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Protective Effect of COVID-19 Vaccination on Post-Infection Visuospatial Deficits

Running title: COVID-19 Vaccination and Visuospatial Deficits

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Abstract

Objective: COVID-19 has been associated with persistent cognitive deficits months after SARS-CoV-2 infection. Vaccination reduces severe disease, but its effect on post-infection cognition remains uncertain. We evaluated whether COVID-19 vaccination attenuates cognitive deficits after SARS-CoV-2.
Methods: We assessed 237 adults with COVID-19 and 105 controls. Patients were grouped by vaccination status at infection (vaccinated n=87; unvaccinated n=150). The neuropsychological assessment covered language, visuospatial ability, visual memory, verbal memory, attention, executive functions, and working memory. Group differences were tested with Aligned Rank Transform ANOVA with Holm-corrected post hoc comparisons, adjusting for education.

Results: Significant group differences were observed in visuospatial ability and visual memory, assessed with the Rey-Osterrieth Complex Figure Test (Copy, Immediate and Delayed Recall) (all $p < 0.001$). The vaccinated group outperformed the unvaccinated group ($p = 0.022$) on visuospatial performance. The Rey-Osterrieth Complex Figure Test Copy did not differ significantly among participants vaccinated with CoronaVac, AstraZeneca, or Pfizer.
Conclusions: The findings suggest that COVID-19 vaccination may mitigate post-infection visuospatial deficits, reinforcing the importance of immunization in preventing cognitive sequelae associated with the disease.
Keywords: Neuropsychological Tests; Cognitive Dysfunction; Post-Acute COVID-19 Syndrome; SARS-CoV-2; Spatial Processing.

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Introduction

In May 2023, the World Health Organization[1] declared the end of COVID-19 pandemic, but many individuals are still affected by symptoms that persist after the initial infection, known as post-COVID conditions.[2] These post-COVID conditions have impacted on the quality of life of millions of people worldwide,[2] with symptoms that often impair individuals' ability to carry out daily functions.[3] Despite the wide variation in symptoms, cognitive deficits have frequently been associated with post-COVID conditions,[4] with alterations affecting different domains such as attention,[5] visuospatial processing,[6] memory, and executive functions.[7]

The mechanisms underlying post-COVID conditions are still under investigation, but several hypotheses have been proposed by recent studies, such as the persistence of viral reservoirs in human tissues[8] and the persistence of the inflammatory processes.[9] Cognitive symptoms appear to be associated with the excessive release of pro-inflammatory cytokines during infection,[10] which may contribute to neuronal tissue damage.

COVID-19 vaccination emerged in late 2020 as an effective strategy to reduce severe cases, hospitalizations, and deaths caused by the disease.[11] Recent studies have also highlighted its role in mitigating the long-term effects of infection.[12,13] Vaccination also appears to influence post-infection cognitive symptoms, with vaccinated individuals reporting fewer cognitive complaints compared to their unvaccinated counterparts.[13,14]

A large portion of studies on the effect of vaccination on post-COVID conditions, however, rely on subjective measures, such as patients' self-reports of symptoms, which are clinically relevant for capturing perceived cognitive difficulties, such as brain fog, although they may also be influenced by perceptual factors.[15] The perception of cognitive difficulties may also be influenced by contextual and psychological factors. The use of objective measures, such as neuropsychological assessment, can help reduce the influence of perception biases on symptom reporting. However, this approach remains scarce in the scientific literature, with a shortage of data investigating the role of vaccination in post-COVID cognitive deficits through objective instruments, as highlighted by Winter and Braw (2022).[15]

Among the few studies that have investigated the role of vaccination in post-COVID cognitive deficits, the findings remain inconsistent, with no clear consensus in the literature. The studies vary in their methodologies, the instruments employed, and even in how a vaccinated individual is defined. Some studies, such as those by Elmazny et al. (2023)[14] and Zhang et al. (2022),[16] found no statistically significant differences between vaccinated and unvaccinated groups, although they used brief cognitive screening tools (the Montreal Cognitive Assessment and the Mini-Mental State Examination, respectively). In contrast, the study by Hampshire et al. (2024)[17] showed that individuals vaccinated with two doses exhibited a slight cognitive advantage compared to unvaccinated individuals. Despite its large sample of 112,964 participants, the online assessment conducted by Hampshire and colleagues did not cover cognitive functions that are known to be affected by COVID-19 infection, such as visuospatial processing.[6,18]

The present study, therefore, aims to address this gap in the current scientific literature by evaluating whether COVID-19 vaccination is associated with a reduction in cognitive deficits among infected individuals, using a comprehensive neuropsychological assessment.

