Changes in memory function in adults following SARS-CoV-2 infection: findings from the Covid and Cognition online study

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Abstract (177 words)

SARS-CoV-2, the virus responsible for the Covid-19 pandemic, has been shown to have an impact on cognitive function, but the specific aspects of cognition that are affected remain unclear. In this Registered Report, we present a study aimed at further understanding the effects of SARS-CoV-2 on cognition, focusing especially on memory function, and to examine whether vaccination offers protection against long term cognitive symptoms of Covid-19. To this end, we will aim to replicate previous findings showing an effect of Covid-19 on memory, and will extend these findings by examining whether the effect varies as a function of memory type (item vs. associative) and stimulus type (verbal vs. pictorial). Moreover, we will compare cognitive functioning amongst vaccinated and unvaccinated individuals to explore the role of vaccination status in cognitive symptoms associated with Long Covid. Overall, the study will provide valuable insights into effects of SARS-CoV-2 infection on cognitive functions, and whether (and how) these are moderated by vaccination status. Comprehensive understanding of these aspects can inform and guideline public attitudes and policies related to Covid-19 and vaccination.

Introduction

Recently, the World Health Organisation (WHO) announced that Covid-19 is no longer considered to be a public health emergency of international concern. But is Covid-19 really over? Even if the acute phase of the pandemic had passed, there is wide agreement that the effects of the virus remain profound and are expected to significantly affect the world population for years to come. In this context, it is increasingly apparent that SARS-CoV-2 infection has several long-lasting effects on the brain and cognition (Douaud et al., 2022; Guo et al., 2022b; Hampshire et al., 2021; Wild et al., 2022). These are part of a multisystemic condition referred to as Long Covid, with one study showing that up to 50% of individuals with Long Covid reported having problems with memory, cognition, or concentration along with other symptoms (Dennis et al., 2023).

While several studies using cognitive tasks show lasting cognitive impairment following Covid-19, there are mixed results concerning which areas of cognition are affected. A study on 81,337 individuals showed that those who indicated they had experienced SARS-CoV-2 infection had lower scores on cognitive tasks, particularly those requiring reasoning, planning and problem solving (Hampshire et al., 2021). Similarly, a study by Wild et al. (2022) found deficits in reasoning and verbal abilities in participants post SARS-CoV-2 infection compared to pre-pandemic controls, but no significant differences in short-term memory. A study with post Covid-19 patients with complains of cognitive problems found impairment in executive functions, in particular phonemic fluency and attention in the MoCA test, in comparison to normative scores (Hadad et al., 2022). In turn, Guo et al. (2022) found that those who had experienced Covid-19 infection had significantly lower performance on long-term memory tasks. This effect was found for verbal item memory and nonverbal associative memory. However, as the tasks looking at nonverbal item memory and verbal associative memory were not included, it is impossible to disentangle whether the effects result from a general decrease in memory performance, or whether there are also more specific effects, depending on the modality via which the stimuli is perceived (verbal vs. pictorial) or the type of information that is being memorised (item vs. associative).

Memory for past events can be comprised of various components (items) and the links between them (associations) (Tulving, 1993). In this context, item memory refers to the ability to remember individual items within an episode, whereas associative memory refers to the ability to remember the relationships between two or more items or between items and their context (Dennis & McCormick-Huhn, 2018). A large corpus of previous research suggests that these abilities rely on distinct neurocognitive mechanisms. For example, studies using functional magnetic resonance imaging (fMRI) have shown that encoding activity in the rhinal cortex selectively predicts item memory performance, while activity in the hippocampus and posterior parahippocampal cortex selectively predicts associative memory performance (Ranganath et al., 2004).

The distinction between processes involved in these tasks is explained by the Dual-Process Theory (Yonelinas, 2002). This theory posits that there are two functionally and neurally distinct processes involved in recognition. The first is familiarity whereby an individual feels that they have previously encountered the specific stimulus without any additional information. The second is recollection where stimulus is remembered along with contextual details. Arguably, item memory tasks can be solved using either of these processes while performance in associative memory tasks requires recollection. This means that impaired recollection will affect participants' performance in associative memory tasks but will not necessarily affect item memory tasks.

Available literature shows that associative memory is usually the first to decline in disorders affecting cognition such as Mild Cognitive Impairment (Chen & Chang, 2016), Dementia (McKhann et al., 2011) or Major Depressive Disorder (Fairhall et al., 2010). Associative memory decline is also one of the most prominent cognitive effects of normal ageing (Bender & Raz, 2012; Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000; Old & Naveh-Benjamin, 2008). The Associative Deficit Hypothesis ascribes this decline to age related loss in the ability to create and retrieve links between multiple units of information (Naveh-Benjamin, 2000). Indeed, studies using histological techniques in brains of deceased Covid-19 patients (Bayat et al., 2022) and animal models (Klein et al., 2021) found reduced neurogenesis in the hippocampus. Hence, given this relative greater vulnerability of associative memory in various circumstances, and findings of reduced neurogenesis in the hippocampus caused by Covid-19, we predict that mnemonic deficits caused by Covid-19 would have greater effect on associative (vs. item) memory.

