterations affecting memory. This study aimed to assess OLM in a group of Long-COVID patients, n=66, and a Control group of healthy individuals with similar age and sex composition, n=21, using an immersive virtual reality (iVR)-based OLM task. We also explored associations between the performance in the iVR-based OLM task and general cognitive function (MoCA), and both verbal (VSTM) and visuospatial (SSTM) span. The Long-COVID group showed fewer correct responses, made more task attempts, and invested more time in the iVR-based OLM task than the Control group. Delayed memory was more severely altered than immediate memory in Long-COVID participants. Better MoCA scores of the Long-COVID group were strongly associated with shorter times to complete the immediate recall of the iVR-based OLM task. Besides, the months elapsed since the COVID-19 infection were slightly associated with fewer correct responses in the immediate and 24-hour recalls. These results corroborate previous findings of memory alterations in the Long-COVID syndrome using an iVR-based OLM task, adding new evidence on spatial memory and long-term memory in this population. Implementing spatial iVR tasks to clinical research may improve our understanding of neuropsychological disorders.

1. Introduction

Object-location memory (OLM) is a type of declarative memory for spatial information and consists of the individual's ability to establish accurate associations between objects and their spatial locations [1,2]. OLM is mainly sustained by the medial temporal lobes (including the hippocampus) [3,4].

OLM takes place in navigational space. For this reason, the use of applications based on immersive Virtual Reality (iVR) could be an interesting option for OLM assessment [5]. Specifically, iVR uses headset devices to immerse users in a 3D environment [6], allowing them to learn a variable number of object locations in a free-walking space and

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test them later in the same environment [7]. This can provide more ecological measures than other assessment tests that do not involve user immersion in the spatial environment (e.g., paper-and-pencil tests and non-immersive computerized tests) because it is more similar to how an individual perceives the real environment [8]. In this way, previous studies have shown similar outcomes between spatial memory tasks performed in real and virtual environments [6]. This is probably because, in comparison to non-immersive Virtual Reality, iVR involves sensory inputs necessary for spatial cognition, such as vestibular, proprioceptive, and optic flow, maintaining the user's full control over the visuals of the environment and increasing their spatial memory recall [6,9]. Another advantage of iVR is that it facilitates experimental control over environmental aspects, which is crucial in spatial navigation research [8]. Moreover, a review concluded that only a small percentage of older adults suffer from cybersickness associated with the use of iVR [10], confirming the potential of this technology for use in any type of population.

OLM was previously assessed in healthy adults [11], healthy older adults, and older adults with Mild Cognitive Impairment, Alzheimer's Disease, or Subjective Cognitive Decline [6,12,13], as well as in stroke patients [4], among other conditions. However, OLM has not been explored in other more recent conditions, such as the Long-COVID syndrome.

Long-COVID is a multisystemic syndrome defined by the World Health Organization (WHO) as a condition that occurs beyond three months from the onset of COVID-19 disease, lasts for at least two months, and cannot be explained by an alternative diagnosis [14]. This syndrome is characterized by a number of broadly different neurological, psychological, and neuropsychological symptoms such as fatigue, headache, myalgia, brain fog, anosmia, hyposmia, sleep disturbances, anxiety, depression, attention disorder, executive dysfunction, visuospatial alterations, and memory loss, among others [15–19]. Regarding memory impairment, recent studies have found alterations of both verbal and visuospatial declarative memory and consolidation of procedural memory in Long-COVID patients [20,21]. In their review of memory deficits in long-COVID, Llana et al. [21] found that most investigations have focused on assessing the verbal memory component. These investigations mainly conducted a single assessment approximately 4–6 months following the onset of infection, with evaluations of short-term and long-term recall extending up to 30 minutes post-infection. The studies consistently found impairments in verbal learning, with reported incidence rates ranging from 6 % to 58 %. Deficits in both long-term (ranging from 4 % to 58 %) and short-term (ranging from 4 % to 37 %) verbal memory were frequently observed. Investigations into the visuospatial memory component were comparatively limited and utilised the Rey-Osterrieth Complex Figure [22,23] and the Brief Repeatable Battery of Neuropsychological Tests [24,25]. Studies in this area have primarily highlighted difficulties with long-term retention of visuospatial information. Reported incidence rates of impaired long-term retention of visuospatial items range from 10 % to 49 % [22–26]. However, the impairment observed in short-term retention of visuospatial information and visuospatial recognition appears to be less pronounced. Specifically, only 8–16 % of cases [23,24] and 6 % of cases [23] reported incidences of impairment. When comparing clinical and control groups, Crivelli et al. [27] identified significant impairments in long-term visuospatial memory among long-COVID patients in the Benson Complex Figure Test. In a delayed object recognition task, Zhao et al. [28] reported that individuals with long-COVID displayed a higher number of orientation-specific false alarms compared to the control group. This memory deficit was strongly associated with time since the onset of acute symptoms of COVID [28].

When considering the variables that could affect memory performance in Long-COVID patients, it is important to take into account the time elapsed between the COVID-19 infection and the neuropsychological assessment. Over time after diagnosis, long-term declarative memory deteriorates [29], while working memory improves, as demonstrated by performance in immediate object or word memory tests [28]. Long-term declarative memory impairment persists over time, but short-term attention and vigilance recovered. The dysfunction of brain regions involved in these processes could show a differential pattern of evolution. Longitudinal studies indicate that the frontoparietal regions, which are involved in attention and working memory, recovered over several months [30]. However, dysfunction in the temporal lobe, which is involved in long-term declarative memory, persisted over time [31,32]. The precise mechanisms responsible for cognitive impairments in Long-COVID are not yet fully understood. Although a direct viral presence in the brain cannot be ruled out, indirect pathways involving mechanisms such as immunological alterations and microvascular changes, may also play a significant role [33].

The neural circuit responsible for encoding complex episodic-like memories involves the prefrontal cortex, the lateral entorhinal cortex, and the hippocampus. This circuitry processes memory for object, place, temporal order, and object-location inter-relationships [34,35]. The hippocampus plays a vital role in processing spatial information and is involved in OLM. Rodent studies have extensively demonstrated this through object place preference tests [36–39]. These tests assess the capacity for recognizing previously encountered stimuli and their associated locations. In humans, the hippocampus is essential for retrieving object-place paired associate memory of a set of objects presented in a 2D computer screen [3,4] or navigational VR environment [3].

Disruptions in hippocampal function or connectivity may impair the ability to encode and recall object locations, thereby affecting accurate OLM performance. Studies exploring the relationship between hippocampal dysfunction and SARS-CoV-2 infection [32] have found that neurogenesis in the hippocampus was altered in people and rodents infected by the SARS-CoV-2 virus [31]. Neuroimaging studies have also detected degeneration and volume reduction in the hippocampus and parahippocampal cortex in subjects suffering from mild COVID-19 infection [40]. Functional neuroimaging studies have observed hypometabolism in the right temporal lobe of Long-COVID patients, including the hippocampus [41], and hypoconnectivity between left and right parahippocampal areas [42].