Methods

Ethics statement

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE: 33768820.1.0000.5149) and adhered to the

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ethical principles of the Declaration of Helsinki, as well as Brazilian regulations for research involving human subjects. All participants provided informed consent, and data collection followed local health safety guidelines during the pandemic.

Design

Data collection for the clinical group was conducted in Belo Horizonte, Minas Gerais, between 2020 and 2023, during the COVID-19 pandemic. Recruitment was carried out with the support of the Center for Diagnostic Support Actions and Research (Núcleo de Ações e Pesquisa em Apoio Diagnóstico - NUPAD) at Federal University of Minas Gerais (Universidade Federal de Minas Gerais - UFMG), which provided a list of patients diagnosed with COVID-19 for invitation purposes. Neuropsychological assessments were conducted at the Center for Technology in Molecular Medicine at UFMG (Centro de Tecnologia em Medicina Molecular - CTMM) and at the Aimorés unit of the Hermes Pardini Laboratory. Data collection for the control group took place in the pre-pandemic period, between 2015 and 2016. The control group participants were recruited through a second project titled “Multidimensional Predictors of Everyday Cognitive Failures” and approved by the Research Ethics Committee of the Faculty of Medical Sciences of Minas Gerais (CAAE: 57378016.5.0000.5134). Both the clinical and control groups were convenience samples, with no additional randomization procedures.

The data were analyzed at the Laboratory for Teaching and Research in Neuropsychology (Labep_neuro), affiliated with the Federal University of Minas Gerais (UFMG). Vaccination information was recorded during in-person assessments, either through the presentation of a vaccination card or by consulting the *Conecte SUS* app. In cases where participants did not bring their vaccination card or did not have access to the app, they were asked to send a photo of the card via messaging applications.

All participants completed the study procedures in a single individual assessment session lasting approximately 60 minutes. After providing informed consent, participants underwent the neuropsychological assessment, during which participants in the clinical group also provided information regarding their vaccination status.

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Sample

The inclusion criteria for the clinical group were: confirmed SARS-CoV-2 diagnosis via RT-PCR test, age over 18 years, and a history of mild COVID-19 (levels 1 and 2 of the WHO clinical progression scale). All included participants had non-hospitalized infections and none required any form of respiratory support. In addition, no participant had experienced more than one SARS-CoV-2 infection before the neuropsychological assessment. Exclusion criteria included self-reported history of autoimmune diseases, past or current psychiatric disorders, neurological conditions, recurrent infections, substance abuse, central nervous system surgeries, and the need for intubation during treatment. The clinical group was subdivided according to vaccination status at the time of the SARS-CoV-2 infection. Vaccinated participants were those infected at least fourteen days after receiving two vaccine doses, whereas unvaccinated participants were those infected before receiving any vaccine dose. Participants infected between the first and second doses, or those who did not provide their vaccination card, were excluded. Participants were initially enrolled in the clinical cohort according to the eligibility criteria of the umbrella study. For the present analysis, they were subsequently classified according to vaccination status at the time of SARS-CoV-2 infection. Participants with unavailable vaccination data or whose infection occurred between the first and second vaccine doses were excluded from the present analyses.

In the control group, inclusion criteria were aged over 18 years and provision of written informed consent. Exclusion criteria also included severe sensory or motor deficits that could impair performance on the tasks, a history of psychotropic substance abuse, and a history of neurological disease and/or severe psychiatric disorders with potential impact on global cognitive status (e.g., stroke, epilepsy, developmental disorders, multiple learning disorders, and uncontrolled systemic diseases).

Neuropsychological Assessment

The neuropsychological assessment was conducted based on the protocol established by the umbrella research project entitled *Neuropsychiatric Manifestations and Sequelae of COVID-19: Clinical and Molecular Aspects (Manifestações e Sequelas Neuropsiquiátricas da COVID-19: Aspectos Clínicos*

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e Moleculares), to which this study is affiliated. The instruments used were previously validated for the Brazilian adult population and assessed language, visuospatial ability, visual and verbal memory, attention, executive functions, and working memory.