The neural basis of memory for verbal (i.e., words) and nonverbal (e.g., pictures) stimuli has been relatively less investigated than the distinction between item and associative memory. This distinction, however, is particularly important as verbal difficulties have been reported among Long Covid symptoms (Miskowiak et al., 2022) and have been detected in people who have recovered from Covid-19 (Hampshire et al., 2021). Some studies aiming to investigate a potential neural distinction for verbal vs. pictorial memory do not report any differences between the two modalities. For example, a study which included data from 226 patients in a memory clinic, showed a positive correlation between bilateral hippocampal volumes for both verbal and nonverbal memory measures (Bonner-Jackson et al., 2015). Nevertheless, other studies showed a neural differentiation in encoding and retrieval processes for the two modalities of memoranda. For example, Kelley et al. (1998) reported left-lateralized activation in dorsal prefrontal cortex during the encoding of verbal stimuli and bilateral activation during pictorial object encoding. A similar pattern was found in medial temporal regions, with stronger left than right activation during word encoding and bilateral activation for pictorial object encoding (Kelley et al., 1998; Rosazza et al., 2009). Schloerscheidt and Rugg (1997) studied event-related potentials (ERPs) during retrieval of verbal and pictorial stimuli and

found differences between the modalities in the frontally distributed signals but not in temporo-parietally distributed signals (Schloerscheidt & Rugg, 1997). Galli and Otten (2011) have also found a difference between ERP scalp distribution for verbal and pictorial stimuli during retrieval in an associative memory task. Namely, ERPs for pictures (faces and objects) showed a more frontal scalp distribution, while both pictures and words elicited activity over left posterior scalp sites (Galli & Otten, 2011). As verbal difficulties have been reported by Long Covid patients (Miskowiak et al., 2022), it is possible that these difficulties underline previous findings of effect of Covid-19 on verbal item memory (Guo et al., 2022b). Taken together, it is apparent that both memory type and stimulus type are important factors to be considered when examining specific mnemonic outcomes of Covid-19 infection.

Studies focusing on the impact of vaccination on Long Covid incidence and cognitive symptoms have so far shown mixed results. A study using Israeli healthcare services data found no difference in concentration and memory impairment as indicated by the primary care physicians in vaccinated and unvaccinated individuals who have undergone SARS-CoV-2 infection (Mizrahi et al., 2023). Other studies reported reduced risk of Long Covid symptoms, including cognitive symptoms or neurological symptoms, in those who were vaccinated prior to infection (Al-Aly et al., 2022; Ayoubkhani et al., 2022). Additionally, a recent meta-analysis looked at risk factors associated with development of Long Covid symptoms overall. Out of their sample, 4 studies including 249,788 patients examined the effect of vaccination status and found that those who had been vaccinated with 2 doses had 40% lower risk of developing Long Covid (Tsampasian et al., 2023). However, to the best of our knowledge, there are no studies that looked at the protective effect of vaccination using cognitive tasks rather than other measures (i.e., self-reported cognitive symptoms or diagnosis from primary care physician) to measure cognitive performance. It is of note that even if vaccination does not offer individual protection against Long Covid, it could still lower the Long Covid incidence on population level through lowering the rates of transmission of the SARS-CoV-2.

In the current study we aim to extend published literature on the association between SARS-CoV-2 infection and cognition. A previous study (Guo et al., 2022b) has shown that there was an effect of infection status on memory. Our primary aim is to extend this result. We will use an improved design which allows us to replicate the previous effect obtained by Guo et al. (2022b), but to further disentangle the effect of infection status on various components of long-term memory, namely, memory type (item vs. associative) and stimulus type (verbal vs. non-verbal). To this end we will analyse data from a modified version of the Guo et al. (2022b) study, which includes verbal and nonverbal versions of both item and associative memory task, collected online from a new cohort of participants. Second, we aim to evaluate whether vaccination status affects the severity of cognitive symptoms using a number of different cognitive tasks. We will do this by comparing performance on

cognitive tasks of fully vaccinated participants (at least 2 vaccine doses prior to date of infection) against those who were not vaccinated prior to infection.

Methods

Participants

The data is being collected by members of the Cambridge Cognition and Motivated Behaviour Lab (CambLab) as part of the Covid and Cognition study ("CovCog"). This multi-cohort longitudinal study has published early findings (Guo et al., 2022a; 2022b) with their first cohort. This work will concentrate on the new cohort. In total, 430 participants have taken part in the study. After excluding duplicates, unfinished questionnaire entries, participants unsure of their Covid status and participants who have not completed at least the two memory tasks that our analysis mainly focuses on, there are 325 remaining participants in the sample (COVID group N=232, No COVID group N=93). Compared to the previously published study, the new dataset includes additional tasks and measures as well as more detailed information about the vaccination status of the participants (details below).