Although OLM has not been objectively assessed in Long-COVID patients, a computerized memory task that included an immediate recognition test and a delayed test performed 30 minutes later revealed impaired delayed memory for the appearance and orientation of line-drawn objects, but unaltered memory for the objects themselves [28]. Likewise, a rodent model of hippocampal SARS-CoV-2 infection showed deficits in an OLM task. Mice injected with SARS-CoV-2 S1 protein exhibited reduced discrimination capacity in a novel location recognition task using the place preference paradigm with no delay interval [43]. Additionally, 20 % of Long-COVID patients reported OLM alterations, specifically difficulties in recalling where they placed everyday objects, when their subjective memory complaints were assessed one year after the infection using a questionnaire [44].

This study aims to assess OLM in a group of Long-COVID patients and a group of healthy individuals with similar age and sex composition using an iVR-based OLM task. The medial temporal lobes, which are brain areas involved in OLM, exhibit alterations in Long-COVID patients. The iVR-based OLM task provides ecological validity for assessing this spatial learning. A secondary aim of this study is to investigate the associations between the performance of the Long-COVID patients in the iVR-based OLM task and the time elapsed since their infection diagnosis until the assessment of OLM and other cognitive tasks encompassing a wide range of cognitive functions, including general cognitive status, and both verbal and visuospatial span. Verbal and spatial spans, both forward and backward, are associated with performance in spatial navigational tasks that require object localization [45]. These processes indicate the ability to encode, store, and retrieve verbal and spatial information related to object-location associations. The retention and manipulation of verbal and visuospatial information during task

performance can affect OLM results. Some Long-COVID patients have shown alterations in these processes [22,27]. Additionally, cognitive status, as measured by the Montreal Cognitive Assessment (MoCA), correlates with VR spatial memory tasks, in which participants learn and recall everyday objects within immersive environments from a first-person perspective [46]. The MoCA is a widely used screening tool for assess overall cognitive function and detect mild cognitive impairment. Given that individuals with Long-COVID have reported diverse cognitive sequelae, including deficits in attention, executive function, and memory, measured by the MoCA screening test [47], it is important to include this test to capture any potential association of global cognition with OLM performance. The study also examines the same associations in a group of healthy individuals. As Long-COVID patients have reported deficits in OLM through subjective assessment questionnaires and have presented low performance in some standardized memory tests, we expect to find poorer performance in this group compared to the healthy individuals in the iVR-based OLM task. It is difficult to establish hypotheses regarding the secondary objective due to the absence of studies exploring the association of performance in navigational OLM tasks and clinical conditions or scores on other standardized memory tests. However, considering the general trend of associations reported in other studies, performance in the OLM task could be positively associated with memory span and overall cognitive functioning.

2. Materials and methods

2.1. Participants

One hundred thirty-two Long-COVID volunteers were recruited from Long-COVID associations, of whom 66 were willing to participate in all the study sessions and met eligibility criteria. The inclusion criteria aligned with the WHO definition of Long-COVID mentioned briefly above [14], encompassing three aspects. First, eligible participants were required to have a history of probable or confirmed SARS-CoV-2 infection at least three months prior to their enrolment in the study. Confirmed infection could be either through Reverse Transcription Polymerase Chain Reaction (PCR) or antigen tests. Probable infection refers to symptomatic patients whose medical records indicated a suspected infection but who had not undergone testing due to limited access to diagnostic tests. Second, the severity of SARS-CoV-2 infection ranged from mild clinical symptoms without respiratory distress to severe cases that required hospitalization. Third, participants had to have experienced symptoms temporally associated with the SARS-CoV-2 infection. These symptoms extend beyond three months from the onset of the infection, last for a minimum of two months, and cannot be attributed to an alternative diagnosis. Participants were required to be either native Spanish speakers or demonstrate a high level of proficiency in Spanish.

Exclusion criteria were: the presence of cognitive complaints before the onset of COVID-19; a history of previous or existing neurological disorders that might be linked to cognitive or sensory impairments; the existence of severe psychological or psychiatric disorders, either current or past; and the presence of uncontrolled medical conditions that had the potential to introduce bias in the cognitive assessments.

Thus, the final sample comprised 66 participants who suffered from Long-COVID (Long-COVID group), of whom 59 were women (age in years: mean = 43.42, *SD* = 6.22) and 7 men (age in years: mean = 44.29, *SD* = 6.26). Table 1 presents the symptoms of chronic COVID-19 in the Long-COVID group. This information was collected using a Spanish adaptation of the National Health Service (NHS) Long COVID Pre-Assessment Questionnaire version 3 [48]. A Control group of 21 healthy participants, of whom 15 were women (age in years: mean = 41.67, *SD* = 7.24) and 6 men (age in years: mean = 47.00, *SD* = 4.69) were recruited from social media, interviews on the radio, and local newspapers. The Control group comprised individuals who had no history of SARS-CoV-2 infection or a confirmed or probable case of SARS-CoV-2 infection and had fully recovered (with no symptoms for at least four months prior to assessment, a symptom duration of less than two months from symptom onset or confirmation of infection, and had no new pathology attributed to SARS-CoV-2 infection). The participants of the Long-COVID group and the Control group had similar ages (independent sample two-tailed t-test: p =.839), and the proportion of women and men in each group was similar in the two groups (Fisher's exact test: p =.074).

Table 1
Symptomatology of chronic COVID-19 in the Long-COVID group (n = 66).

Long-COVID group	
Months since infection	***M (Range)***
	14.79 (3–30)
Symptom	***n* (%)**
Anosmia	17 (25 %)
Ageusia	13 (20 %)
Fatigue	62 (94 %)
Breathing difficulties	48 (73 %)
Heart Palpitations	44 (67 %)
Myalgia	55 (84 %)
Sleep disturbances	53 (80 %)
Nightmares	34 (52 %)
Cognitive difficulties	66 (100 %)
Recurrent fevers	17 (25 %)
Joint pain	55 (84 %)
Headache	42 (64 %)
Chest pain	37 (56 %)
Visual disturbance	48 (73 %)
Tinnitus	35 (53 %)
Nausea	18 (27 %)
Rashes	27 (41 %)
Cough	31 (47 %)
Concentration difficulties	65 (98 %)
Mental fog	60 (91 %)

Participants gave written informed consent. The study was conducted following the European Community Council Directive 2001/20/EC and the Declaration of Helsinki for biomedical research involving human subjects. It was approved by the ethics committee of the Universitat Politècnica de València (P04_16_02_2022).

