

Rapid vigilance and episodic memory decrements in COVID-19 survivors

Sijia Zhao¹, Kengo Shibata², Peter J. Hellyer^{3,4}, William Trender³, Sanjay Manohar^{1,2},
Adam Hampshire³, Masud Husain^{1,2}

¹ Department of Experimental Psychology, University of Oxford, Oxford OX1 3PH

² Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford OX3 9DU

³ Department of Brain Sciences, Imperial College London, 926, Sir Michael Uren Hub, 86 Wood Lane, London, W12 0BZ

⁴ Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

Corresponding Author:

Sijia Zhao

sijia.zhao@psy.ox.ac.uk

Department of Experimental Psychology, University of Oxford, Oxford OX1 3PH

Number of figures: 3

Number of tables: 2

Number of references: 43

Number of words: 6636

Abstract

Recent studies indicate that COVID-19 infection can lead to serious neurological consequences in a small percentage of individuals. However, in the months following acute illness, many more suffer from fatigue, low motivation, disturbed mood, poor sleep and cognitive symptoms, colloquially referred to as 'brain fog'. But what about individuals who do not report any ongoing symptoms after recovering from COVID-19? Here we examined a wide range of cognitive functions critical for daily life (including sustained attention, memory, motor control, planning, semantic reasoning, mental rotation and spatial-visual attention) in people who had previously suffered from COVID-19 but were not significantly different from a control group on self-reported fatigue, forgetfulness, sleep abnormality, motivation, depression, anxiety and personality profile. COVID-19 survivors displayed significantly worse episodic memory (up to 6 months post infection) and greater decline in vigilance and motivation with time on task (for up to 9 months). Overall, the results show that chronic cognitive impairments following COVID-19 are evident on objective testing even amongst those who do not report a greater symptom burden. Importantly, in the sample tested here, these were not significantly different from normal after six-nine months, demonstrating evidence of recovery over time.

Keywords: COVID-19; post-COVID-19; long-COVID; cognitive deficits; sustained attention; memory

Abbreviations: COVID-19 = Coronavirus disease 2019 caused by the Coronavirus SARS-CoV-2

Introduction

People who survive COVID-19 infection present a significantly higher risk of major neurological and psychiatric conditions, particularly if they were hospitalised.¹⁻³ These include acute cerebrovascular events such as ischaemic stroke and intracerebral haemorrhage.⁴ In addition to severe neurological conditions, there can also be more chronic, longer-term consequences such as fatigue, low motivation, disturbed mood and poor sleep—all commonly reported symptoms amongst survivors, the so-called ‘long-COVID’ (see recent review⁵).

While many studies employ questionnaires reliant on patients’ subjective self-reports, recent investigations have begun to document a wide range of post-COVID-19 cognitive deficits using objective cognitive testing of inpatients. Particular impairments were found in *attention*⁶⁻¹², *memory*^{6-8,10-13} and *executive functions*.^{10-12,14-16} More recently, using ¹⁸F-FDG PET, it has been demonstrated that in the most severely affected patients, the degree of cognitive impairment was accompanied by frontoparietal hypometabolism.^{10,11}

Understandably, most of these small-scale reports have, to date, predominantly focused on symptomatic, hospitalised patients (however see¹⁷). But what about individuals who have not been hospitalised and do not report any ongoing symptoms after recovery? Do they suffer cognitive deficits that they are not aware of? Here, we examined people who had previously contracted COVID-19 but were not significantly different from a control group with respect to self-reported fatigue, forgetfulness, sleep abnormality, motivation, depression, anxiety or personality profile. In total, 135 participants were tested on a series of twelve on-line cognitive tasks encompassing a wide range of cognitive functions critical for daily life, including the ability to sustain attention, memory, motor control, speed of response, planning, semantic reasoning, mental rotation, and spatial-visual attention. In all of these functions, COVID-19 survivors showed the same initial baseline performance. However, after only two minutes on an attentionally demanding task, there was a significantly larger decline in perceptual sensitivity, despite reporting the same levels of fatigue compared to healthy controls. Subsequent testing also revealed a significantly larger episodic memory decrement. These results demonstrated that chronic cognitive impairments following COVID-19 are evident upon objective testing even in people who do not report long-COVID symptoms.

Materials and methods

Participants

135 participants (49 females, mean age 26.2 years (SD 8.0)) were recruited from the Prolific online recruitment platform (www.prolific.co, see **Table 1** for demographics). All participants were naïve about the aim of this study; the study was advertised as “a brain game” testing how well people could perform.

62 people had contracted COVID-19, while 73 reported that they had not. Of the COVID group, the majority of respondents had tested positive with a PCR test and did not require hospitalisation. None received treatment in an intensive care unit, suggesting that participants likely did not experience severe acute illness. However, three participants did have an overnight hospital stay. The average time from COVID-19 diagnosis was 167.3 days (SD: 127.9). None of the participants were seeking post-COVID care at the time these studies were conducted.

There was no significant group difference in gender ($\chi^2(1, N=135)=0.8, p=0.4$) or age ($t(133)=2.0, p=0.05$), but participants in the COVID group tended to be more elderly; thus to control for the effect of age, the analyses below include age as a random effect or use a partial correlation controlling age, where applicable.

All participants were required to complete the experiments on the Chrome browser on a desktop with a keyboard and mouse.

To compare the episodic memory deficit observed in the COVID group (see below), we ran the same memory test on healthy elderly people (>50 years old). 64 participants, who reported no neurological conditions, were recruited. All participants provided written informed consent and the study was approved by the University of Oxford ethics committee. Participants were initially contacted by email, followed up by calls and completed the task on their own computer devices. 53 participants completed the task and one participant was excluded due to COVID-19 history. The results of 52 participants (30 females, mean age 67.4 years (SD 7.2)) are reported below.

Questionnaires

The questionnaires included were:

- **Fatigue and sleep:** Neurological Fatigue Index (NFI), which has been used to assess fatigue in persons with multiple sclerosis.¹⁸ Our motivation for including this index was driven by the fact that it probes the interactions between sleep and fatigue. Specifically, it asks questions related to abnormal nocturnal sleep, sleepiness, and the need for diurnal sleep/rest.
- **Distractibility and forgetfulness:** Cognitive Failures Questionnaire (CFQ)¹⁹, a 25-item questionnaire about minor mistakes in daily life over the last two weeks. E.g.: “Do you find you forget appointments?” “Do you fail to notice signposts on the road?” “Do you find you forget which way to turn on a road you know well but rarely use?”
- **Personality:** A short 15-item Big Five Inventory (BFI-S)²⁰ and the Short Grit Scale (GRIT-S)²¹. One of BFI-S components—conscientiousness—provides information about the conscientiousness personality trait, describing an individual’s perseverance of effort combined with passions for a particular goal. To ensure that this is well-captured, we also included GRIT-S: this estimates the same trait but with different questions. We indeed found that these two scales were strongly positively correlated (Spearman’s rho = 0.65, $p<0.0001$).
- **Motivation:** Apathy Motivation Index (AMI), an 18-item questionnaire, sub-divided into three subscales of apathy: emotional, behavioural and social apathy.²²

- **Mood:** Hospital Anxiety and Depression Scale (HADS), a 14-item questionnaire, subdivided into depression and anxiety.²³

All 135 participants completed the NFI questionnaire, of which 105 also completed the CFQ. 95 of these 105 participants completed the full set of questionnaires which were NFI, CFQ, BFI-S, GRIT-S, AMI, and HADS.

Vigilance test

All participants were first tested on a version of an established, sustained visual attention task²⁴ adapted into a modern online version hosted on the Pavlovia platform (pavlovia.org). An online demo is available at https://run.pavlovia.org/sijiazhao/vigilance_english_demo (please open it with the Chrome internet browser on a desktop computer). This task is designed to assess the performance decrement during sustained visual attention. A single digit (0-9) was presented at the centre of the screen for 50ms every second (**Fig 1 Vigilance**). Participants were instructed to press the spacebar on their keyboard as soon as they saw “0” (the target, presented randomly with a probability of 25%); no response was required for other digits. A semi-transparent jittered checkerboard pattern masked the digits, with the level of difficulty manipulated by adjusting the opacity of the mask. Pilot testing allowed us to obtain an accuracy level of ~80% in the first minute of the experiment. The practice phase consisted of 90 trials, equivalent to 90 seconds. The difficulty was gradually increased and feedback was provided after each trial. The first 12 practice trials were highly visible stimuli and participants were required to get 100% accuracy to proceed. Subsequent non-practice trials and blocks contained no feedback. In total, each participant completed 540 trials, divided into 9 blocks, each containing 60 trials and lasting one minute.