The general aim of establishing this cohort was to study the effect of Covid-19 on cognitive function in adults. The term Long Covid is in connection with the sample referring to those who had confirmed Covid-19 diagnosis in the past and are experiencing lasting symptoms. A medical diagnosis of Long Covid was not a requirement to take part in the study. Compared to the previously published study, the new dataset includes additional tasks and measures as well as more detailed information about the vaccination status of the participants (details below).

Participants were recruited through word of mouth, social media platforms such as Long COVID Facebook support groups, from Addenbrooke's Hospital Long Covid clinic, and the Prolific recruitment site (https://www.prolific.co/) through majority English-speaking countries (UK, US, Ireland, Canada, Australia, New Zealand, South Africa). Recruitment ran between February 2022 and May 2023.

The study received Ethical approval from the University of Cambridge Department of Psychology Ethics Committee (PRE.2020.106, 8/9/2020) and from the NHS South Central – Hampshire B Research Ethics Committee (21/SC/0258, 1/02/2022).

Sampling plan

The effect size from the memory factor detected in Guo et al., (2022b) translates to Cohen's F of 0.19 (partial eta square = 0.03). Based on this effect size, power simulations with Bayes Factor (BF) of 6, repeated over 1,000 iterations, indicated that with 320 in total, and with group numbers imbalance proportional to the one in our data we should be able to detect a positive (one-tailed) result in 79% of

iterations (equivalent to power of 0.79). Our simulations further suggested that we should be able to detect a true null effect in 75% of the iterations. Thus, overall, the expected sample is sufficiently powered to detect the predicted memory effect, and to provide evidence for the null hypothesis.

The simulations were done using the Bayesian t test.

Study design

The cohort is comprised of a mix of longitudinal and cross-sectional data. The preregistration applies only to the cross-sectional data at the baseline timepoint, since the collection of follow-up data is still ongoing. All data were collected using the online platform Gorilla (www.gorilla.sc) which is a research tool used for designing and running tasks and experiments.

Participants are first presented with information about the study and then complete the consent form. Informed consent to use anonymised data is obtained from participants prior to testing. In addition to the cognitive tasks (described below), the testing session consists of a questionnaire covering demographics, medical history, and experience of Covid-19 (see below for more details). Altogether, the testing session takes about 1 hour to complete. At the end of the first testing session, participants are asked about their willingness to be contacted for a follow-up testing. Those who indicate their willingness to be contacted again will be sent a link to an online follow-up questionnaire at approximately 6-weeks after the completion of the first session. If participants had Covid-19 infection within less than 3 weeks prior to testing, the testing is interrupted, and they are contacted to take part at later point.

Measures

Questionnaires

A questionnaire was used to collect data on demographics (including sex, age, education, country of residence, region and ethnicity), experience of Covid-19 (e.g. infection status, number of times the individual had Covid-19, severity of illness for each, symptoms, including cognitive, during the first 3 weeks after infection, following the first 3 weeks after infection, and in the past 1-2 days) and other medical history (including height, weight, medical history, and health-related behaviours).

Participants were also asked about their vaccination status, including: number of doses, time since the most recent vaccine dose, type of vaccine received upon each dose, and the timing of Covid-19 infection (if any) relative to the vaccination. The specific questions concerning vaccination can be found in Appendix A.

Cognitive tasks

Overall, participants complete 6 cognitive tasks. For the purpose of the current study, we will focus mainly on the long-term memory tasks (i.e., the verbal and non-verbal memory tasks described below). Nevertheless, for completeness and in order to provide more context, data from the other tasks (i.e., Digit Span, Category Fluency, Word/Syntax Understanding, and Wisconsin Card Sorting) will also be analysed. To ensure participants are able to perform all cognitive tasks, practice trials are included prior to the start of a given task. Size of the stimuli varied depending on participants' device screen size. Using phone screen for the task has been prevented in the task settings.

Long-term Memory Tasks. Participants are tested on item and associative memory using both verbal and non-verbal task. The procedures of the memory tasks are depicted in Figure 1. In the non-verbal task, during an initial encoding phase, participants are asked to memorise 16 picture pairs comprised of a food item and a stationery item. Each pair is presented for 3 seconds followed by a fixation cross for 0.5 seconds. The recognition phase starts immediately after the encoding phase is completed, and includes an item recognition task and an associative recognition task. During the item recognition task participants are presented with 16 picture pairs comprised of one old item and one novel item and are asked 'Which item have you seen before?'. Participants have unlimited time to answer by either clicking on one of the items or on a button with an 'I don't know' option. All trials of the item recognition tasks are completed before the associative recognition task starts. In this task, participants are presented with one target item out of the 16 original pairs and 9 forced choice items. They are then asked 'Which of these was shown/paired with [target item].' Within the 9 forced choice options, there is one correct item (original pair-associate), 5 old but not associated items and 3 items that were not presented during the encoding phase. Additionally, there is also an "I don't know" option. For both recognition tasks, the dependent variables are the percentage of correct responses and overall reaction time.