2.2. OLM assessment

2.2.1. iVR application

The assessment of OLM was carried out through an iVR application that immersed the users in a 3D-modeled environment. The iVR application required a VR headset (Fig. 1A) from the Meta Quest 2 (or superior). The iVR application used the touch controllers for interaction (Fig. 1A). The information on the headset's screen was transmitted to a computer or laptop so that the test supervisor could see what the participant was seeing. An internet connection was required between the headset and the computer/laptop. A supported web browser (e.g., Google Chrome) was used for streaming. User navigation through the environment was achieved with the physical displacement of the user through the real environment. Controllers could also be used for this navigation. Therefore, navigation using physical displacement required a room at least the size of the virtual room. In this case, a 4.4 × 7 m testing room was required to perform the OLM task with the iVR application. The iVR environment consisted of an office with a blackboard, desks, chairs, computers, a door, a coat stand, and a wardrobe (Fig. 1B). Nine everyday objects (a hammer, a watch, a toy car, a screwdriver, a pen, a coffee cup, a camera, a comb, and a cutter) were used in the OLM task (Fig. 1C). They appeared on the desks of the virtual office in specific places (Fig. 1D). The iVR application allowed users to interact with these objects; users could touch, pick up, move, and place the objects in any position within the virtual environment. Fig. 1E shows a subject using the iVR application and pointing at one of the objects (a

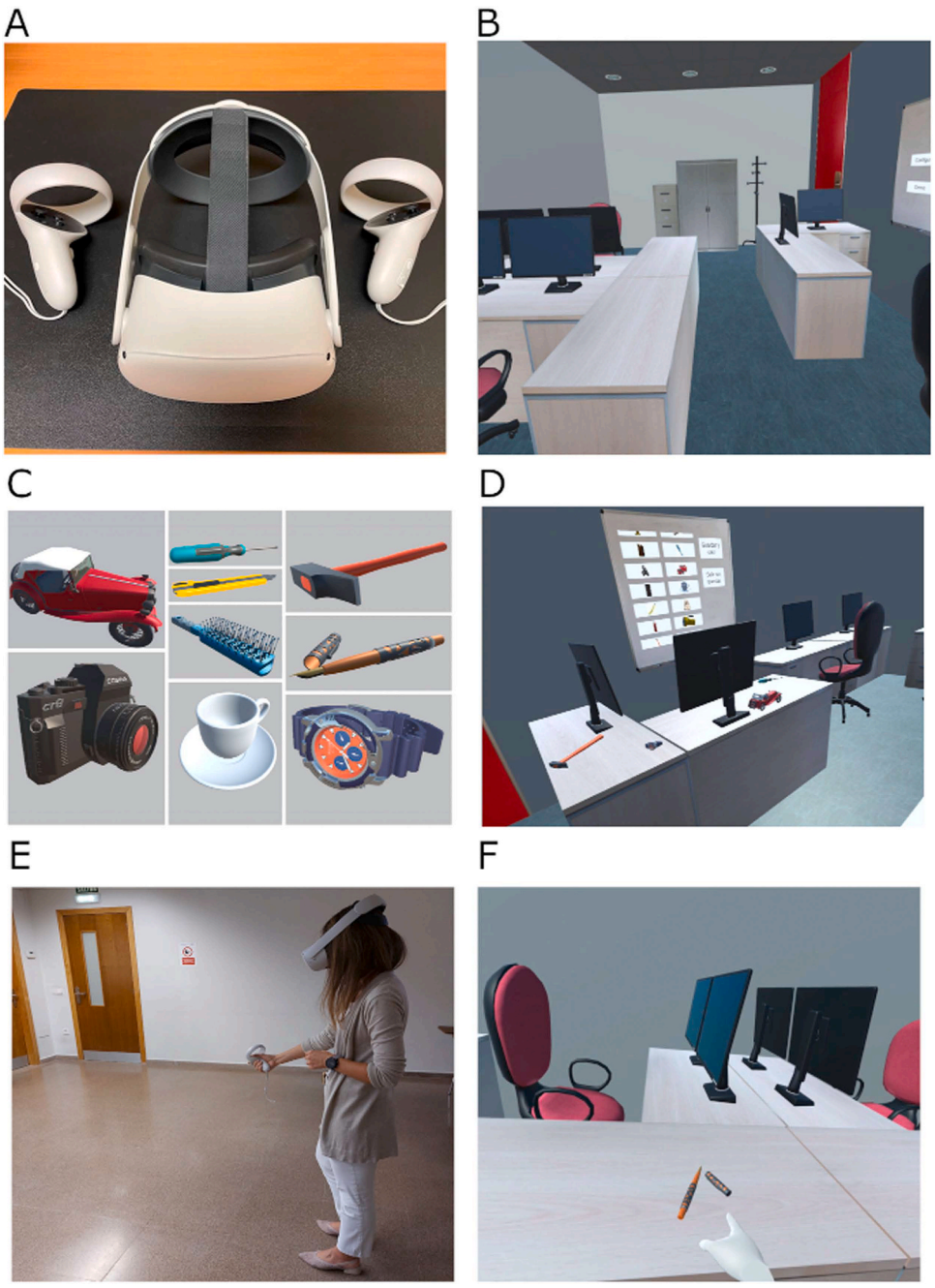

Fig. 1. iVR application. (A) Photo of the Oculus Quest 2 headset and its controllers. (B) Example of view of the iVR environment. (C) Objects used in the OLM task. (D) Example of the view of the environment with objects placed on the desks. (E) A subject using the iVR application and pointing at one of the objects (a pen). (F) User's view shown in E.

pen). Fig. 1F shows her view. Section 2.2.2 OLM task describes the task for assessing the OLM using the iVR application.

2.2.2. *OLM task*

First, the participants completed a habituation trial to become familiar with the iVR application and feel comfortable using it. This trial involved catching an object (a bell) and placing it on one of the desks of the virtual office. Following that, the participants completed the OLM task, which consisted of one learning trial and three trials of OLM recall: immediate recall (Im-R), recall after 20 minutes (20 min-R), and recall after 24 hours (24 h-R).

In the learning trial, nine everyday objects, described above (Fig. 1C), appeared on the desks of the virtual office in specific locations. A supervisor had previously told participants that they had 60 seconds to explore the environment and memorize the objects and their locations. Each participant was required to confirm that they viewed all 9 objects and their locations by touching each object (i.e., when approaching the hand controller toward each object, a green circle bordering the object appeared). All participants started this learning trial from the same position of the virtual environment, and the object locations were the same for all of them.

Immediately after the learning trial, participants carried out the Im-R trial, which assessed their ability to recall the location of the objects learned in the previous trial. The objects were presented one by one, floating in space near the hands and in a randomized order. Participants were asked to place each object in its correct location with no time limit.