The experiment was implemented using PsychoPy v2021.1.2.²⁵ To minimise the variance in latency caused by different browsers, all participants were required to use the Chrome browser on a desktop computer, although the operating system was not restricted. To minimise potential instability, the use of custom-written code was deliberately avoided and all functions used were as provided by PsychoPy. Only the questionnaires were implemented using in-house code.

Motivation and fatigue ratings with time on the task. After each minute during testing, participants were asked to report their level of fatigue (“How tired do you feel now?”) and motivation (“How motivated do you feel?”) using a visual analogue scale. Responses were registered by clicking on the appropriate position on each scale. After completing all ratings, a “confirm” button appeared at the bottom of the screen, allowing participants to validate their ratings and start the next block. To control the time between blocks and to reduce variance between participants, a 15-second countdown timer was displayed at the top of the screen, and the next block would begin automatically once the timer lapsed. There were six participants who had missing ratings. The exclusion of these participants did not affect the rating results or behavioural data, and there were no group differences in age, gender or any questionnaire measures ($p>0.05$).

Statistical analysis

Measuring of vigilance decrement: The accuracy of each minute was measured as an F1 score, the harmonic mean of precision and sensitivity, given by

$$F1 = \frac{2 \times TP}{2 \times TP + FP + FN}$$

where TP is the true positive rate, FP is the false positive rate, and FN is the false negative rate. F1 score is a particularly suitable accuracy measure for this task because it emphasises true positives (responses to the rare target) and disregards true negatives (non-responses to non-targets). For RT, only trials with correct responses were considered. In each block, trials with outliers (two standard deviations away from mean) were excluded, representing 3.7% of trials overall.

To investigate the effect of group and time on minute-wise performance and the three ratings, all the values were z-scored across participants and mixed-effects generalised linear models (GLM) were conducted using the MATLAB function *fitglme* with Laplace approximation as the method for estimating model parameters. The models included fixed effects of group and time, and random effects of participants and their age.

The vigilance decrement for each individual was computed by subtracting the average accuracy over the first three minutes from the average over the last three minutes and then normalised by dividing the average over the first three blocks. The reason for using the average over the first three blocks as a performance baseline is because, in COVID-19 participants, the vigilance decrement happened relatively quickly, at the group level the accuracy was significantly lower than the first minute from the 4th minute ($p=0.007$, Bonferroni adjusted).

Trial-by-trial accuracy rate of the vigilance test: The second approach entailed analysing the accuracy rate as a function of trial: For each participant, the event time series were summed: when the trial was a target, if the response was a hit, then it scored 4 ($=1/0.25$, where 0.25 is the target probability); if the response was a miss, then it scored -4 ($=-1/0.25$). when the trial was not a target; if the response was a correct rejection, it scored 1.33 ($=1/0.75$, where 0.75 is the non-target probability); if the response was a false positive, then it scored -1.33 ($=-1/0.75$). This weighted scoring system makes the measure more sensitive to the behavioural changes in this task. Then, an unweighted rectangular smoothing was applied with a window of 60 trials, paralleling a similar technique for computing neural firing rates from neuronal spike trains.²⁶ The time series obtained was then baseline corrected over the first block. Mean accuracy rate time series, obtained by averaging across participants, are used for the analyses reported here.

Time-series analysis: To identify time intervals in which groups exhibit accuracy rate difference, a non-parametric bootstrap-based statistical analysis was used.²⁷ In each iteration, N data sets (N=62 here; based on the number of participants in the COVID group) were selected with replacement from each group and a difference between means was computed. These time series were subjected to bootstrap re-sampling (10000 iterations). At each time point, differences were deemed significant if the proportion of bootstrap iterations

that fell above or below zero was more than 95% (i.e. $p < 0.05$). Any significant differences in the baseline interval (the first block) would be attributable to noise and the largest number of consecutive significant samples was used as the threshold for the statistical analysis for the entire experiment. Similar permutation tests were applied to the ratings (**Fig 2b** and **2c**) but baseline correction was not applied.

Group comparison: T-test statistics and Bayesian Factor (BF) are reported. All p values reported are two-tailed. When the sample sizes are not balanced, a bootstrap-based permutation test was used to confirm the reliability of the significance. For example, when comparing the vigilance decrement in participants who had COVID within two months ($n=13$) vs the control participants ($n=73$), in each iteration, N data sets ($N=13$ here; based on the number of participants who had COVID-19 within two months) were selected with replacement from each group and a difference between means was computed. This process was then repeated 10000 times. Group difference was deemed significant if the proportion of bootstrap interactions that fell above or below zero was more than 95% (i.e. $p < 0.05$).

Correlation: To control for outlier effects, all reported bivariate and partial correlations were performed using the conservative Spearman's rank correlation method. Additionally, we conducted partial correlations after controlling for the effect of age, motivation ratings, and the grit scale of personality.

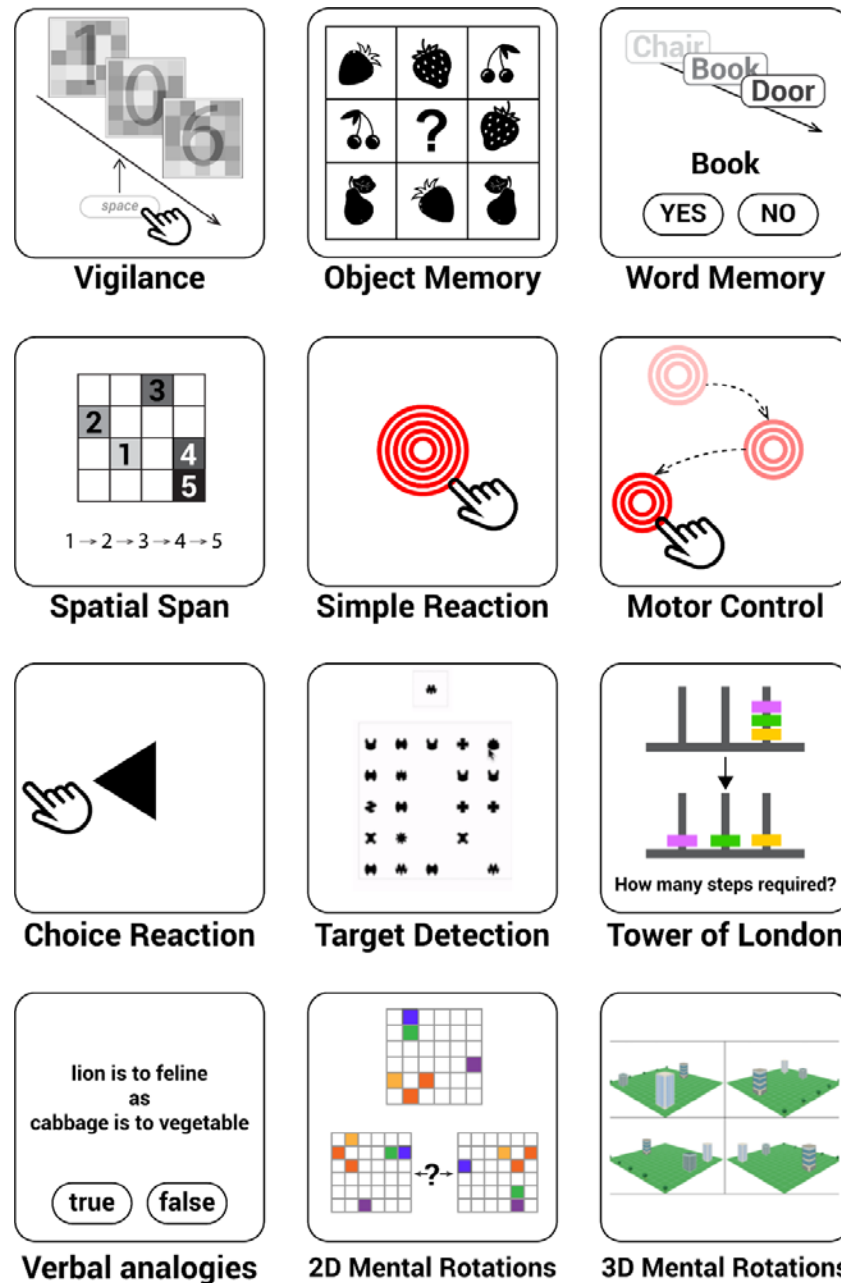


Figure 1. Twelve cognitive tasks measured distinct aspects of human cognition, memory, attention, motor control, planning and verbal reasoning abilities. The vigilance task was tested through the online experiment hosting server Pavlovia and conducted first. The rest of the 11 tasks were provided by Cognitron and ran in the following order: Motor control, Object memory (immediate), Word memory (immediate), Simple reaction task, Choice reaction time, 2D mental rotations, 3D mental rotations, Spatial span, Target detection, Tower of London, Verbal analogies, Object memory (delayed) and Word memory (delayed). The object memory and word memory tasks were both tested twice: once at the beginning (“immediate”) and again at the end of the experiment (“delayed”), with an interval of about 30 minutes. The delayed task was solely testing memory of the stimuli

displayed in the first instance of the task so the memory probes were not displayed before the delayed task.