The verbal memory task follows the same procedure as the non-verbal memory task. However, instead of pictures, participants are asked to memorise 16 word pairs comprised of an household item and an animal. Here too, the dependent variables for both recognition tasks are the percentage of correct responses and overall reaction time.

Digit Span task. This task is used to assess working memory. Participants are played an audio recording of a list of numbers and asked to repeat them back in order. There are in total 8 recordings, two for each list length of 3 digits, 5 digits, 7 digits and 9 digits, played in this order. Participants are asked to respond directly after each list. For this task, the dependent variable is the number of lists accurately recalled and maximum span size.

Category Fluency Task. This task assesses access to semantic knowledge of category membership. Participants are given the category 'Animals' and have to name out loud as many animals as they can

in 60 seconds. In contrast to previous (Guo et al., 2022b, 2022a) study, the participants do not type their answers but instead their verbal responses are audio recorded and later manually coded. The dependent variable is the number of correct responses excluding repetitions.

Word/Syntax Understanding Task. This task is used to assess linguistic understanding. In this task, participants hear a short descriptive sentence and have to pick one picture out of four options which best illustrated the content of the sentence. If participants do not respond, they are automatically moved to next trial after 8 seconds. There are 72 trials in total, with a break in the middle. The dependent variable is overall reaction time and percentage of correct responses.

Wisconsin Card Sort Task (WCST). This task assesses executive function, namely task switching and inhibition. Participants are instructed to match one target card to one of four other cards based on colour, shape or number of symbols. They are not told the matching rule, instead they have to infer it from the feedback given on their choices. There is no time limit for the response. There are 64 trials in total. Every few trials the rule changes and participants have to infer the new rule. The dependent variables are the total number of correct responses and the overall reaction time.