To do this, participants used the hand controller to pick up the object and place it in the position they considered to be correct. There was a margin of error of a 50-centimeter radius from the correct point and the point determined by each participant. Participants could make three attempts to place each object in its correct location. Feedback about correct answers consisted of the object covered with a semi-transparent dome and then, the next object appeared. Feedback about incorrect answers was a message displayed indicating the number of remaining attempts. If an object was placed in an incorrect location in the third attempt, the object remained in this position, and then, the next object appeared.

After finishing the Im-R trial, there was a 20-minute time interval during which participants completed other tasks (see Section 2.5). When 20 minutes had elapsed, they completed the 20 min-R trial. On the following day, when 24 hours had elapsed since the performance of the learning trial, participants completed the 24 h-R trial. The three trials of OLM recall (i.e., Im-R, 20 min-R, and 24 h-R) were similar except for the order of presentation of the objects, which was randomized across the trials.

Performance variables with the OLM task were registered for each of the three trials of recall (Im-R, 20 min-R, and 24 h-R) and were: number of correct responses (i.e., the number of objects replaced in their correct location; maximum score was 9), number of attempts (i.e., the number of attempts made; maximum score was 27), and time (i.e., seconds spent in completing each trial).

2.3. Assessment of general cognitive function

General cognitive function was assessed using the Spanish Version 8.1 of the Montreal Cognitive Assessment Scale (MoCA) [49]. This test has a maximum score of 30. Scores below 26 indicate cognitive impairment.

2.4. Assessment of memory span

Verbal and visuospatial spans of memory were assessed. For the assessment of verbal span, verbal short-term memory (VSTM) and verbal working memory (VWM) were measured using the Digits subtest of the Wechsler Adult Intelligence Scale 4th edition (WAIS-IV) [50]. The Digits Forward task of this subtest measures the VSTM and consists of a number recall task that measures rote recall of a sequence of numbers. The Digits Backward task of this subtest measures the VWM and consists of a recall of a sequence of numbers but in reverse order. The memory span assessed with these two tasks was defined by the longest sequence that participants repeated with no errors, and they were allowed two attempts for each length. Maximum score was 9 in the VSTM and was 8 in the VWM.

To measure spatial span, spatial short-term memory (SSTM) and spatial working memory (SWM) were assessed by a computerized version of the Corsi Block Span Test [51,52]. In this task, participants sat in a chair in front of a laptop. Nine black blocks were randomly placed on the screen. In SSTM, a sequence of blocks flashed on the screen; each flash filled a block in yellow with a flashing time of 500 ms and an inter-onset interval of 1000 ms. A sound was emitted with the last block flash, indicating that participants could start clicking the mouse on the blocks in the same serial order. When clicked, the laptop emitted a different sound to confirm that a response was detected. In SWM, participants were required to click the blocks in reverse serial order from the last block that flashed to the first one. Both the SSTM task and the SWM task started from sequences of two blocks (i.e., two items), and if participants reproduced at least one sequence of the same length (two attempts per length) correctly, they proceeded to sequences that were one item longer [51]. The memory span assessed using these two tasks was defined by the longest sequence participants repeated with one or no errors [51]. Both SSTM and SWM have a maximum score of 9.

2.5. Procedure

Once the participants agreed to participate, they received an email containing a link to a sociodemographic survey. Long-COVID individuals also received a link to the Long COVID Pre Assessment Questionnaire version 3 [48]. When participants had completed these instruments, they were scheduled to complete the in-person assessment, which was carried out in the facilities of the University of Oviedo, the University of Zaragoza, and the Polytechnic University of Valencia.

In-person assessment was carried out during two consecutive days. On Day 1, participants completed tasks in the following sequence: habituation trial, learning trial, and Im-R of the OLM task; MoCA; VSTM; VWM; 20 min-R of the OLM task; SSTM; and SWM. On Day 2, participants completed the 24 h-R of the OLM task. Both sessions were held between 09:00 A.M. and 01:00 P.M. or between 04:00 and 08:00 P.M., depending on the availability of each participant. The timing of the task sessions was not controlled. However, the groups were assessed in a pseudo-random distribution across different times of the day to minimize group differences on this variable. In addition, participants were instructed to maintain their regular sleep and wake times and to avoid significant changes in their daily routines to minimize potential disruptions to their circadian rhythms.

2.6. Statistical analyses

Kolmogorov-Smirnov and Levene's tests were conducted with the dataset variables to examine whether their distributions were normal and their variances were homogeneous, respectively. None of the variables of the OLM tasks had a normal distribution. We opted for Mann-Whitney tests to compare the Long-COVID and Control groups in each dependent variable and used the r statistic to calculate the effect size when a test was significant. Also, each performance variable of the OLM task was analyzed separately, using the Friedman test to assess differences among the three trials of OLM recall (i.e., Im-R, 20 min-R, and 24 h-R) within each group, and post-hoc pairwise comparisons were conducted with the Wilcoxon signed-rank test when specific pairs of within-subject variables exhibited differences. Bonferroni correction was applied for each test. Consequently, significant p-values were set at $<.0167$.

Spearman's correlations between measures of performance on the OLM task (number of correct responses, number of attempts, and time) and months after the COVID-19 infection, and scores on MoCA and on memory span tests were calculated separately in the Long-COVID group and the Control group. Months since the COVID-19 infection were not considered in correlations computed in the Control group. FDR correction was applied for each of the correlations computed within each group [53] (Long-COVID group: $q < .005$, and Control group $q < .003$). Cohen's [54] guidelines were used to interpret the strength of the correlations.

The level of significance was $p < .05$ in all the uncorrected tests. Statistical analyses were carried out using SPSS 25.0.

Regarding missing data, one participant of the Long-COVID group could not attend the second session of the study, so no data were available for the variables collected in that session for this participant. These missing data were coded as empty cells within the database.

3. Results

3.1. OLM performance

3.1.1. Differences between groups in OLM performance

Table 2 shows the number of correct responses, number of attempts, and time in seconds recorded for each trial in the OLM tasks for the Long-COVID and Control groups. The participants in the Long-COVID group achieved fewer correct responses than their counterparts in the Control group in all the trials (Fig. 2A): Im-R ($U = 475.500$, $z = -2.248$,

Table 2
Means ± standard deviations of the number of correct responses, number of attempts, and time in seconds recorded for each trial in the OLM task.