Cognitive test battery

On a subsequent occasion, a subset of participants also completed a sequence of eleven cognitive tasks to measure distinct aspects of human cognition, episodic memory, attention, motor control, planning, mental rotation and verbal reasoning abilities (**Fig 1**). These eleven tasks can be viewed at <https://oxmh1.cognitron.co.uk>. They were adapted from established behavioural paradigms in a manner that is sensitive to population variables of interest whilst being robust against the type of device that a person is tested on. The tasks were conceived, designed and programmed in HTML5 with JavaScript by A.H. and W.T., and hosted on a custom server system 'Cognitron' developed by P.J.H. on the Amazon EC2 platform.

This study was conducted independently to the vigilance task. All 135 participants were invited to attend this experiment, and 82 completed this part of the study between 6 and 20 May 2021, with 36 from the COVID group (mean time since COVID-19 diagnosis: 231.7 days (130.0), age 28.5(8.8), 13 females) and 46 from the control group (age 25.4(7.2), 17 females). No significant difference in age ($t(80)=1.8$, $p=0.08$, $BF=1.1$) or gender ($\chi^2(1,N=30)=0.01$, $p=0.9$), or any questionnaire-derived measures (all $p>0.10$) were observed in this subset of participants.

Object Episodic Memory: Participants were asked to memorise 20 images, all everyday objects, depicted in black and white. The images were presented sequentially in a random order, each for 2000 ms with an inter-image interval of 500 ms. Immediately after the presentation, participants' memory of the 20 images was tested in 20 randomly ordered trials. Each trial required participants to select a previously displayed image from a set of eight images; incorrect images differed in the object itself, look or orientation (see the example in **Fig 1's Object Memory**) in order to measure not only whether the correct target was identified, but also at higher precision the similarity of selected objects to the original target when errors were made. A delayed memory recall test was repeated at the end of the experiment, i.e., without additional sequential encoding of images; on average the time between the first and second test was 28.3 minutes. Population mean of the immediate accuracy was 59.5% (21.5) compared with the delayed accuracy of 57.7% (21.0), both well above chance level (12.5%). The memory decrement was computed by subtracting the accuracy in the immediate memory test from that in the delayed memory test for each individual. The controls did not show significant memory decrement ($t(45)=0.8$, $p=0.4$, $BF=4.7$).

Word Memory: This task involved memorising a sequence of English words (e.g.: Peas, Monkey, Dress, Aubergine, Mouse etc). Words could be randomly drawn from three categories: animals, vegetables or clothes. The words were presented sequentially in a pseudo-random order, each presented for 1000 ms and with an inter-image interval of 200 ms. Immediately post-presentation, word memory was tested with 24 words, including 50% non-targets, of which half were foils selected as being semantically similar to the targets (population mean of accuracy 90.5% (9.3)). After an average of 27.3 minutes later, participants were tested again to assess the episodic memory (mean accuracy (86.5%

(10.4)). The memory decrement was computed by subtracting the accuracy in the immediate memory test from that in the delayed memory test for each individual. The controls showed significant memory decrement ($t(45)=-4.1$, $p<0.01$, $BF=135.2$).

Spatial Span: This task measured spatial short-term memory capacity. It was a variation of the Corsi Block Tapping Test^{28,29} participants were presented with a 4x4 grid where each individual cell can light up sequentially. Participants were required to memorise the sequence and replicate it by clicking the appropriate squares in the order they lit up. The difficulty was incremented using a ratchet system, every time a sequence was recalled correctly, the length of the subsequent sequence was incremented by one. The test was terminated when three consecutive mistakes were made on a particular sequence length. The outcome measure was the maximum sequence length correctly recalled. Minimum level = 2, maximum level = 16, ISI = 0 ms, encoding time = 1500 ms. Mean sequence length successfully recalled was 6.1 (SD 1.2).

Simple Reaction Task: This task measured the basic cognitive process of perception and response execution. The participants were instructed to click on a red circle as soon as it appeared at the centre of the screen. They were presented with 60 stimuli, the ISI was jittered using a uniform random distribution between 0.5 s and 2 s. The dependent measure was the speed of response (population mean was 0.3 seconds (SD 0.07)).

Motor Control: This task was identical to the reaction time task above, except that the location of the red circle was different each time. Participants had to move their cursor to the target and respond as fast as possible. The participants were presented with 30 stimuli, the next stimulus was presented with a 0 ms delay after the response to the previous stimulus. Here, the population mean was 0.7 seconds (SD 0.2).

Choice Reaction Time: A black arrow either pointing left or right appeared on-screen, indicating the side of the screen the participant needed to click as fast as possible. The participants were presented with 60 stimuli with a 50% chance of each stimulus pointing left. The ISI was jittered using a uniform random distribution between 0.5 s and 2 s. Mean reaction time (RT) over button presses for both sides was computed (population mean was 0.5 seconds (SD 0.09)).

Target Detection: This spatio-visual attention task involved identifying and clicking on a target shape amongst a field of distractor shapes. The participant was presented with a target shape on the left of the screen and a probe area on the right side of the screen. After 3s, the probe area began to fill with shapes, the participant must identify and click the target shape while ignoring the distractor shapes. Shapes were added every 1s and a subset of the shapes in the probe area are removed every 1s. The trial ran for a total of 120 addition/removal cycles. The target shape was included in the added shapes pseudo randomly, at a frequency of 12 in 20 cycles. The outcome measure was the total number of target shapes clicked. Population mean was 59.8 (SD 12.0).

Tower of London: This task measured spatial planning and was a variant of the original Tower of London task.³⁰ The participant was shown two sets of three prongs with coloured beads on them. The first set was the initial state and the second set was the target state.

The task was to work out the lowest number of moves it would take to transition from the initial state to the target state, then input this number using an on-screen number pad. The test consisted of 10 trials of variable difficulty, scaled using the number of beads and the convolutedness, defined as the number of moves that must be made that do not place a bead in its final target position. The outcome measure was the total number of correct trials. Unlike in the original task³⁰, the pegs were of equal height and the task was done mentally—the beads could not be moved. The total number of correct trials was recorded (population mean was 5.8 (SD 2.7)).

Verbal Analogies: This task examined semantic reasoning. Participants were presented with two written relationships that they must decide if they had the same type of association or not (e.g. “Lion is to feline as cabbage is to vegetable”). Participants indicated their decision by selecting the True or False buttons presented below the written analogies. Analogies were varied across semantic distance to modulate difficulty and association types switch throughout the sequence of trials. To obtain maximum points, participants must solve as many problems as possible within three minutes. For every correct response, the total score increased by one. For every incorrect response, the total score decreased by one. The outcome measure was the total score (population mean total point score was 21.4 (SD 12.5)).

2D Mental Rotation: The 2D Mental rotation test measured the ability to spatially manipulate objects in the mind.³¹ In this version, we used 6x6 grids with various arrangements of coloured cells. Provided with a target grid and a set of four further grids, participants had to identify which of the four was the target but merely rotated by 90, 180 or 270° (incorrect grids had five incorrectly coloured cells). Participants were given three minutes to answer as many as possible, with correct trials being awarded with one point to their score (population mean was 34.5 (SD 8.6), technical issues caused the loss of three participants’ records for this task).