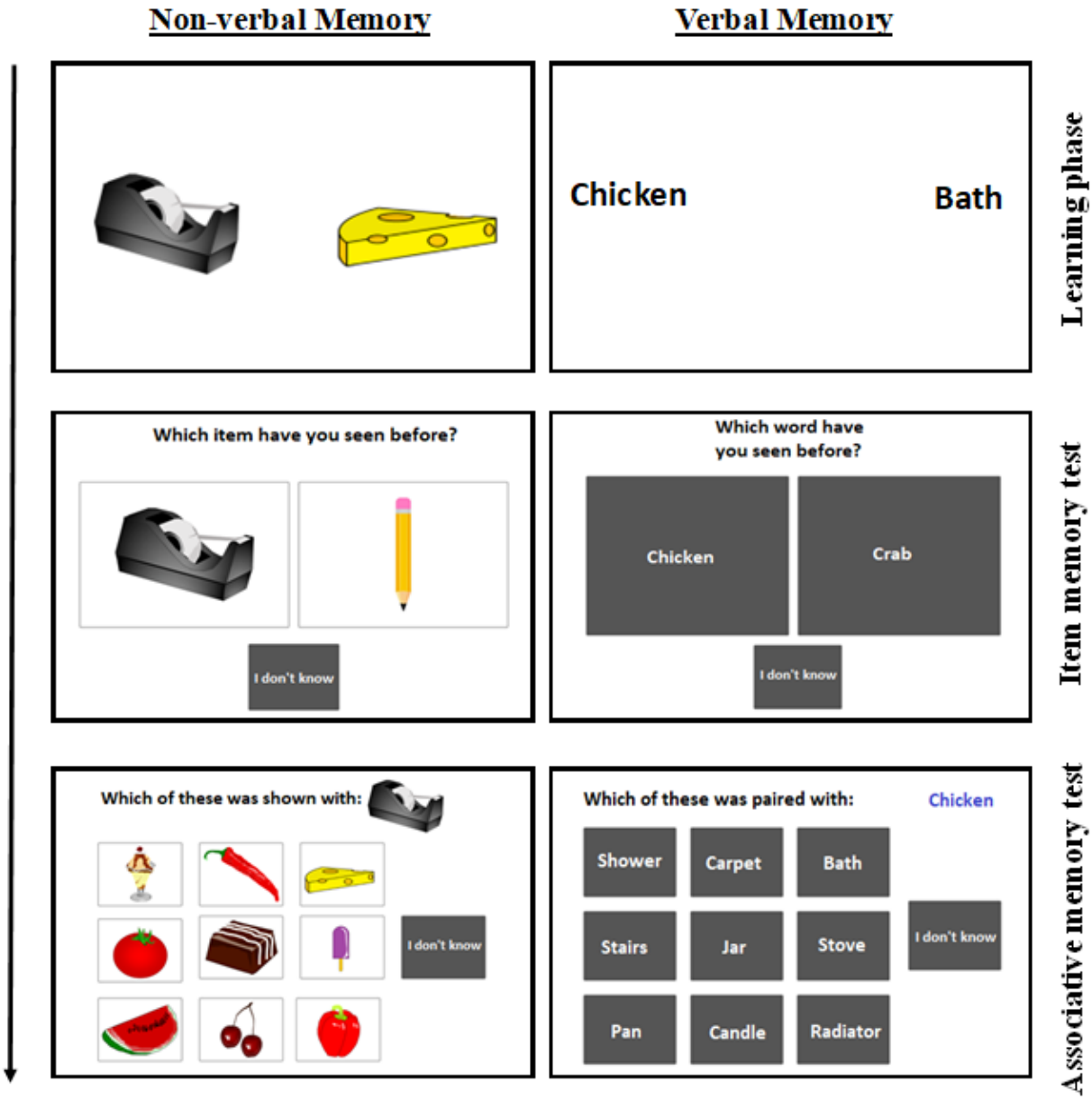

Figure 1 The procedure of the Non-verbal and Verbal Memory task. Participants are first presented with the nonverbal task and then the verbal task. Within each task, participants are first presented with all the pairs (17 picture pairs in nonverbal and 16 word pairs in verbal memory task), then all the trials of the item memory test (16 trials in both nonverbal and verbal memory task) and lastly all the trials of the associative memory test (16 trials in both nonverbal and verbal memory task).

Predictions and Analysis Plan

Exclusion criteria

We will exclude anyone who reported: having a diagnosis affecting cognitive functioning (including, e.g., schizophrenia, bipolar disorder, epilepsy etc.), having a neurodegenerative disorder (e.g., dementia, Alzheimer's disease), having another condition affecting cognitive performance, or being in recovery from non-covid related serious illness or medical procedure (e.g., chemotherapy, organ

transplant, etc.) in the last 6 months. Otherwise, all participants who have completed the full set of memory tasks will be included.

Group definition

For the purpose of the analysis, participants' Covid status will be established based on their answer to the question "Q3.01 Have you had Covid-19?" (see appendix A for exact answer). Participants unsure of their Covid status will be excluded from the analysis ("unsure" is defined as answering "Yes" based solely on symptoms or symptoms of close contacts, or answering "No" but reporting experiencing symptoms). Otherwise, if they answer "Yes with positive PCR test", "Yes with positive Lateral Flow Test", or "Yes, no test", they will be assigned to the COVID group for analysis. If they answer any of the "No" answers, they will be grouped in the No-COVID group.

For the analysis looking at vaccination status, we will consider as fully vaccinated those participants who have received at least 2 doses of vaccine (or one dose if vaccinated by a one dose vaccine type) at least 3 weeks prior to infection onset. This is to ensure the 14 days delay recommended by the Centers for Disease Control and Prevention (CDC).

Analyses 1 and 2: Replication of Guo et al., 2022b

These analyses correspond to research question Q1 in the Study Design Table in Appendix B. The analysis in Guo et al. (2022b) revealed a significant association between Covid-19 status and memory performance, expressed as reduced accuracy and longer reaction times for participants who were previously infected by Covid-19. Based on these results, we predict that the No-COVID group will demonstrate higher accuracy compared to the COVID group in both the Word List Item Memory and Pictorial Associative Memory tasks. To test this hypothesis, we will conduct a direct replication using two separate ANCOVAs (as was done by Guo et al.,2022b). The first analysis will include group (COVID, No-COVID) as the independent measure, with age, sex, country, and education level as covariates, and accuracy in the Word List Item Memory task as the dependent measure. The second analysis will follow the same design, but with accuracy in the Pictorial Associative Memory task as the dependent measure.

Similarly, we predict that the No-COVID group will demonstrate faster reaction times compared to the COVID group in both the Word List Item Memory and Pictorial Associative Memory tasks. We will test this in the same way as above but with reaction times in the Word List Item Memory task and in the Pictorial Associative task as the dependent measures in the two ANCOVAs.

Apart from this direct replication, we will run the same analysis using Bayesian ANCOVA with the same dependent variables and covariates to enable us to quantify evidence for the null in case our

predictions are not met. The Bayesian analysis will be performed in JASP (JASP Team, 2023) using the uniform prior (default setting in JASP) and the default setting of coefficient priors. The Bayes Factor > 6 will be used to infer conclusions for the alternative or the null hypothesis based on the Bayes Factor of the full model against a model that includes all factors apart from the effect of interest.

Analyses 3 and 4: Comparison of mnemonic effects:

These analyses correspond to research question Q2 in the Study Design Table in Appendix B. To test whether there are any differences in performance between the Word List Item Memory and Pictorial Associative Memory tasks, we will compare performance in these tasks directly. This analysis was not performed by Guo et al. However, previous research had shown that associative memory is often more susceptible than item memory. For example, associative memory shows greater reduction during healthy ageing (Old & Naveh-Benjamin, 2008), and is also more vulnerable than item memory in clinical populations, such as in patients with Mild Cognitive Impairment (Chen & Chang, 2016), dementia (McKhann et al., 2011), or Major Depressive Disorder (Fairhall et al., 2010). Additionally, multiple studies of brains of deceased Covid-19 patients as well as animal models report reduced neurogenesis in brain areas that are implicated in associative memory (Bayat et al., 2022; Klein et al., 2021). Therefore, we predict greater influence of Covid status on associative memory vs. item memory.