Examiners involved in both the study from which the control sample was drawn and the COVID-19 cohort study received standardized training from the same senior neuropsychologist, who supervised both projects. In both studies, the neuropsychological battery was administered individually in a quiet and private room, following the same test order, instructions, administration procedures, and scoring criteria. Although different examiners assessed the two cohorts, the assessment procedures were standardized across studies.

The neuropsychological tests were administered in the same standardized order for all participants: Verbal Fluency (Animals, Fruits, and Alternating), Rey-Osterrieth Complex Figure Test (Copy), Logical Memory (Immediate Recall), Rey-Osterrieth Complex Figure Test (Immediate Recall), Digit Span (Forward and Backward), Trail Making Test (A and B), Five-Point Test, Logical Memory (Delayed Recall), and Rey-Osterrieth Complex Figure Test (Delayed Recall).

To assess language, the Verbal Fluency Test (Animals, Fruits, and Alternating) was used, based on the original paradigm by Benton (1968)[19] and validated for the Brazilian population by de Paula, Paiva & Costa (2015).[20] Visuoconstructive ability was measured through the Rey-Osterrieth Complex Figure Test (ROCFT), originally developed by Rey (1941).[21] The Brazilian version validated by Oliveira & Rigoni (2014)[22] and the administration recommendations by Shin et al. (2006)[23] were followed. Verbal memory was assessed using the Logical Memory subtest from the Wechsler Memory Scale, originally developed by Wechsler (1945)[24] and adapted for Brazilian use by Nitrini et al. (2008).[25] Attention was evaluated through the Trail Making Test Part A (TMT-A), originally part of the Army Individual Test Battery by Reitan (1958)[26] and administered according to Bowie & Harvey (2006).[27] Executive functions were assessed using the Five-Point Test, initially developed by Regard et al. (1982),[28] and validated for the Brazilian population by Bartolomeu & Pessoto (2023),[29] as well as the Trail Making Test Part B (TMT-B). Finally, working memory was evaluated with the Digit Span subtest, originally from the

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Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955),[30] and adapted for the Brazilian population by Figueiredo & Nascimento (2007).[31]

Verbal Fluency Test: This test assesses verbal fluency processes, involving language skills and access to the semantic memory system. The version used comprised three stages. In the first stage, participants were asked to recall as many animals as possible within one minute. In the second stage, they were instructed to list fruits, also within one minute. The third and final stage required alternating between naming an animal and a fruit, again within one minute. This last stage allows for a more direct assessment of cognitive flexibility and working memory. Scoring was based on the total number of unique words produced in each condition.

Rey-Osterrieth Complex Figure Test (ROCFT): The test aims to assess visuospatial abilities, executive functions, and memory. In the copy trial, participants are shown a complex figure and asked to reproduce it. The recall trials, conducted without the presence of the stimulus, occurred at two intervals: immediate (three minutes after the copy) and delayed (thirty minutes after the copy). Items were scored using the conventional 0–2 scale.[32] Completion time was not recorded during the administration of the test.

Logical Memory Test: This test assesses immediate and delayed recall (25 to 30 minutes after presentation) of a short story read aloud to the participant. It evaluates episodic declarative memory, requiring the participant to recall the narrative details. Scoring is based on the amount of information accurately remembered from the story.

Trail Making Test (TMT): TMT is designed to assess visual search abilities, processing speed, mental flexibility, and executive functioning. The test is divided into two parts. In Part A, the participant is instructed to connect numbers in ascending order (1 to 25) as quickly as possible. In Part B, the task requires alternating between numbers (1 to 13) and letters (A to L) in sequence, also as quickly as possible. Both parts assess visuospatial attention, visual scanning, and psychomotor speed. Part B, specifically, is more strongly associated with executive functioning due to the requirement to alternate between numeric and alphabetic sequences. Scoring is based on the time, in seconds, taken to complete each part (A and B), which were scored separately.

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Five-Point Test: Aims to assess motor processes and the non-verbal component of fluency, an aspect associated with executive functioning. During the test, participants are asked to create distinct patterns by connecting two to five dots arranged within separate rectangles. Scoring is based on the number of unique designs produced within a timed period of three minutes.

Digit Span: This test evaluates working memory. Participants are asked to repeat a series of numbers that were read to them. Both the forward span (repeating the digits in the same order as presented) and the backward span (repeating the digits in reverse order) were administered.