3D Mental Rotation: Akin to the 2D version above, participants were tasked with recognising a rotated version of the target from four options. In this 3D version, the grids were instead 3D scenes of buildings arranged upon a green surface. Again, the correct answer was identical to the target but from a different viewpoint (rotated by 90, 180 or 270°), while the others had their buildings in the wrong locations. Each participant was presented with 12 trials scored in the same manner as before (population mean was 4.5 (SD 8.6)).

Statistical analysis

For each cognitive function, a Principal Component Analysis (PCAs) was performed to derive a global index (PCA scores) quantifying its level across all relevant tasks used to assess it:

- Short-term memory score: PCA of full recall correct rate of *Object Memory*, full recall correct rate of *Word Memory*, and *Spatial Span* memory capacity.
- Executive and attentional function score: PCA of reaction times in *Simple Reaction Task*, *Motor Control*, and *Choice Reaction Time* and the overall score in *Target Detection*.

- Mental Rotation score: PCA of scores in *2D* and *3D Mental Rotation*. This quantifies each individual's mental ability to spatially manipulate objects.

Group comparisons and correlations were performed as in *Vigilance*.

Ethics statement

All participants gave electronic informed consent prior to the experiment. The study was approved by the local ethics committee and carried out in accordance with the relevant guidelines and regulations.

Data availability

The data supporting the findings of this study are available from the corresponding author, upon reasonable request. A demo of the vigilance task is available at https://run.pavlovia.org/sijiazhao/vigilance_english_demo (please use the Chrome internet browser on a desktop computer). The experimental code is available at https://gitlab.pavlovia.org/sijiazhao/vigilance_english_demo.

Results

COVID-19 survivors in this study were young, with many testing positive for COVID-19 several months before attending this study. Compared to the age-matched control group who did not report contracting COVID-19 before, there were no difference in gender or baseline group differences in a wide range of measures including fatigue/sleep abnormality (NFI), motivation (AMI), distractibility/forgetfulness (CFQ), mood (HADS) and personality (GRIT-S and BFI-S) (**Table 1**).

Compared with the controls, COVID-19 survivors showed significantly larger decline in performance in a 9-minute-long sustained visual attention task (**Fig 1 Vigilance**). There was no significant group difference in accuracy over the first minute ($t(133)=-1.6$, $p=0.1$, $BF=1.6$). However, COVID-19 participants showed a greater and more rapid decline in accuracy over time (significant interaction between group and time using a mixed-effects generalised linear model (GLM) ($F(1,1346)=18.8$, $p<0.0001$) along with main effects of time ($F(1,1346)=15.1$, $p=0.0001$) and group ($F(1,1346)=8.1$, $p=0.005$)).

Measure		All (n=135)	COVID (n=62)	Control (n=73)	Statistic	
Age, mean years (SD)		26.26 (7.98)	27.71 (8.51)	25.03 (7.33)	t(133)=1.97, p=0.05, BF=0.94	
Gender, female (%)		49 (36.30)	25 (40.32)	24 (32.88)	$\chi^2(1, N=49) = 0.80$, p=0.37	
COVID-19	Time from COVID-19 diagnosis, mean days (SD)		167.32 (127.89)			
	COVID-19 test type: PCR / Lateral flow / Unknown / Not tested		48/4/3/7			
	Stayed at hospital overnight for COVID-19 treatment, yes (%)		3 (4.84)			
	Stayed at ICU for COVID-19 treatment, yes (%)		0 (0.00)			
Questionnaires	NFI	Physical fatigue (SD)	9.22 (4.56)	9.03 (4.70)	9.38 (4.46)	t(133)=-0.44, p=0.66, BF=4.94
		Cognitive fatigue (SD)	4.47 (2.77)	4.42 (2.99)	4.52 (2.58)	t(133)=-0.21, p=0.83, BF=5.30
		Sleep Relief (SD)	7.85 (3.32)	7.73 (3.29)	7.96 (3.37)	t(133)=-0.40, p=0.69, BF=5.02
		Sleep abnormality (SD)	7.28 (2.80)	7.42 (3.04)	7.16 (2.59)	t(133)=0.53, p=0.60, BF=4.77
	CFQ	Forgetfulness (SD)	12.82 (5.04)	13.36 (4.94)	12.20 (5.14)	t(103)=1.17, p=0.24, BF=2.90
		False triggering (SD)	8.84 (4.67)	9.39 (4.66)	8.20 (4.65)	t(103)=1.30, p=0.19, BF=2.50
		Distractibility (SD)	12.52 (4.88)	12.71 (4.91)	12.31 (4.88)	t(103)=0.43, p=0.67, BF=4.98
	BFI-S	Conscientiousness (SD)	10.51 (2.37)	10.4 (2.08)	10.61 (2.70)	t(93)=-0.41, p=0.68, BF=5.01
	GRIT-S	Grit scale (SD)	3.18 (0.69)	3.12 (0.66)	3.26 (0.73)	t(93)=-0.93, p=0.35, BF=3.64
	AMI	Behavioural apathy (SD)	10.43 (4.38)	11.00 (4.55)	9.77 (4.12)	t(93)=1.37, p=0.17, BF=2.31
		Social apathy (SD)	13.11 (4.73)	13.02 (5.10)	13.20 (4.31)	t(93)=-0.19, p=0.85, BF=5.32
		Emotional apathy (SD)	7.98 (4.17)	8.41 (4.30)	7.48 (4.00)	t(93)=1.09, p=0.28, BF=3.15
	HADS	Depression (SD)	5.62 (3.66)	5.94 (4.03)	5.25 (3.17)	t(93)=-0.92, p=0.36, BF=3.68
		Anxiety (SD)	8.31 (3.86)	8.27 (4.03)	8.34 (3.71)	t(93)=-0.08, p=0.93, BF=5.39

Table 1. Self-reported participant demographics and questionnaire-derived measures. T- and χ^2 tests were used to assess between-group differences, with Bayes Factor (BF) reported. The questionnaires included are Neurological Fatigue Index (NFI), Cognitive Failures Questionnaire (CFQ), Short Big Five Inventory (BFI-S), Short Grit Scale (GRIT-S), Apathy Motivation Index (AMI), and the Hospital Anxiety and Depression Scale (HADS). For all the questionnaire-derived indices, the mean score is shown with one standard deviation (SD) in the bracket.