To allow direct comparison of mnemonic effects, dependent measures (accuracy and reaction times in both tasks) will be normalised using z-scores. First, we will run a 2-way Bayesian ANCOVA with group and task as factors, task accuracy as dependent variable, and age, sex, country, and education level as covariates. We predict that there will be an evidence for interaction between group (COVID, No-COVID) and task (Word Item, Pictorial Associative), with a greater decrease in accuracy observed in the Pictorial Associative Task for the COVID group compared to the No-COVID group.

Second, we will run the same analysis using reaction times as the dependent measure. We will run a 2-way Bayesian ANCOVA with group and task as factors, and age, sex, country, and education level as covariates. We predict that there will be an evidence for interaction between group and task, with a greater increase in reaction times observed in the Pictorial Associative task for the COVID group compared to the No-COVID group.

Analysis 5: Disentangling memory effects.

These analyses correspond to research question Q3 in the Study Design Table in Appendix B. In comparison to the previous data published by Guo et al., the current design includes additional tasks involving verbal associative memory and nonverbal item memory. To investigate whether the results

of the original study were influenced by the type of memory or type of stimulus, the following analysis will be conducted on normalised values (accuracy and reaction times; in two separate models). We will employ a 3-way Bayesian ANCOVA with group as a between-subject factor (COVID, No-COVID), and memory type (item, associative) and stimulus type (verbal, pictorial) as within-subject factors. Covariates will include age, sex, country, and education level.

First, we predict there will be a main effect of group, with better memory performance (higher accuracy rates and lower reaction times) expected for the COVID group compared to the No-COVID group. Second, as detailed above (Analyses 3 and 4) we expect to see an interaction between memory type and covid status, with better associative memory performance for the No-COVID group compared to the COVID group, but less difference in item memory performance. Third, we are interested in whether there will be an interaction between stimulus type (verbal, non-verbal) and covid status. Currently, we are only aware of one study of Long Covid patients in which specific verbal deficits were reported (Miskowiak et al., 2022). However, as this study did not include a direct comparison between verbal and pictorial stimuli, we believe that it does not form a firm ground for any strong predictions. We therefore do not have any predictions regarding potential interactions with stimulus type, and consider any results concerning this factor to be exploratory.

Analyses 6 and 7: Effect of vaccination.

These analyses correspond to the research question Q4 in the Study Design Table in Appendix B. In light of the conflicting evidence regarding the protective effect of vaccines against cognitive symptoms of Long Covid, at current we cannot make any strong predictions regarding the effect of vaccination on cognitive function.

For this analysis, we will compare a subgroup of participants who have experienced Covid-19 infection only once. This is to avoid the effect of multiple exposures to Covid-19 with different vaccination status. In the first analysis, these participants will be divided into those who have received two doses of vaccination (or one dose if vaccinated by one dose vaccine type) at least 2 weeks before the infection, and those that have not been vaccinated prior to infection (but could have been vaccinated since).

A one-way Bayesian ANCOVA will be conducted with vaccination group (Vaccinated, Not-vaccinated) as between-subject factors, and accuracy and RTs for each cognitive task analysed separately as dependent variables. Covariates, including age, sex, country, and education level, will be included in the analysis. The second analysis will also include participants who have had 3 doses of vaccine in the vaccination group. The analysis will be the same as above.

Additional analyses

For completeness, we will also analyse the association between Covid status and other cognitive tasks' scores. To do this, each tasks' dependent measures (detailed above, see tasks description) will be analysed using a one-way Bayesian ANCOVA with Covid group (COVID, No-COVID) as between subject factor and accuracy scores and reaction times separately as dependent variables. Age, sex, country and education level will be included in the model as covariates. This will be done for all of the remaining cognitive tasks. We do not have specific predictions for these analyses and results will therefore be exploratory.

Code availability

The code for data analysis and pre-processing will be made available at Stage 2 submission.

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Appendix A.

Q3.01: Have you had COVID-19:

1. Yes (I had a positive PCR test)
2. Yes I think so (positive Rapid (Lateral Flow) test, but no/unclear PCR test)
3. Yes I think so (but no test)
4. No (I don't think so)
5. No (and I have had a recent negative *antibody* test)

Q3.01.1: Have you had the COVID-19 Vaccine?

1. Yes
2. No

Q3.01.2: How many doses (including booster, if any) of the COVID-19 vaccine have you received?

1. 1
2. 2
3. 3 (dose or booster)
4. 4 or more (Please specify the total number of doses)

Q3.01.3: When did you receive your most recent dose of the COVID-19 Vaccine?