	Long-COVID group (n = 66)	Control group (n = 21)
Number of correct responses		
Im-R	7.33 ± 1.74	8.10 ± 1.61
20 min-R	6.67 ± 2.09	7.81 ± 1.50
24 h-R	6.32 ± 2.06	8.00 ± 1.52
Number of attempts		
Im-R	14.32 ± 3.80	12.95 ± 3.60
20 min-R	15.68 ± 4.21	13.04 ± 3.57
24 h-R	16.34 ± 3.88	12.52 ± 3.14
Time		
Im-R	128.42±69.05	77.08±29.04
20 min-R	139.08±82.23	74.19±30.96
24 h-R	136.43±69.10	96.06±45.56

Note. Im-R = Immediate recall; 20 min-R = 20-minute recall; 24 h-R = 24-hour recall.

p =.025, r = −.241), 20 min-R (U = 463.000, z = −2.332, p =.020, r = −.250), and 24 h-R (U = 339.500, z = −3.503, p <.001, r = −.378). Also, participants in the Long-COVID group needed more attempts to complete the OLM task than those of the Control group in the two trials with delayed recall (Fig. 2B): 20 min-R (U = 438,000, z = −2.539, p =.011, r = −.272), and 24 h-R (U = 287.500, z = −3.985, p <.001, r = −.430). However, the participants in both groups made a similar number of attempts in the immediate recall (Im-R: U = 526.000, z = −1.665, p =.096). In addition, individuals of the Long-COVID group spent more time completing the task than those of the Control group in all the trials (Fig. 2C): Im-R (U = 387.000, z = −3.035, p =.002, r = −.325), 20 min-R (U = 278.000, z = −4.116, p <.001, r = −.441), and 24 h-R (U = 240.000, z = −4.448, p <.001, r = −.480).

3.1.2. OLM recall within the long-COVID group

The number of correct responses performed by the participants of the Long-COVID group changed significantly across the three trials [χ^2(2) = 20.270, p <.001; Fig. 2A]. Post-hoc comparisons revealed that the number of correctly placed objects was higher in the trial of immediate recall than in the two trials with temporal delays: 20 min-R (z = −3.259, p =.001, r = −.401) and the 24 h-R (z = −3.827, p <.001, r = −.471). Also, these participants' number of attempts differed across the three trials [χ^2 (2) = 19.840, p <.001; Fig. 2B], as they needed fewer attempts to complete the task in the trial of Im-R than in the two trials with temporal delays (20 min-R: z = −3.619, p <.001, r = −.445; and 24 h-R: z = −3.951, p <.001, r = −.490). The participants' performance did not differ between 20 min-R and 24 h-R trials for the number of correct responses and attempts made (z = −1.397, p =.163, r = −.017; and z = −.898, p =.369, r = −.111, respectively). Moreover, individuals in the Long-COVID group took a similar time completing the three recall trials [χ^2 (2) = 4.092, p =.129; Fig. 2C].

3.1.3. OLM recall within the control group

The number of both correct responses and attempts performed by the participants of the Control group did not differ among the trials [correct responses: χ^2(2) = 3.897, p =.142; and attempts: χ^2(2) =.478, p =.788; see Fig. 2A and B, respectively]. However, the time spent by these participants to complete the trials differed among them [χ^2(2) = 9.524, p =.009; Fig. 2C]. Post-hoc comparisons revealed that these participants took a longer time to complete Im-R than 20 min-R (z = −2.485, p =.013, r = −.542), but they took a similar time to complete Im-R and 24 h-R (z = −2.138, p =.033) or 20 min-R and 24 h-R (z = −1.303, p =.192).

3.2. General cognitive performance

Table 3 shows means and standard deviations of the scores obtained by the participants of the Long-COVID and the Control group. The groups' scores in MoCA differed because the participants of the Long-COVID obtained lower scores (U = 321.500, z = −3.721, p <.001, r = −.399).

Table 3
Means ± standard deviations of scores on MoCA and memory span tests.

	Long-COVID group (n = 66)	Control group (n = 21)	U (p-value)
MoCA	26.00 ± 2.42	28.10 ± 1.41	-321.500 (<.001)
VSTM	5.58 ± 1.12	6.10 ± 1.34	566.000 (.191)
VWM	4.50 ± 1.06	5.29 ± 1.15	430.500 (.007)
SSTM	5.21 ± 1.07	5.81 ± 1.12	486.500 (.030)
SWM	4.52 ± 1.27	4.90 ± 1.14	580.000 (.245)

Note. MoCA: Montreal Cognitive Assessment scale; VSTM: Verbal short-term memory; VWM: Verbal working memory; SSTM: Spatial short-term memory; SWM: Spatial working memory. U = Mann-Whitney U test statistic.

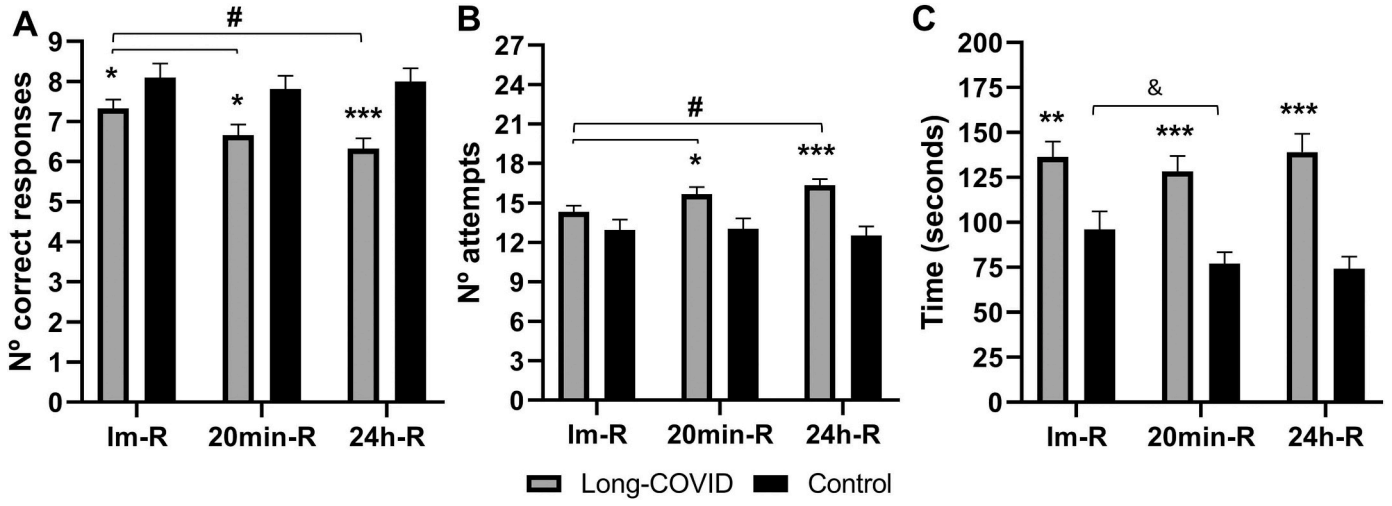

Fig. 2. Performance in the iVR-based OLM task. (A) Number of correct responses, (B) number of attempts, and (C) time in seconds registered in each of the trials (immediate recall: Im-R; 20-minute recall: 20 min-R; and 24-hour recall: 24 h-R) and for the two groups (Long-COVID group and Control group). Depicted values are means, and error bars represent the SEM. Significant differences between the two groups: * p <.05, ** p <.01, and *** p <.001. Significant differences between trials within each group (Bonferroni adjusted p-values <.0167): # p ≤.001 and $^{\&}$ p =.013.