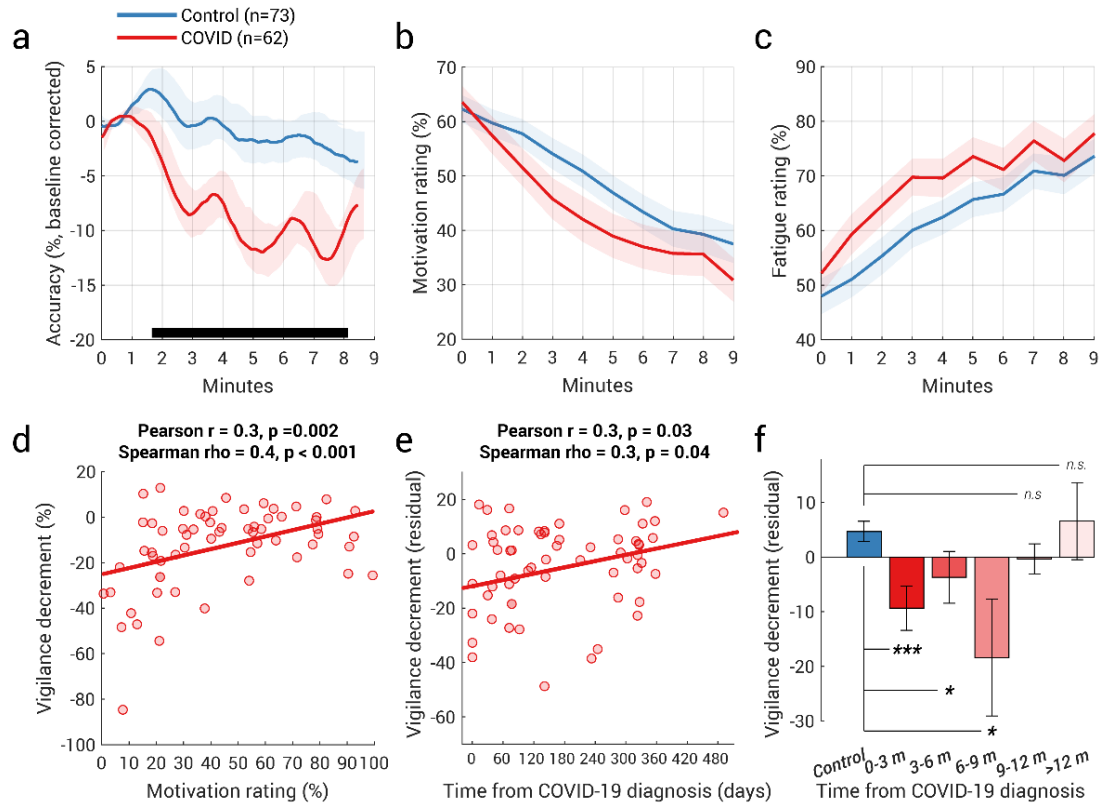


Figure 2. COVID group showed a larger and faster vigilance decline and greater loss of motivation on the task. (a) Accuracy rate as a function of time on task, computed by filtering each response on a per-trial level and baseline correcting by each participant's performance in the first minute (60 trials). The shaded area shows ± 1 SEM and the black horizontal line at the bottom indicates time intervals where bootstrap statistics confirmed significant differences between the two groups; the divergence was significant from 118 to 506 seconds. (b) Group average of self-reported ratings of motivation against time (shaded area shows ± 1 SEM). COVID-19 survivors had a greater loss in motivation over time, even though both groups started with equivalent baseline levels. (c) No group difference was found in the fatigue rating over time (shaded area shows ± 1 SEM). (d) In COVID-19 survivors, the size of the vigilance decrement was significantly correlated with their motivation rating, a relation not observed in the control group. (e) Vigilance decrement (controlling age) showed a significant correlation with the time from COVID-19 diagnosis. Both Spearman's and Pearson's correlation coefficients and their two-tailed p values are shown above the plot. (f) Participants who had COVID-19 within the last nine months displayed significantly larger vigilance decrements than the controls. Group comparison performed by t -test, further confirmed by permutation test (with 10000 iterations). * = $p < 0.05$, ** = $p < 0.01$, m (months). Y-axis shows residuals, not absolute values of vigilance decrement.

In the control group, accuracy decreased from 81.4% (SEM 1.9) in the first minute to 76.7% (SEM 2.6) by the end of the experiment but this was not a significant change. In the COVID group, average accuracy decreased rapidly from 76.8% (SEM 2.2) in the first minute to 69.6% (SEM 3.2) after three minutes ($p = 0.007$, $t(61) = 4.0$, Bonferroni adjusted). Comparing the

baseline-corrected trial-by-trial accuracy rate which provides better temporal resolution (**Fig 2a**), the group difference began to emerge by the start of the 3rd minute.

Across both groups, lower motivation (**Fig 2b**) and greater fatigue (**Fig 2c**) were reported as the experiment progressed (mixed effects GLM, main effect of time $p < 0.001$). Crucially, the COVID group showed accelerated loss of motivation over time (interaction of group x time, $F(1,1320)=4.1$, $p=0.04$), but this was not significant for fatigue ratings. In COVID survivors, overall lower motivation ratings (across all time points) was associated with larger vigilance decrements (Spearman's $\rho=0.4$, $p < 0.001$, **Fig 2d**) but this was not observed in the control group ($\rho=0.1$, $p=0.3$).

There was a significant positive correlation between individual vigilance decrement (normalised difference in average accuracy between first and last three minutes) and time from COVID diagnosis ($\rho=0.3$, $p=0.04$; Partial correlation after controlling age: $\rho=0.3$, $p=0.04$, **Fig 2e**). Furthermore, participants who had COVID-19 in the last nine months showed a significantly larger vigilance decrement than the control group ($t(113)=-3.9$, $p < 10^{-4}$, $BF=152.7$, bootstrap-based $p < 0.001$), with this difference no longer apparent in participants who had COVID-19 more than nine months previously ($t(91)=-1.0$, $p=0.3$, $BF=2.5$, bootstrap-based $p=0.2$).

In order to obtain a more comprehensive examination of our COVID-19 survivors' cognitive profiles, we subsequently invited all participants to complete a cognitive battery comprising 11 cognitive tests (all bar *Vigilance* in **Fig 1**) two months after the *Vigilance* test. 36 COVID-19 survivors had been diagnosed on average 231.7 days previously (130.0) and 46 age-matched controls attended the battery (**Table 2** for demographics).

Memory was a key cognitive function measured in this battery. In one of the memory tests—*Object Memory*—participants were shown 20 images of everyday objects to memorise. Specifically, participants needed to remember not only the object (e.g. a spoon), but also its look (e.g. a spoon with a long handle) as well as its orientation (e.g. handle pointing towards top-right). This provides us details about the preciseness of the memory recalled. One novel feature of this test is that *Object Memory* was tested twice, once immediately after presentation and again around 30 minutes later, which provides a measure of memory decrement over time.

On average, the controls achieved 61% accuracy in the immediate memory test. COVID-19 survivors showed a similar short-term memory performance to the control group ($t(80)=-0.9$, $p=0.4$, $BF=3.0$, **Fig 3a**). However, a difference emerged in the later (delayed) test; while the controls displayed no memory decrement (no difference from zero, one sample t-test: $t(45)=0.8$, $p=0.4$, $BF=4.7$), COVID-19 survivors showed a significant memory decrement ($t(35)=-3.1$, $p=0.004$, $BF=8.6$), which was larger than in controls by 7.5% ($t(80)=-2.7$, $p=0.01$, $BF=5.1$) (**Fig 3b**). Importantly, this difference in episodic memory decrement was not due to the variance in memory maintenance duration, because there was no difference in the duration between the immediate and delayed memory tests across the two groups (COVID: 26.7 minutes (5.2), Control: 29.5 minutes (9.6), $t(80)=-1.6$, $p=0.10$, $BF=1.4$).

Measure		All (n=82)	COVID (n=36)	Control (n=46)	Statistic	
Age, years, mean (SD)		26.78 (8.08)	28.53 (8.82)	25.41 (7.25)	t(80)=1.76, p=0.08, BF=1.14	
Gender, female, n (%)		30 (36.59)	13 (36.11)	17 (36.96)	$\chi^2(1, N=30) = 0.01$, p=0.94	
COVID-19	Time from COVID-19 diagnosis, mean days (SD)		231.69 (129.95)			
	COVID-19 test type: PCR / Lateral flow / Unknown / Not tested		28/1/3/4			
	Stayed at hospital overnight for COVID-19 treatment, yes (%)		3 (8.33)			
	Stayed at ICU for COVID-19 treatment, yes (%)		0 (0.00)			
Object memory	Immediate memory test	Accuracy, mean % (SD)	59.45 (21.46)	56.94 (17.66)	61.41 (24.03)	t(80)=-0.94, p=0.35, BF=2.96
		RT in s, mean (SD)	3.32 (1.78)	3.24 (1.63)	3.38 (1.90)	t(80)=-0.34, p=0.74, BF=4.11
	Delayed memory test	Accuracy, mean % (SD)	57.68 (20.97)	50.97 (20.63)	62.93 (19.90)	t(80)=-2.66, p<0.01, BF=4.66
		RT in s, mean (SD)	2.33 (0.84)	2.18 (0.56)	2.45 (0.99)	t(80)=-1.43, p=0.16, BF=1.79
	Memory decrement (delayed minus immediate accuracy)	Accuracy, mean % (SD)	-1.77 (12.97)	-5.97 (11.76)	1.52 (13.03)	t(80)=-2.70, p=0.01, BF=5.07
	Time between immediate and delayed tests	Duration in minutes, mean (SD)	28.28 (8.06)	26.65 (5.24)	29.56 (9.58)	t(80)=-1.64, p=0.10, BF=1.35
Word memory	Immediate memory test	Accuracy, mean % (SD)	90.55 (9.28)	89.58 (12.06)	91.30 (6.38)	t(80)=-0.83, p=0.41, BF=3.20
		RT in s, mean (SD)	0.96 (0.27)	0.96 (0.32)	0.95 (0.22)	t(80)=0.14, p=0.89, BF=4.29
	Delayed memory test	Accuracy, mean % (SD)	86.53 (10.42)	85.53 (11.55)	87.32 (9.50)	t(80)=-0.77, p=0.44, BF=3.34
		RT in s, mean (SD)	0.91 (0.28)	0.91 (0.37)	0.91 (0.18)	t(80)=0.04, p=0.97, BF=4.32
	Memory decrement (delayed minus immediate accuracy)	Accuracy, mean % (SD)	-4.01 (6.46)	-4.05 (6.34)	-3.99 (6.63)	t(80)=-0.05, p=0.96, BF=4.32
	Time between immediate and delayed tests	Duration in minutes, mean (SD)	27.30 (7.41)	25.58 (3.42)	28.65 (9.25)	t(80)=-1.89, p=0.06, BF=0.93
Spatial short-term memory capacity	Spatial span	n, mean(SD)	6.59 (1.27)	6.44 (1.40)	6.70 (1.15)	t(80)=-0.89, p=0.38, BF=3.06
Motor control	Simple reaction time	RT in s, mean (SD)	0.31 (0.07)	0.30 (0.06)	0.32 (0.08)	t(80)=-0.83, p=0.41, BF=3.20
	Motor control	RT in s, mean (SD)	0.73 (0.21)	0.75 (0.22)	0.71 (0.20)	t(80)=0.83, p=0.41, BF=3.21
	Choice reaction time	RT in s, mean (SD)	0.51 (0.09)	0.51 (0.09)	0.51 (0.09)	t(80)=0.11, p=0.91, BF=4.30
Spatial visual attention	Target detection	Score, mean (SD)	59.78 (12.01)	58.22 (14.33)	61.00 (9.83)	t(80)=-1.04, p=0.30, BF=2.70
Spatial planning	Tower of London	Score, mean (SD)	5.82 (2.73)	5.44 (2.85)	6.11 (2.63)	t(80)=-1.09, p=0.28, BF=2.57
Semantic reasoning	Verbal analogies	Score, mean (SD)	21.38 (12.51)	19.83 (11.18)	22.59 (13.46)	t(80)=-0.99, p=0.33, BF=2.83
Mental rotation	2D mental rotation	Score, mean (SD)	34.48 (8.59)	33.97 (8.01)	34.89 (9.09)	t(77)=-0.47, p=0.64, BF=3.93
	3D mental rotation	Score, mean (SD)	4.46 (6.02)	4.33 (6.35)	4.57 (5.82)	t(80)=-0.17, p=0.86, BF=4.27