1. Within the last 7 days
2. Within the last 14 days
3. Within the last month
4. Within the last 3 months
5. Within the last 6 months
6. Over 6 months ago

Q3.01.4: Which COVID-19 vaccine did you receive as your FIRST dose?
Q3.01.5: Which COVID-19 vaccine did you receive as your SECOND dose?
Q3.01.6: Which COVID-19 vaccine did you receive as your THIRD dose?

1. Pfizer (BNT162b2)
2. Moderna COVID-19 Vaccine (mRNA-1273)
3. COVID-19 Vaccine AstraZeneca (AZD1222)
4. Johnson & Johnson's Janssen (JNJ-78436735)
5. CoronaVac (Sinovac)
6. Sputnik V (Gamaleya Research Institute - Russia)
7. BBIBP-CorV (Beijing Institute of Biological Products)
8. EpiVacCorona (Federal Budgetary Research Institution State Research Center of Virology and Biotechnology - Russia)
9. Covaxin (Bharat Biotech - India)
10. Not sure
11. Other (none of the above), please specify: (Text box)

Q3.05.2: At which point had you had *test-confirmed* COVID-19? (If you had COVID-19 more than once, tick all that apply)

1. before I was vaccinated
2. after I had had 1 dose for less than 3 weeks
3. after I had had 1 dose for more than 3 weeks (but before second dose)

4. after I had had 2 doses for less than 3 weeks
5. after I had had 2 doses for more than 3 weeks (but before third dose)
6. after I had had 3 doses for less than 3 weeks
7. after I had had the 3 doses for more than 3 weeks
8. Not applicable – I have not had any vaccination
9. If you had COVID at other time points (e.g. after you had had 4 doses), please specify

(Q3.05.3:) I never had test confirmation for the infection, but I think I had COVID-19…

1. before I was vaccinated
2. after I had had 1 dose for less than 3 weeks
3. after I had had 1 dose for more than 3 weeks (but before second dose)
4. after I had had 2 doses for less than 3 weeks
5. after I had had 2 doses for more than 3 weeks (but before third dose)
6. after I had had 3 doses for less than 3 weeks
7. after I had had the 3 doses for more than 3 weeks
8. Not applicable – I have not had any vaccination
9. If you had COVID at other time points (e.g. after you had had 4 doses), please specify

Q3.06: How many times do you think you have had COVID-19?

1. 1
2. 2
3. 3
4. 4 or more

Q3.06.1: Please give the approximate date of each infection

1. 1st infection

If you have more than 1 infection, please also indicate the date of other infections (DD/MM/YYYY):

2. 2nd infection
3. 3rd infection
4. 4th infection…

Appendix B.