3.3. Performance in VSTM, VWM, SSTM, and SWM

Regarding verbal spans, the participants of the two groups showed similar scores in the VSTM (U = 566.000, z = −1.308, p =.191) but different scores in the VWM (U = 430.500, z = −3.710, p =.007, r = −.398) because participants of the Long-COVID group retained a shorter sequence in the backward version of the task (Table 3). Concerning spatial spans, the participants of the Long-COVID group performed worse in the SSTM than those of the Control group (U = 486.500, z = −2.175, p =.030, r = −.233; Table 3), but both groups showed similar SWM scores (U = 580.000, z = −1.163, p =.245).

3.4. Relationships between performance on the OLM task and months since the COVID-19 infection, and scores on MoCA and memory span tests

Spearman correlation coefficients (r_s) and p-values (p) are shown in Table 4 for the Long-COVID and the Control group. For the sake of brevity, this section only reports correlations between variables that achieved a significance level below.05, as determined by the p-value.

In the Long-COVID group, the number of months since infection with COVID-19 was negatively associated with the number of correct responses made by the participants in both the immediate and the 24-hour delayed trials of the OLM task (r_s = −.261, p =.034; and r_s = −.292, p =.018, respectively), and was positively associated with the number of attempts they made in the 24-hour delayed trial (r_s =.256, p =.040). Also, their score on MoCA was negatively associated with the number of correct responses they made in the immediate trial of the OLM task and the time they took to complete the OLM task with a delay of 20 minutes (r_s = −.281, p =.022; and r_s = −.257, p =.037, respectively). However, the strength of the association between all of these variables was small, and the level of significance did not exceed the FDR correction (q <.005). The Long-COVID participants' MoCA scores were negatively associated with the time they took to complete the OLM task in the immediate recall trial. The strength of the association between these two variables was medium, reaching a significant level after applying the FDR correction (r_s = −.355, p =.003).

In the Control group, the longer the participants' memory span was in the short-term retrieval of verbal information, the fewer attempts they made in the immediate trial of the OLM task (r_s = −.606, p =.004). Also, the longer these participants' memory span was in the short-term retrieval of spatial information, the more time they needed to complete the 24-hour delayed trial of the OLM task (r_s =.468, p =.033). However, these two associations did not reach significance after the FDR adjustment (q <.003).

4. Discussion

This study assessed OLM in Long-COVID patients and healthy controls using an iVR-based OLM task and explored the association between OLM performance and general cognitive function, and both verbal and visuospatial span. Given the small sample size obtained for the control group and the predominance of women in the entire sample, we posit

Table 4
Spearman's correlations.

		Months	MoCA	VSTM	VWM	SSTM	SWM
Long-COVID group							
Correct resp._Im-R	r_s	-.261*	-.281*	.081	.122	.040	.157
	p	.034	.022	.518	.329	.748	.208
Attempts_Im-R	r_s	.234	-.235	-.069	-.165	.069	-.091
	p	.059	.058	.581	.187	.580	.468
Time_Im-R	r_s	.102	**-.355***	.190	-.235	-.220	-.156
	p	.416	.003	.127	.058	.076	.211
Correct resp._20min-R	r_s	-.078	.067	.049	.068	.027	.019
	p	.531	.593	.696	.588	.827	.879
Attempts_20min-R	r_s	.146	-.177	-.090	-.185	-.092	-.087
	p	.243	.156	.472	.136	.464	.488
Time_20min-R	r_s	.137	-.257*	-.160	-.156	-.216	-.169
	p	.274	.037	.199	.210	.081	.175
Correct resp._24h-R	r_s	-.292*	.003	.099	.140	-.031	.072
	p	.018	.978	.431	.266	.806	.566
Attempts_24h-R	r_s	.256*	-.006	-.069	-.071	-.041	-.167
	p	.040	.963	.583	.575	.748	.184
Time_24h-R	r_s	.117	-.107	-.123	-.081	-.134	-.206
	p	.352	.398	.330	.522	.287	.100
Control group							
Correct resp._Im-R	r_s		-.041	.355	.223	.137	-.078
	p		.862	.114	.331	.555	.737
Attempts_Im-R	r_s		-.025	-.606*	-.388	-.202	-.182
	p		.916	.004	.082	.381	.431
Time_Im-R	r_s		.115	-.324	-.415	-.569	.077
	p		.618	.152	.061	.007	.741
Correct resp._20min-R	r_s		.250	.364	.064	.075	-.057
	p		.275	.105	.782	.747	.805
Attempts_20min-R	r_s		-.249	-.418	-.209	-.121	-.160
	p		.276	.059	.363	.603	.488
Time_20min-R	r_s		.093	.003	-.093	.036	.174
	p		.687	.988	.690	.878	.450
Correct resp._24h-R	r_s		.133	.277	-.066	-.068	-.178
	p		.625	.225	.776	.769	.439
Attempts_24h-R	r_s		-.041	-.243	.075	.225	.078
	p		.861	.288	.746	.326	.736
Time_24h-R	r_s		.313	.054	.204	.468*	.272
	p		.166	.816	.375	.033	.233

Note. * p <.05; bold type shows significant r_s -value after FDR adjustment (q <.005) in Time_Im-R vs. MoCA within the Long-COVID group; Months: Months since infection of COVID-19; MoCA: Montreal Cognitive Assessment scale; VSTM: Verbal short-term memory; VWM: Verbal working memory; SSTM: Spatial short-term memory; SWM: Spatial working memory; resp = response.

that this study represents a preliminary exploration, and it is imperative to consider these factors moving forward to improve interpretation and facilitate generalization.

Participants of the Long-COVID group made fewer correct responses and invested more time in the immediate trial than those of the Control group. However, the Long-COVID participants showed more severe impairment in delayed memory than in immediate memory. Overall, the Long-COVID group, compared to the Control group, showed greater differences in short-term (20 min-R) and long-term (24 h-R) recall of object locations. The patients made fewer correct responses, made more attempts, and spent more time on the delayed trials than the healthy persons. The Long-COVID group's better MoCA scores were strongly associated with shorter times to complete the immediate recall. Additionally, there were other associations that did not surpass FDR correction and should be interpreted with caution. These included the associations between MoCA scores and recall performance, as well as between the time since the COVID-19 infection and recall accuracy.