Table 2. Results of the 11 cognitive tasks in the battery test. 82 out of 135 participants attended, and their demographics are reported. The time from COVID-19 diagnosis was computed as the days between the date they attended this battery test and the self-reported date of their

positive COVID-19 test. T - and χ^2 tests used to assess between-group differences, with Bayes Factor (BF) reported. The significant t -tests are highlighted in bold.

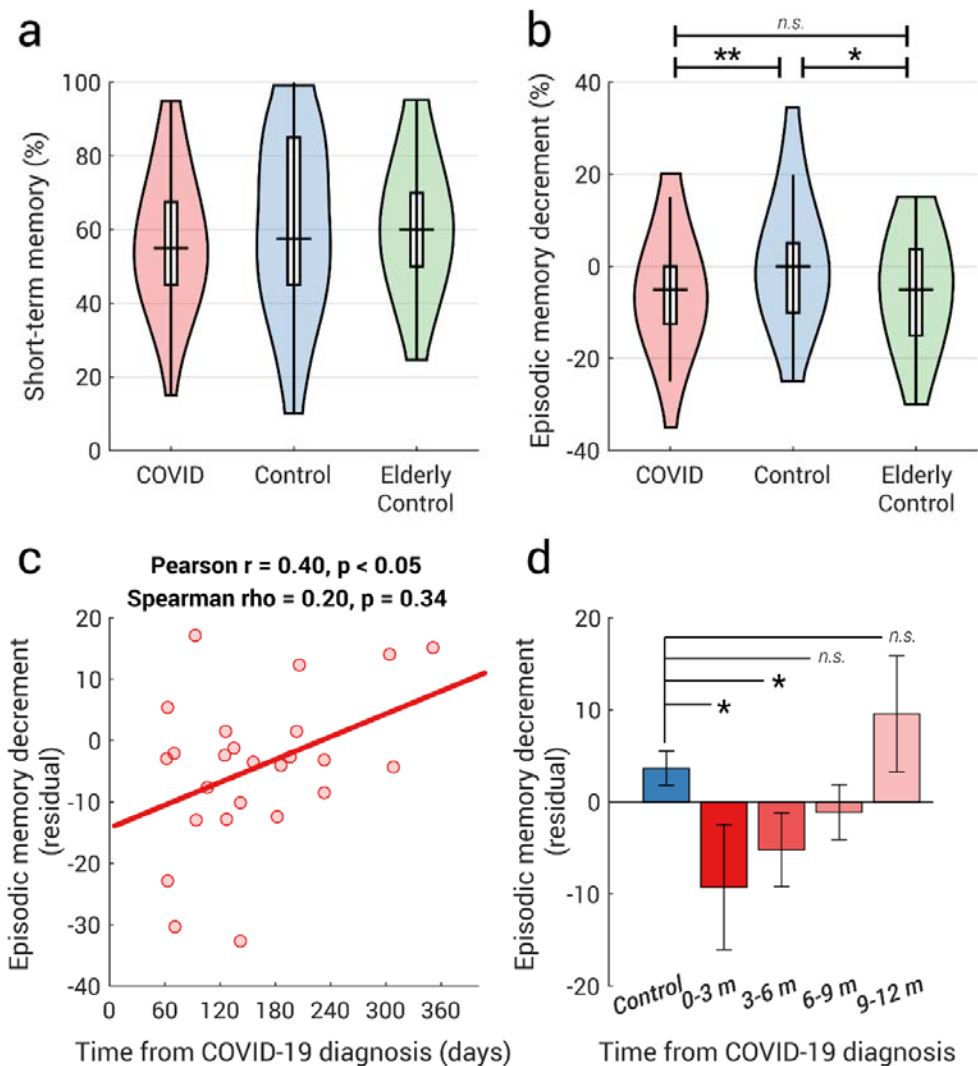


Figure 3. COVID group showed a mild episodic memory deficit compared with age-matched controls. (a) The distribution of the short-term memory, measured as the correct percent in the memory test immediately after viewing the sequence of objects, is plotted as a violin for COVID ($n=36$), Control ($n=46$) and Elderly Control ($n=52$, all above 50 years old, data collected separately). There were no statistical differences between groups in the short-term memory (all $p>0.2$). (b) Approximately 30-minutes later, their memory was tested again. COVID and Elderly controls showed significantly larger memory decrements than the younger controls (COVID vs Control: $t(80)=-2.7$, $p=0.01$, $BF=5.1$; Elderly Control vs Control: $t(96)=2.6$, $p=0.01$, $BF=4.2$; COVID vs Elderly Control: $t(86)=-0.5$, $p=0.6$, $BF=4.0$). (c) In COVID-19 survivors who contracted COVID-19 within 1 year, the size of memory decrement after controlling the effect of age was positively correlated with the time from COVID-19 diagnosis. Both Spearman's and Pearson's correlation coefficients and their two-tailed p values are shown above the plot. (d) Participants who had COVID-19 within the last six months showed significantly larger memory decrement than the younger controls. Group comparison performed by t -test, and further confirmed by permutation test. * = $p<0.05$, ** = $p<0.01$, m (months).

Note that y-axis shows the residuals after controlling the effect of age, not absolute values of memory decrement.

Furthermore, the larger episodic memory decrement amongst COVID-19 survivors was driven by errors in which the wrong orientation was chosen for a correct item. In the immediate memory test, COVID-19 survivors had a 30.6% (13.3) false alarm rate where they chose the right object but wrong orientation, misbinding object identity with object orientation. This was not significantly different from controls (28.6 (18.3), $t(80)=0.5$, $p=0.6$, $BF=3.8$). However, this orientation-specific false alarm rate increased to 35.3% (15.7) 30 minutes later in the COVID group, which was significantly higher than the controls (27.3% (14.7), $t(80)=2.4$, $p=0.02$, $BF=2.6$). This difference suggests that the deficit in episodic memory in the COVID group might be associated with a deficit in binding information in memory.

In another memory test (**Fig 1 Word Memory**), participants were instructed to memorise 24 simple English words. Although both COVID and control groups showed significant memory decrement (COVID: $t(35)=-3.8$, $p=0.0005$, $BF=58.3$; Control: $t(45)=-4.1$, $p=0.0002$, $BF=135.2$), they did not differ significantly from each other ($t(80)=-0.05$, $p=1.0$, $BF=4.3$). Because our participants reported having different first languages, we also ran a 2 (group: COVID vs control) x 2 (first language: English or non-English) ANOVA on the memory decrement. There were no main effects of first language ($F(1,77)=0.02$, $p=0.9$) or group ($F(1,77)=1.3$, $p=0.3$) and no language-group interaction ($F(1,78)=1.5$, $p=0.2$), indicating that this null effect was not due to differences in first language amongst participants. This null effect in word memory decrement might be due to the fact that the word memory task was much simpler than *Object Memory* which also had precision manipulation.