Table 1 Study design table

Question	Hypothesis	Sampling plan	Analysis Plan	Rationale for deciding the sensitivity of the test for confirming or disconfirming the hypothesis	Interpretation given different outcomes	Theory that could be shown wrong by the outcomes
Q1: Is there an effect of Covid status on item and associative memory? (replication)	H1a: No-COVID group will demonstrate better performance compared to COVID group on verbal item memory task. H1b: No-COVID group will demonstrate faster RTs compared to COVID group on verbal item memory task. H1c:No-COVID group will demonstrate better performance compared to COVID group on nonverbal associative memory task. H1d: No-COVID group will demonstrate faster RTs compared to COVID group on nonverbal associative memory task.	Participants who have been tested as part of the Wave 2 of COVCOG study will be divided into those who had Covid-19 and those who did not. These are secondary data analyses. As such we could not have influenced the number of participants being collected. In total 430 participants have taken part in the study. After excluding duplicates, unfinished questionnaire entries, participants who have not completed at least the two memory tasks our analysis mainly focuses on, and those unsure about their Covid status, there is 325 remaining participants in the sample (COVID group N=232, NoCOVID group N=93).	For the direct replication, we will use ANCOVA with Covid status as independent between subjects measure, accuracy and RTs on the two tasks separately as dependent variable and age, sex, country and education as covariates. We will also run the same analysis using the Bayesian variant of ANCOVA.	Analysing the data both as direct replication and also with bayesian alternative should give us the ability to quantify evidence for the null in case the predicted results are not obtained. The effect size from the memory factor detected in the original study translates to Cohen's F of 0.19 (partial eta square = 0.03). Based on this effect size, power simulations with Bayes Factor (BF) of 6, repeated over 1,000 iterations, indicated that with 320 participants in total and with group imbalance proportional to that of our sample, we should be able to detect a positive (one-tailed) result in 79% of iterations (equivalent to power of 0.79). Our simulations further suggested that we should be able to detect a true null effect in 75% of the iterations. Thus, overall, the expected sample is sufficiently powered to detect the predicted memory effect, and to provide evidence for the null hypothesis.	Conclusive evidence for the alternative hypothesis (i.e., support for H1) would replicate the findings in Guo et al. (2022). BF>6 will be interpreted as sufficient evidence in favor of the alternative hypothesis of better memory performance in the COVID vs. No-COVID group. BF<1/6 will be interpreted as evidence for the null hypothesis of no difference between the groups. Any other result will be interpreted as inconclusive. If evidence is found for any of the hypotheses H1a-d, we will conclude that memory has been affected.	Covid-19 affects item and associative memory.
Q2: Is nonverbal associative memory more affected by Covid status than verbal item memory?	We predict greater influence of Covid status on associative memory vs. item memory. In particular we predict H2a: There will be an interaction between covid status and memory type, with better associative memory accuracy for the No-Covid group compared to Covid group, but less difference in item memory. H2b: There will be an interaction between covid status and memory type, with faster associative memory RTs for the No-Covid group compared to Covid group, but less difference in item memory.	These are secondary data analyses. As such we could not have influenced the number of participants being collected. In total 430 participants have taken part in the study. After excluding duplicates, unfinished questionnaire entries, participants who have not completed at least the two memory tasks our analysis mainly focuses on, and those unsure about their Covid status, there is 325 remaining participants in the sample (COVID group N=232, NoCOVID group N=93).	Both of the analyses will be run on normalised values. First, we will run a 2-way Bayesian ANCOVA with group and task as factors, task accuracy as dependent variable, and age, sex, country, and education level as covariates. Second, we will run the same analysis using reaction times as the dependent variable..	The main purpose of our sampling plan was to show that with the expected sample size, we are able to detect an overall effect of COVID group on memory performance (Q1). Once this overall effect is established, we can test whether it is further modulated by other factors (i.e., the specific memory type). We do not have an estimation regarding the effect size for a group X memory type interaction, but as shown above, with the expected sample size we should be able to gather sufficient evidence for a small-to-medium-sized effect, as well as for a null effect.	BF>6 will be interpreted as evidence for the alternative hypothesis of greater memory impairment for associative vs. item memory in the COVID vs. No-COVID group. BF<1/6 will be interpreted as evidence for the null hypothesis. Any other result will be interpreted as inconclusive. Any evidence for either alternative hypothesis will be taken as support for associative memory being more affected. In the unlikely case of discrepancy between the measures (e.g, lower RTs for item memory, but increased accuracy for associative memory) we will treat the results as inconclusive.	Covid-19 preferentially affects associative memory.
Q3: Is the previously observed effect on long-term memory arising due to the type of memory or the type of stimulus?	The notation H3a and H3b refer to the predictions as described here for accuracy and RTs as the dependent variables within the model respectively. First, we predict there will be a main effect of group, with better memory performance expected for the No-COVID group compared to the COVID group. Second, as detailed above (Q2) we expect to see an interaction between memory type and covid status, with better associative memory performance for the No-COVID group compared to the COVID group, but less difference in item memory performance. Third, we are interested in whether there will be a an interaction between stimulus type (verbal, non-verbal) and covid status, though we do not have any specific predictions regarding this aspect of the analysis.	Same as above	We will employ a 3-way Bayesian ANCOVA with group as a between-subject factor (COVID, No-COVID), and memory type (item, associative) and stimulus type (verbal, pictorial) as within-subject factors. Covariates will include age, sex, country, and education level.	Same as above	BF>6 will be interpreted as evidence for the alternative hypothesis of interaction between the memory and/or stimulus type and the COVID vs. No-COVID group. BF<1/6 will be interpreted as evidence for the null hypothesis. Any other result will be interpreted as inconclusive. Any evidence for either alternative hypothesis will be taken as support for associative memory being more affected. In the unlikely case of discrepancy between the measures (e.g, lower RTs for item memory, but increased accuracy for associative memory) we will treat the results as inconclusive.	Same as above
Q4: Does vaccination affect the cognitive symptoms of Long Covid?	In light of the conflicting evidence regarding the protective effect of vaccines against cognitive symptoms of Long Covid, at current we cannot make any strong predictions regarding the effect of vaccination on performance in cognitive tasks.	The analyses will compare a subgroup of participants who have experienced Covid-19 infection only once. This is to avoid the effect of multiple exposure to Covid-19 with different vaccination status.	A Bayesian ANCOVA will be conducted with vaccination group (Vaccinated, Not Vaccinated) as a between-subject factor, and performance in each cognitive task analysed separately as dependent variables. Covariates, including age, sex, country, and education level, will be included in the analysis to control for potential confounding variables.	Based on data already collected, we estimate ~N=45 participants per group (vaccinated / not-vaccinated). We acknowledge that this sample size is underpowered to detect a small effect size (Cohen's D = 0.2; 8.3% power, or medium effect size (51.2%), but according to our simulations is well-powered to detect large effects (94%).	BF>6 will be interpreted evidence for the alternative hypothesis of greater cognitive impairment in the given cognitive area in the Not-Vaccinated vs. Vaccinated group. BF<1/6 will be interpreted as evidence for the null hypothesis. Any other result will be interpreted as inconclusive.	No established theory is currently available.