In long-COVID syndrome, the visuospatial component of memory has been studied less than the verbal component [21]. To our knowledge, this is the first study to objectively report OLM deficits in Long-COVID patients, assessing immediate and long-term memory for spatial locations using an iVR-based OLM task. Notably, no symptoms related to VR-induced motion sickness have been reported among any of the evaluated participants, confirming that this technology is well-tolerated [55]. We hypothesized that Long-COVID patients would present worse performance in the iVR-based OLM task than healthy individuals because the Long-COVID syndrome has shown deficits in OLM through subjective assessment of memory by questionnaires [44], and some standardized memory tests have shown impaired long-term retention of visual items in this population [21]. Our results corroborate this hypothesis, as Long-COVID individuals not only showed worse general performance in OLM, but also long-term retention of spatial locations was more altered than immediate retention. The Long-COVID group showed impaired short-term (20 min-R) and long-term (24 h-R) recall of object locations. This was demonstrated by their inferior performance across all variables in these delayed trials compared to the control group, suggesting an impairmet of consolidation processes in memory formation. Considering that the completion time did not differ between the trials in the Long-COVID group, we exclude fatigue or decreasing interest as an explanatory factor for this worse performance. During immediate recall, participants can rely on short-term memory mechanisms and rehearsal strategies to retain information, resulting in relatively better performance. However, in delayed recall tasks, participants must rely on long-term memory storage and retrieval processes, which may be impaired in individuals with Long-COVID due to temporal lobe dysfunction [32]. Previous studies have already shown long-term deficits in the consolidation of procedural, verbal, and episodic memories in the Long-COVID syndrome [20,22,56,57]. The brain network that supports spatial memory retrieval is the medial temporal lobe, and the hippocampus is the main actor of this memory process [58,59]. There is evidence of brain-related abnormalities in COVID-19 that points to this region. A review of studies concluded that alterations in the hippocampus were detected in the acute stage and after several months of infection [32]. Several clinical studies revealed alterations in hippocampal connectivity and metabolism [32]. When assessing neuropsychological sequelae, most of the studies reported memory alterations that correlated with altered function of the hippocampus or changes in grey matter volumes of the medial temporal lobe [32]. Besides, post-mortem and preclinical studies on this topic observed alterations in hippocampal neurogenesis and dendrites, as well as neuroinflammation [32].

Long-COVID participants obtained lower scores than controls in MoCA, including a screening assessment of visuospatial abilities, orientation, short-term memory and working memory. However, Long-COVID participants' scores were considered indicative of normal cognitive performance, as these scores were at the suggested cut-off of 26 points. We observed no differences between Long-COVID participants and controls in the VSTM. However, Long-COVID participants failed to retain longer sequences in the backward version of the Digits task, indicating, in accordance with previous studies [27], alteration of VWM in this population, with preserved VSTM. The deficits observed are primarily in executive functions, involving the manipulation of verbal information that requires attentional and inhibitory processes. These cognitive processes are closely related to the robust engagement of the dorsolateral prefrontal cortex and ventral stream [60], brain regions known to be affected by the neurobiological sequelae of COVID-19 [32,61]. Regarding the spatial spans, the Long-COVID group presented a worse forward spatial span than controls but similar backward spatial span. The forward condition of the spatial span task involves maintaining and reproducing spatial information in the exact order it was presented, primarily relying on the dorsal stream, including the posterior parietal cortex and the temporo-parietal junction [62]. A study that assessed SSTM with the Corsi Block Span Test in this population also observed that SSTM alterations were at least two times more frequent than expected in a healthy population [63]. However, the follow-up of COVID-19 patients who did not all meet the diagnostic criteria for Long-COVID revealed that their performance was similar to age-matched controls in a computerized version of the same test [28,64]. This indicates that SSTM could be affected in those individuals who clearly fulfill the diagnostic criteria of Long-COVID. In this sense, cortical thickness changes have been described in Long-COVID individuals with cognitive impairment in the parahippocampal and parietal areas, which could potentially explain altered dorsal stream function [65]. However, more research is needed to understand the nature of cognitive difficulties in Long-COVID in relation to the ability to process verbal and spatial information.

When comparing the raw scores of Long-COVID patients and controls on the verbal and spatial span tasks, an unexpected result is that patients performed worse on the VWM task, but not on the SWM task. They also performed worse than controls on the SSTM task, but not on the SWM task. However, these results are not unusual, as research with individuals with neurological disorders has shown that they obtain lower raw scores on the SSTM task than on the VSTM task [66]. Similarly, raw scores on the SSTM task were lower than on the SWM for one-third of the sample analyzed, with no differences for the remainder. When the mean age normative score was considered, patients also scored lower on the SSTM than on the SWM. Therefore, it cannot be established that there is equivalence between the verbal and spatial versions of the span tasks, nor can it be assumed that the effort and difficulty of the spatial span task is greater in the SWM task than in the SSTM task [66]. In addition, the SSTM task is more complex than the VSTM task in terms of the strategy for performing the span tasks, as it requires the use of a combination of strategies [67]. Long-term COVID patients may show a delay in adopting the most effective strategies for performing the SSTM task, and differences between patients and controls on the SWM task may have been reduced due to prior experience with the SSTM task.

Considering the associations found between iVR-based OLM task performance and the previously mentioned verbal and spatial memory spans and overall cognitive functioning, OLM was associated with MoCA scores in the Long-COVID group but not in healthy participants. Better MoCA scores were associated with shorter times to complete immediate OLM recall in the Long-COVID group. A slight association between MoCA and OLM completion-time was also observed for the 20-minute delayed recall, although this association did not reach significance after the FDR adjustment. Declarative memory assessed by Paired-Associate Learning correlated with MoCA scores in Long-COVD [20]. However, most of the studies of Long-COVID evaluated global cognitive function with screening tests rather than specific cognitive domains [68]. Therefore, it is difficult to find results about associations between memory-specific neuropsychological assessments and global cognition in this population. The difficulties shown by the Long-COVID group during immediate and short-term OLM retrieval could be reflected in

this global cognition index, as MoCA includes a brief test of immediate and short-term verbal memories [49]. Therefore, associations between MoCA scores and OLM performance in Long-COVID participants are unsurprising. However, the slight relationship between the MoCA score and the number of correct responses during the immediate recall trial in the Long-COVID group is striking. In this group, the analysis of the associations between these two variables suggested that the fewer correct responses during immediate recall, the better the MoCA score. However, this correlation did not meet the threshold for FDR and it should be interpreted with caution. One explanation is that population with lower MoCA scores, who encounter more challenges with daily cognitive tasks, may rely more on compensatory mechanisms compared to individuals with higher MoCA scores (and greater confidence in their cognitive abilities). Qualitative observations revealed that Long-COVID participants experiencing more pronounced cognitive difficulties often participated in neuropsychological rehabilitation programs, which provide instruction on memory tasks strategies; thus, they might be more accustomed to memory challenges due to their previous experience. These compensatory strategies could be more effective during encoding and immediate retrieval tasks, where long-term retention and retrieval are not critical. Regrettably, we did not collect data on our participants' involvement in rehabilitation programs. Further investigation in this area is needed.