Data modelling and statistical analysis

Each participant's score was converted to a z-score based on age-adjusted Brazilian normative data. Individuals who scored below 1.5 standard deviations (equivalent to the eighth percentile) were classified as "impaired", following commonly adopted criteria in the study of neurocognitive disorders.[33]

Subsequently, data normality was assessed using the Shapiro-Wilk test. Given the non-normal distribution of the variables, the Aligned Rank Transform ANOVA (ART) was used to identify which cognitive domains differed among the groups. Performance on each neuropsychological measure was compared between male and female participants using the Mann-Whitney test, while the association between education and performance on each measure was examined using ART-ANOVA. Education was included as a covariate in the comparative analyses between groups.

In cases where significant differences were observed, Holm's post-hoc test was performed to identify the specific group differences. As a sensitivity analysis, outcomes showing significant group effects in the primary analyses were additionally examined using permutation-based ANCOVA, with age and years of education entered as continuous covariates. Permutation tests were performed using the Freedman-Lane procedure with 50,000 permutations. For outcomes with a significant omnibus group effect, pairwise comparisons were performed using permutation-based marginal tests, with p-values adjusted using Holm's procedure. Finally, an additional ART-ANOVA was conducted to investigate the potential effect of different vaccine manufacturers on neuropsychological performance.

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All statistical analyses were performed using R software (version 4.4.2),[34] with the packages ARTool, effectsize, emmeans, permuco, and tidyverse.

Results

Data collection resulted in a total of 280 participants with confirmed COVID-19 diagnoses. The average interval between diagnosis and study inclusion was 4.71 months (±3.09), and the mean age of participants was 38 years (±10.3). The majority were female (73%) and had a high level of education (16.63 ± 3.35 years of formal education). A total of 43 participants were excluded from the analysis: 34 because vaccination data were unavailable and 9 because SARS-CoV-2 infection occurred between the first and second vaccine doses. Their mean age was 38.02 years (±11.02), their mean educational attainment was 15.71 years (±3.76) and 54.8% were female.

The control database comprised 139 participants. Of these, 34 were excluded because of protocol administration errors or incomplete neuropsychological data, resulting in a final control sample of 105 participants.

Figure 1 shows the flowchart of recruitment and corresponding sample stratification.

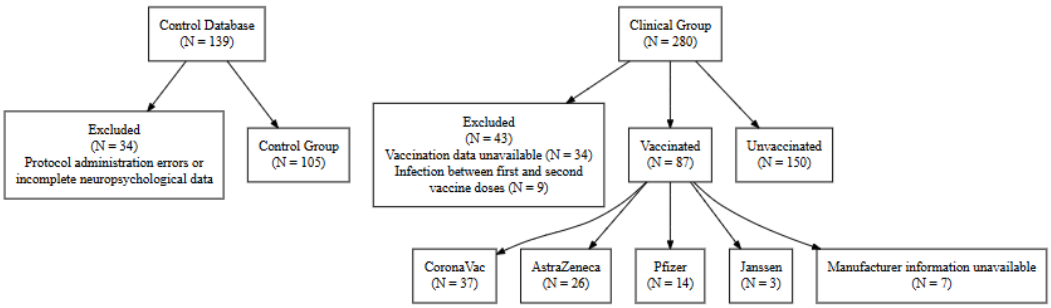


Figure 1. Flowchart of participant recruitment and stratification.

Table 1 presents the descriptive characteristics of the sample, stratified according to vaccination status at the time of infection.

Table 1. Descriptive characteristics of the sample

Group	N	Age (years)	Female (%)	Education (years)
Unvaccinated	150	38.11 ± 9.82	73	16.22 ± 3.54
Vaccinated	87	40.33 ± 10.99	79	17.2 ± 2.84
Control	105	29.18 ± 10.75	73	13.71 ± 3.29

Note. Values are presented as mean ± standard deviation (SD).

Among the 150 participants classified as unvaccinated at the time of infection, 125 were infected before the national vaccination campaign, when COVID-19 vaccines were not yet available. The other 25 participants were infected after the vaccination campaign had begun. Although they had not received any vaccine dose at the time of infection, all were subsequently vaccinated.

Among the 87 participants in the vaccinated group, 41 (47.1%) had received two vaccine doses, 42 (48.3%) had received three doses, and four (4.6%) had received four doses before SARS-CoV-2 infection. In the vaccinated group, most participants received the Coronavac vaccine (43%), followed by AstraZeneca (30%), Pfizer (16%), and Janssen (3%). Vaccine manufacturer data were not recorded for 8% of participants.