As part of a separate study, we ran the same memory tests on 52 healthy elderly participants (Elderly Control group: 53–82 years old, mean 67.4 (7.2), 30 females, no self-report COVID-19). Amongst controls ($n=98$, including all from Control and Elderly Control groups), there was a weak correlation between memory decrement and age (Pearson $r=-0.2$, $p=0.04$; Spearman's $\rho=-0.2$, $p=0.08$). Compared with young controls, elderly participants had a significantly larger memory decrement (mean -4.8 (10.9), $t(96)=2.6$, $p=0.01$, $BF=4.16$), but importantly elderly participants' episodic memory decrement was not statistically different from COVID-19 survivors ($t(86)=0.5$, $p=0.6$, $BF=4.0$, **Fig 3b**), indicating that COVID-19 survivors performed as if they were older.

However, the elderly controls spent a longer time completing other tasks between the immediate and delayed memory tests (mean 39.2 (6.1) minutes) than the COVID group ($t(86)=-10.1$, $p<0.01$, $BF>10^{13}$). The requirement to maintain memory for a longer period was associated with greater memory decrements (partial correlation of time between memory tests and memory decrement amongst young and elderly controls after controlling the effect of age: Pearson $r=0.2$, $p=0.03$; Spearman $\rho=0.05$, $p=0.6$). Therefore, we regressed out the effect of the memory maintenance time from each individual's memory decrement, but the pattern remained unchanged.

Amongst survivors who contracted COVID-19 within the last year, the size of memory decrement after controlling for the effect of age was weakly but significantly correlated with

the time from diagnosis (**Fig 3c**, Pearson $r=0.4$, $p<0.05$; Spearman $\rho=0.20$, $p=0.3$), suggesting that people who had COVID-19 more recently tended to forget more over the 30-minute interval. This significant memory decrement could be observed up to 6 months ($t(59)=-2.7$, $p=0.009$, bootstrap-based $p=0.01$; **Fig 3d**). These analyses provide preliminary evidence that COVID-associated impairments in sustained attention and episodic memory may persist for months, but may normalise subsequently, although the findings have to be taken with caution given the sample size.

Reassuringly, COVID-19 survivors did not show any significant difference from the age-matched controls in a wide range of cognitive capabilities, including short-term memory (*Object Memory, Word Memory, Spatial Span*), the response speed (*Simple Reaction Task, Motor Control, Choice Reaction Time*), spatial-visual attention (*Target Detection*), spatial planning (*Tower of London*), semantic reasoning (*Verbal Analogies*) and mental rotations (2D or 3D) (see **Table 2** for details). Similarly, comparing PCA scores between COVID-19 survivors and controls, no significant difference was found in the short-term memory ($t(80)=-0.8$, $p=0.4$, $BF=3.2$), the executive function ($t(80)=0.7$, $p=0.5$, $BF=3.5$) or the mental rotation ability ($t(77)=-0.5$, $p=0.6$, $BF=3.9$), suggesting that most of the key cognitive functions were normal.

Discussion

In the present study, we examined a wide range of cognitive abilities in COVID-19 survivors and age-matched controls. Most of the COVID group did not require hospitalisation and had not sought medical help for long COVID symptoms after recovery. However, even though their questionnaire-derived measures (fatigue, forgetfulness, motivation, sleep abnormality, depression and anxiety levels) were no different from age-matched controls (**Table 1**), they showed a significantly larger vigilance decrement along with larger motivation loss over the course of a 9-minute-long attentionally demanding task (**Figs 2a** and **2b**). They also had significantly worse episodic memory decrement over time, comparable to a healthy, elderly person in their 60s (**Fig 3b**). Notably, both deficits scaled with the time from COVID-19 diagnosis suggesting a strong relation with COVID-19 itself (**Figs 2e** and **3d**).

To our knowledge, this is the first report describing deficits in sustained attention and episodic memory amongst mildly-affected COVID-19 survivors long after the acute illness, in people who were not complaining of long-COVID symptoms (cf. Zhou et al.⁹ reporting sustained attention impairments in recently-recovered patients). Our findings are consistent with the most prevalent complaints concerning post-COVID cognitive issues, including poor concentration and/or impaired memory in 18-50% of patients post-recovery.^{8,32,33} However, in contrast with previous reports of long-COVID patients^{6-8,12,13,16}, here we found no difference in short-term attention (performance over the first few minutes of a vigilance test; overall performance in tasks measuring executive function and response speed, **Table 2**) or working memory (performance in the immediate object or word memory tests, **Table 2** and **Fig 3a**).

In the present study, COVID-19 survivors began with apparently normal behavioural performance followed by a gradual decline away from age-matched controls, suggesting impaired ability to attentively track and maintain information *over time*. The inconsistency with previous reports might be due to the fact that patients featured in those studies had severe COVID-19 symptoms^{3,4,6,12}, clinically significant cognitive impairment¹⁶, or at least reported persistent cognitive symptoms^{7,8,13}, while our participants were mostly non-hospitalised and devoid of self-reported abnormality.

The mechanisms underlying these cognitive deficits as yet remains unclear. Although a direct effect of virus persisting in the brain cannot be excluded, the evidence from post-mortem studies suggests there is very little presence of virus within the brain in COVID-19 patients.³⁴ Rather, there might be indirect effects of the virus on cognitive function mediated via a range of possible mechanisms, including immunological and microvascular changes (see review³⁵). One investigation of COVID-19 survivors demonstrated that the most severely cognitively affected patients demonstrated a degree of cognitive impairment accompanied by hypometabolism in the frontoparietal regions.¹⁰ These brain regions are implicated in sustained attention³⁶ as well as in episodic memory.³⁷⁻³⁹ Reassuringly, the follow-up study of Hosp and colleagues¹⁰ showed slow but evident improvement after six months.¹¹ This is in line with the mildly-affected individuals reported here: both vigilance and episodic memory decrements gradually resolved over time (**Figs 2e** and **3c**). Episodic memory returned to normal levels after six months (**Fig 3d**) and those who had COVID-19 over nine months ago did not exhibit the vigilance decrement (**Fig 2f**).

Unlike other survey-based reports focusing on self-reported long-COVID symptoms^{33,40-42}, COVID-19 survivors in the present study did neither indicated any sign of higher fatigue, forgetfulness, apathy, anxiety, depression or sleep abnormality (**Table 1**), nor felt any more tired than their age-matched controls over the time course of the vigilance test, suggesting a dissociation between self-report symptoms and objectively measured deficits. Our findings highlight that cognitive impairments are not limited to patients who had prolonged neurological manifestations after recovery^{7,8}, but might exist more widely in a sub-clinical form amongst COVID-19 survivors who would not consider themselves requiring any post-COVID treatment.

At the outset of the pandemic, Hampshire et al.¹⁷ conducted a large-scale online test involving over 13,000 people with suspected or biologically confirmed COVID-19 circa two months. That study shared a subset of tasks with our investigation, covering a wide range of cognitive functions including semantic problem solving, visual spatial attention, speed of response and working memory. All functions showed some degree of cognitive deficit amongst people who had contracted COVID-19, scaling with respiratory symptom severity. In the present study, however, we did not find any group differences in these cognitive domains (**Table 2**). This difference is likely to be attributable to the relative mildness of the symptoms experienced by our COVID-19 survivors, combined with the length of time since infection (some over nine months ago). This suggests that these functional deficits might not be obvious in milder COVID-19 patients, with recovery expected within months.

There are some limitations to our study. Although the majority of participants from our COVID group reported a PCR-confirmed COVID-19 positive result with none reporting the need for post-COVID treatment, our study was limited by our reliance on self-reports of

positive/negative COVID-19 tests and timing of diagnosis, which might increase or decrease our estimate of the prevalence and duration of COVID-associated cognitive deficits. Our study is also constrained by a relatively small sample size (n=135) with under-representation of the over 70s, thus any generalization should be taken carefully.