Neither SSTM assessed by a computerized version of the Corsi Block Span Test nor VSTM assessed by a subtest of verbal memory span were related to the Long-COVID group's iVR-based OLM task performance. In healthy participants, a slight negative association was observed between VSTM and the number of attemps in the immediate recall of the OLM task. However, it is important to note that this association did not meet the threshold for FDR correction. Therefore, while the association is present, it should be interpreted with caution due to the lack of statistical significance after accounting for multiple comparisons. Verbal-based strategies might support the encoding of OLM. In this sense, the association between objects and spatial locations was shown to be influenced by verbal skills [69]. At the same time, spatial span was also slighly relevant for long-term retention of OLM in healthy individuals, as the better their direct spatial span, the more time they took to complete the 24-hour delayed-recall trial. This correlation did not meet the threshold for FDR and there was no correlation between SSTM performance and either the number of correct responses or the number of attempts. However, the ability to retain short-term spatial information on standardized tests has been related to greater accuracy in assigning the spatial location of objects (more precise responses) in children performing an OLM task using augmented reality [29]. Similarly, the ability to hold in mind a relatively larger number of visuospatial items in the extrapersonal space is related to the ability for simultaneous retention of spatial items in the peripersonal space [70]. The test used to assess SSTM presented blocks on an a 2D screen as stimuli and required participants to remember their positions in a correct sequence. In contrast, the OLM task did not require a specific sequence for object placement, allowing for random placement without following a learned sequence. However, it is possible that individuals who excel at remembering spatial locations based on a sequence may use this strategy during the 24-hour delayed-recall trial in the OLM task. This could result in slower performance on this trial. However, we did not collect data on the strategies employed by the participants. Therefore, further investigation is required to explore this relationship.

The months elapsed since the COVID-19 infection were slightly associated with more errors in the immediate trial, as well as more errors and attempts in the 24-hour delayed trial of the iVR-based OLM task. Nevertheless, it is crucial to emphasize that these associations did not meet the threshold for FDR correction, suggesting a trend that warrants cautious interpretation. This slight association could indicate that the chronicity of the syndrome is related to OLM performance and associated with poor consolidation of spatial memories. Neuropsychological alterations in Long-Covid must be studied longitudinalally to determine the progression of memory alterations. One study, which included a small sample of COVID-19-infected subjects and used a cross-sectional approach, revealed that the alterations in visuospatial ability and immediate verbal recall improved over time [71]. However, hypermetabolism in the hippocampus persisted over time and correlated with inflammation status [71]. Specifically, when exploring the association between the time elapsed since COVID-19 infection to neuropsychological assessment in patients who met the diagnostic criteria for Long-COVID, results showed that the more months elapsed, the worse the long-term declarative memory in these patients [29], indicating that hippocampal-dependent cognitive processed worsened over time.

The sample consists mainly of women, which is expected given the current scientific evidence that adult women are predominantly affected by Long-COVID [72]. In international studies assessing large numbers of participants who reported experiencing prolonged symptoms of Long-COVID in online surveys, women represent 80 % of the sample [73,74]. Research suggests that there is a high prevalence of neuropsychological symptoms of Long-COVID in females [75]. Vasilevskaya et al. [76] reported that women are more susceptible to persistent short-term memory symptoms and executive dysfunction. Furthermore, Curtis et al. [77] found that the relationship between anxiety and cognitive outcomes was influenced by gender. Women who reported higher levels of anxiety related to COVID-19 exhibited more memory failures on subjective measures and poorer processing speed on an objective cognitive task compared to men [77]. Therefore, it would be appropriate to compare the impact of sex on performance in the OLM task in a larger, gender-balanced sample.

The strengths of this study are summarized in the following lines. The iVR-task used in this study was designed to improve OLM assessment. While iVR technology is readily available, most neuropsychological assessments of OLM use elements of standard 2D paradigms [78,79] or self-report questionnaires that assess different forms of memory failures, including OLM [80,81]. Standard neuropsychological assessments typically do not evaluate retention periods of more than 20–30 minutes [82]. However, evaluating more enduring forms of memory is clinically important for understanding memory disorders [83]. Our study shows that patients with Long-COVID have OLM deficits as objectively assessed by iVR tasks at immediate, 20-minute and 1-day retention intervals, overcoming previous limitations in this area.

However, this study presents some limitations. Firstly, the recruitment process relied on voluntary participation, resulting in a smaller sample size for the control group compared to the clinical group. Despite efforts to increase the number of control group participants, challenges arose due to the need for in-person assessments over two consecutive days. The requirement to travel to laboratory facilities demanded significant time and effort from participants, which could potentially discourage individuals from volunteering for the control group. Additionally, subjects with severe Long-COVID symptoms may be less prone to accept enrolment in the study, and our sample was mainly composed of moderately or slightly affected subjects. All participants reported cognitive difficulties, which is higher than the 70 % reported in previous studies [33]. This raises questions about the representativeness of our sample. It is possible that individuals with cognitive deficits may have been more motivated to participate in a study focusing on cognitive impairment, leading to an overrepresentation of female subjects with cognitive difficulties in our sample. This means that our findings cannot be completely extrapolated to the total population with this syndrome. Secondly, we ignored participant's pre-COVID cognition, so we cannot draw final conclusions about a causal relationship between COVID infection and long-term OLM alterations. Thirdly, attention and other forms of executive functions, apart from working memory, were not directly evaluated. These neuropsychological functions were also affected in Long-COVID patients [57], and they are also significant processes that could affect OLM performance. Finally, the study protocol involves administering the MoCA, VSTM, and VWM after the Im-R of the OLM task and before the 20 min-R. Both the control and Long-COVID

groups underwent the same protocol to ensure that there was no differential influence on the subsequent 20-minute recall trial. However, to accurately measure the effect size of memory impairment in Long-COVID patients, it would have been better not to administer these tests after the Im-R.

In conclusion, these findings suggest that our iVR task, designed to evaluate OLM, extends, corroborates previous findings of memory alterations in the Long-COVID syndrome and also adds new evidence to the limited literature on spatial memory and long-term memory in this population. Implementing spatial iVR tasks to clinical research may improve our understanding of neuropsychological disorders.

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CRediT authorship contribution statement

Tania Llana: Writing – original draft, Investigation. **Marta Mendez:** Writing – original draft, Supervision, Conceptualization. **Magdalena Mendez-Lopez:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **M.-Carmen Juan:** Visualization, Software, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Sara Garces-Arilla:** Visualization, Investigation, Formal analysis.

Declaration of Competing Interest

None

Data availability

Data will be made available on request.

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