The normality of the neuropsychological test scores was assessed using the Shapiro-Wilk test (S-W). The results indicated that most variables (10 out of 13 measures) did not follow a normal distribution (S-W(342), $p < 0.001$), thereby justifying the use of nonparametric analyses. Comparisons of neuropsychological performance between male and female participants showed no significant differences for most measures, except for Verbal Fluency Animals ($p = 0.020$) and Verbal Fluency Fruits ($p < 0.001$). Education, in turn, was

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significantly associated across all administered tests ($p < 0.05$), and was subsequently included in the group comparisons analyses.

To investigate group differences (control, vaccinated, and unvaccinated) while controlling for education, an Aligned Rank Transform ANOVA (ART) was conducted, which is suitable for nonparametric analyses with covariates.[35] Effect sizes were calculated using partial eta squared (η^2), based on the ratio of the sum of squares for the effect of interest to the total sum of squares (effect + residual). However, as the ART involves data transformation through aligned ranks, the interpretation of effect size magnitudes should be approached with caution. These values are no longer on the original measurement scale and should be interpreted primarily in comparative terms. This methodological approach follows the recommendations provided by the author of the ARTool package.[36]

The results indicated statistically significant differences between groups in the Rey-Osterrieth Complex Figure test, both in the copy phase ($F = 61.90$, $p < 0.001$, $\eta^2 = 0.30$), immediate recall ($F = 13.08$, $p < 0.001$, $\eta^2 = 0.08$), and delayed recall ($F = 14.45$, $p < 0.001$, $\eta^2 = 0.09$). Additionally, performance on the Backward Digit Span test also differed significantly between groups ($F = 6.15$, $p = 0.002$, $\eta^2 = 0.04$). The results are presented in Table 2.

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Table 2 - Neuropsychological Test Performance by Group and Between-Group Comparisons

	Control	Unvaccinated	Vaccinated			
Test	**M (SD)**	**M (SD)**	**M (SD)**	**F**	**p**	**η^2 [IC 95%]**
Verbal Fluency (Animals)	-0.122 (0.976)	0.015 (0.81)	0.048 (0.785)	1.83	0.160	0.01 [0.00; 1.00]
Verbal Fluency (Fruits)	-0.052 (0.892)	0.144 (0.867)	0.092 (0.839)	1.61	0.201	0.01 [0.00; 1.00]
Switching fluency (pairs)	0.098 (0.8)	0.235 (0.765)	0.108 (0.748)	1.26	0.284	0.01 [0.00; 1.00]
ROCFT - Copy	0.497 (0.723)	-0.762 (1.279)	-0.369 (1.211)	61.90	< **0.001**	0.30 [0.23; 1.00]
ROCFT - IR	0.592 (1.02)	-0.057 (0.933)	0.214 (1.024)	13.08	< **0.001**	0.08 [0.04; 1.00]
ROCFT - DR	0.568 (0.962)	-0.087 (0.911)	0.167 (1.036)	14.45	< **0.001**	0.09 [0.04; 1.00]
Logical Memory - IR	-0.01 (0.99)	0.089 (1.107)	0.343 (0.929)	1.64	0.196	0.02 [0.00; 1.00]
Logical Memory - DR	-0.002 (0.987)	0.064 (1.013)	0.344 (0.909)	1.69	0.185	0.02 [0.00; 1.00]
Digit Span Forward	0.593 (0.87)	0.664 (1.048)	0.62 (1.052)	0.04	0.962	0.00 [0.00; 1.00]

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Digit Span Backward	0.162 (0.797)	0.519 (0.945)	0.557 (0.907)	6.15	**0.002**	0.04 [0.01; 1.00]
Five Point Test (unique)	-0.447 (1.201)	-0.529 (1.149)	-0.275 (1.155)	0.48	0.615	0.01 [0.00; 1.00]
Trail Making Test A	-0.079 (1.103)	-0.154 (1.203)	0.324 (0.887)	2.15	0.118	0.03 [0.01; 1.00]
Trail Making Test B	-0.122 (1.391)	0.056 (1.125)	0.384 (0.881)	1.75	0.176	0.03 [0.00; 1.00]

Note: p-values from Aligned Rank Transform (ART) ANOVA, controlling for education. η^2 = partial eta squared (effect size), with 95% confidence intervals (IC). Caution is advised when interpreting η^2, as ART applies rank-based transformations. Bolded values indicate statistically significant differences ($p < .05$). ROCFT = Rey–Osterrieth Complex Figure Test. IR = Immediate Recall. DR = Delayed Recall.