Overall, the findings here show that COVID-19 survivors are significantly impaired in their ability to sustain attention and motivation on a demanding task up to nine months after COVID-19 infection, along with mild, but significantly worse, episodic memory for up to six months. Just as the acute illness of COVID-19 demonstrates a wide severity spectrum from asymptomatic to fatal forms⁴³, our findings show that post-COVID cognitive deficits too can also manifest a wide severity spectrum. They highlight a pressing need to measure cognitive performance objectively in order to better understand how the brain is affected by COVID-19.

Acknowledgements

The authors are grateful to Stephen Walsh for his involvement in the early stage of the project.

Fundings

This work was supported by the Wellcome Trust and NIHR Oxford Biomedical Research Centre. S.Z. and M.H. were funded by the Wellcome Trust (206330/Z/17/Z). S.G.M. was funded by an MRC Clinician Scientist Fellowship (MR/P00878/X). K.S. was funded by the Berrow Foundation. A.H. was supported by the UK Dementia Research Institute Care Research, the National Institute for Health Research (NIHR) Technology Centre and Imperial Biomedical Research Centre. P.J.H. was supported by the NIHR Biomedical Research Centre, South London and Maudsley NHS Foundation Trust and King's College London. W.T was funded by the Engineering and Physical Sciences Research Council (EPSRC) through the Imperial College CDT for Neurotechnology. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflict of interest

The authors declare no competing financial interests.

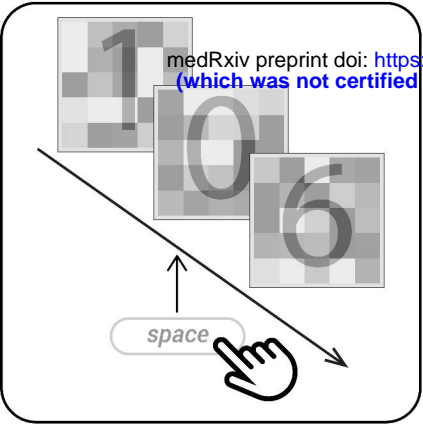
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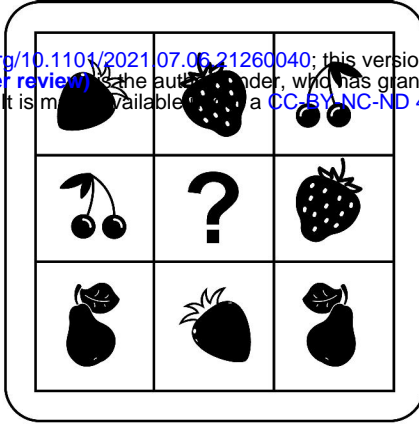
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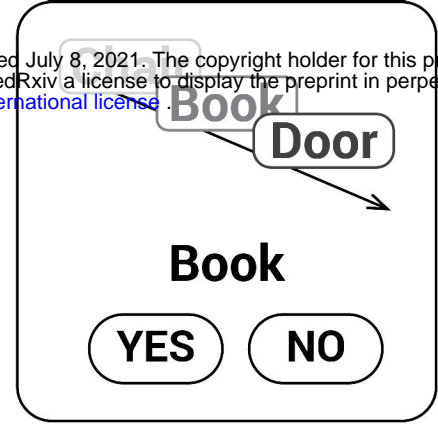
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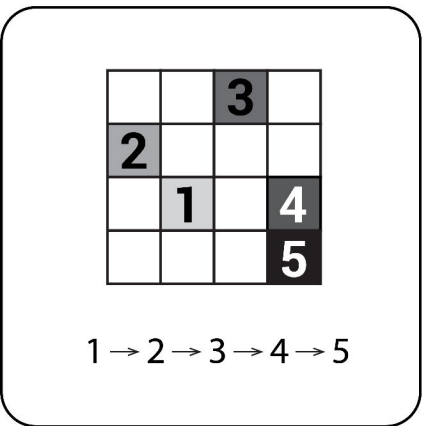
Vigilance



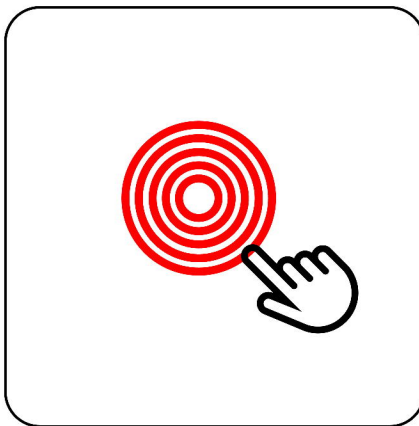
Object Memory



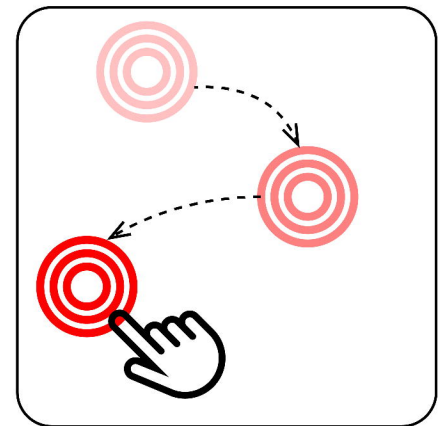
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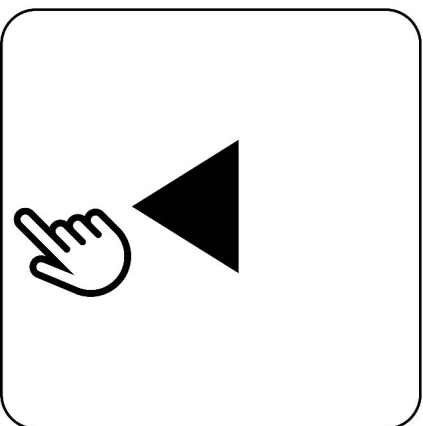
Spatial Span



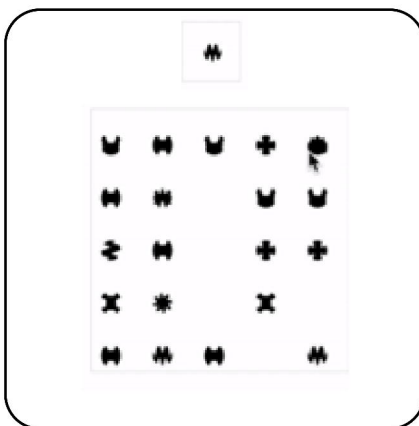
Simple Reaction



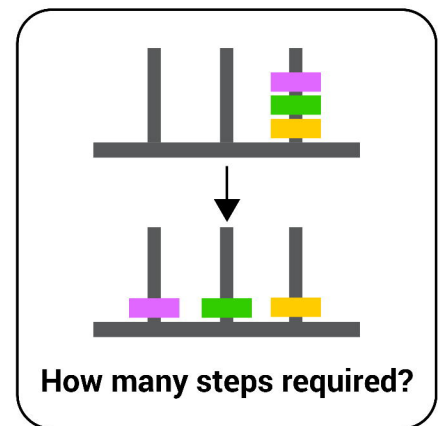
Motor Control



Choice Reaction



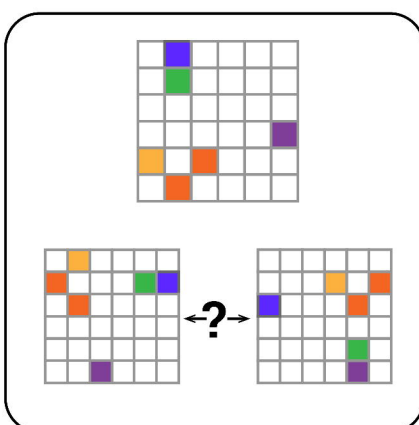
Target Detection



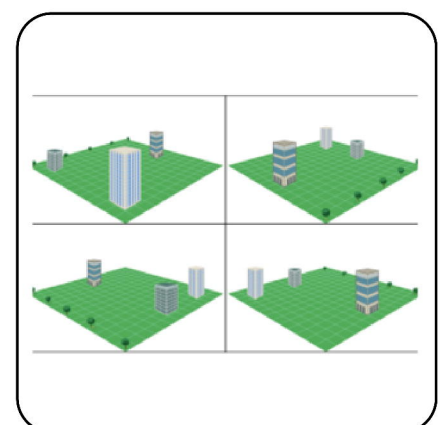
Tower of London



Verbal analogies



2D Mental Rotations



3D Mental Rotations