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After identifying statistically significant differences between groups through the ART ANOVA, Holm's post-hoc test was conducted to specifically investigate between which groups (control, vaccinated, and unvaccinated) these differences occurred.

The results of Holm's post-hoc test showed that participants in the control group performed better on the Rey-Osterrieth Complex Figure copy task compared to both the vaccinated and unvaccinated groups. However, vaccinated participants outperformed the unvaccinated group on the same task. Figure 2 illustrates the differences between groups in the ROCFT copy performance.

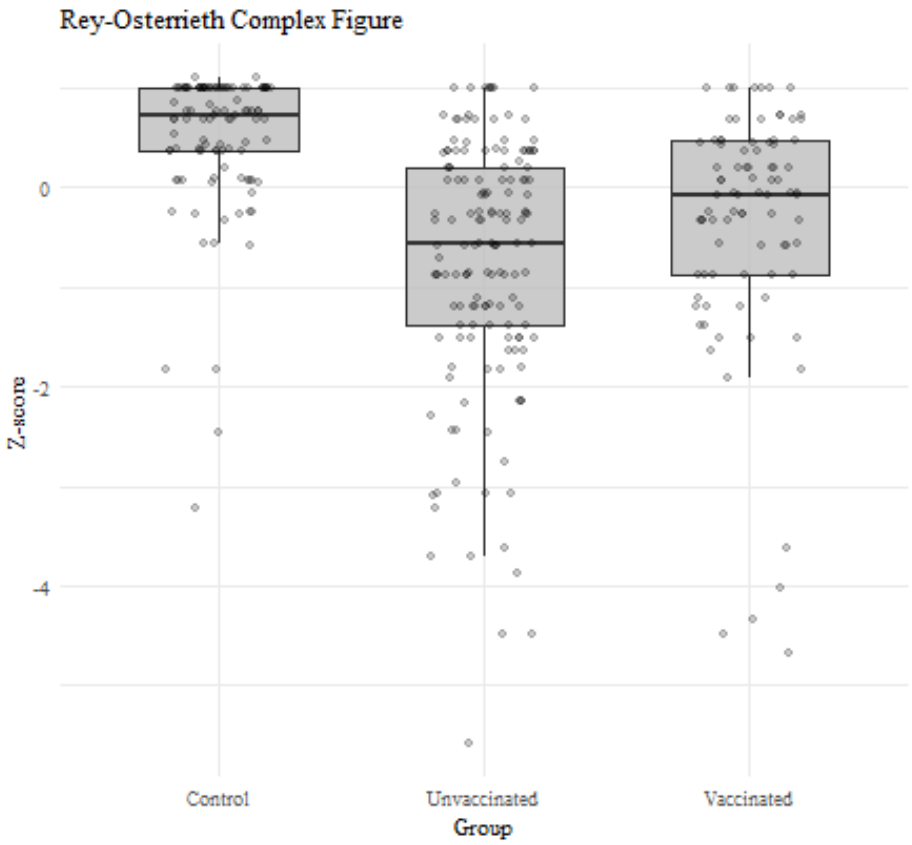


Figure 2. Rey Complex Figure Copy Scores by Group

The post-hoc results for the remaining tests (ROCFT Immediate and Delayed Recall, and Digit Span Backward) were not statistically significant between the vaccinated and unvaccinated groups, indicating that the observed

differences were exclusively between the control group and the infected participants. For the post-ART pairwise comparisons, we estimated Cohen's *d* as the ratio between the estimated mean difference and the pooled standard deviation (approximated SE x √2). Although ART is a nonparametric technique, this approach has been suggested in the official ARTool package documentation as a useful, albeit approximate, way to quantify the magnitude of effects.[36] The values should be interpreted with caution. The results are presented in Table 3.

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Table 3. Holm Post-hoc Comparisons Between Groups on Neuropsychological Tests with Significant Group Effects (ART ANOVA)

Test	**Comparison**	**MD**	**SE**	**t**	**p (Holm)**	***d***
ROCFT (Copy)	Control vs. Unvaccinated	122.5	11.1	11.07	< **0.0001**	7.81
	Control vs. Vaccinated	84.8	16.7	5.07	< **0.0001**	3.60
	Unvaccinated vs. Vaccinated	-37.7	16.4	-2.30	**0.0219**	−1.63
ROCFT (Immediate Recall)	Control vs. Unvaccinated	64.8	12.7	5.10	< **0.0001**	3.61
	Control vs. Vaccinated	40.7	19.2	2.13	0.0685	1.50
	Unvaccinated vs. Vaccinated	-24.1	18.8	-1.28	0.2009	0.91
ROCFT (Delayed Recall)	Control vs. Unvaccinated	67.8	12.6	5.36	< **0.0001**	3.80
	Control vs. Vaccinated	44.6	19.1	2.34	**0.0400**	1.65
	Unvaccinated vs. Vaccinated	-23.1	18.7	-1.24	0.2170	0.87
Digit Span Backward	Control vs. Unvaccinated	-42.0	12.9	-3.25	**0.0038**	2.30

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Test	Comparison	MD	SE	t	p (Holm)	*d*
	Control vs. Vaccinated	-46.7	19.5	-2.30	**0.0341**	1.71
	Unvaccinated vs. Vaccinated	-4.7	19.1	-0.25	0.8061	0.17

Note: MD = Mean Difference; SE = Standard Error; t = test statistic from the linear model applied to ART-transformed data, that represents the ratio between the estimated difference (MD) and its standard error (SE). p (Holm) = Holm-corrected p-value. d = Cohen's d represents the standardized mean difference, calculated as the ratio between the estimated difference (MD) and the pooled standard deviation, approximated by SE × √2. Comparisons were conducted using pairwise post-hoc tests following a significant ART ANOVA. Bolded values indicate statistically significant differences (p < .05). ROCF = Rey–Osterrieth Complex Figure Test. All values are adjusted for education as a covariate.

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Sensitivity analyses adjusting for age and education as continuous covariates confirmed significant group effects for ROCFT Copy ($F = 42.23$, $p < 0.001$), Immediate Recall ($F = 16.93$, $p < 0.001$), and Delayed Recall ($F = 18.09$, $p < 0.001$). Vaccinated participants continued to perform significantly better than unvaccinated participants on ROCFT Copy (Holm-adjusted $p = 0.038$). Control participants also performed significantly better than both COVID-19 groups on ROCFT Copy, Immediate Recall, and Delayed Recall (all Holm-adjusted $p < 0.001$). In contrast, the group effect for Digit Span Backward was no longer significant after adjustment for age and education ($F = 0.86$, $p = 0.425$). Full results are presented in Supplementary Table S1.

A final ART ANOVA was conducted within the vaccinated group to investigate potential differences in Rey-Osterrieth Complex Figure copy performance across different vaccine manufacturers and technologies. However, the small number of participants vaccinated with Janssen (3%) made it impossible to include this group in the analysis. Results among Coronavac, AstraZeneca, and Pfizer showed no significant differences between the vaccines ($F(2, 70) = 0.80$, $p = 0.44$), even after adjusting for education.

Discussion

The results of the neuropsychological assessment conducted in the present study revealed a significant difference between the clinical (vaccinated and unvaccinated) and control groups only on the Rey-Osterrieth Complex Figure Test (Copy, Immediate Recall, and Delayed Recall). Subsequent analyses, however, indicated that the deficits observed in the recall tasks may be secondary to impairments in the copy phase of the figure, reflecting difficulties in the initial visuospatial encoding process. Given that the quality of the copy directly influences the consolidation of visual memory,[23] it is important to interpret recall deficits with caution.

Visuospatial processing is a cognitive function essential for daily functioning, especially in tasks such as driving and spatial orientation. Despite its importance, few studies have included visuoconstruction tasks in their assessment protocols.[6,18] Moreover, the impact of prior vaccination on this cognitive function has not yet been investigated.

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The findings of this study suggest that prior vaccination might attenuate visuospatial processing deficits resulting from COVID-19 infection. Participants in the control group outperformed those in the clinical group on several ROCFT measures, an observation previously reported by de Paula et al. (2023),[6] but the difference was smaller between the vaccinated and unvaccinated groups on ROCFT Copy, indicating a possible mitigating effect of vaccination on post-infection visuospatial deficits.

The neuroinflammatory process has been widely associated with post-COVID-19 cognitive impairments.[37] Vaccination, in turn, has been linked to reduced levels of pro-inflammatory cytokines when comparing individuals infected before and after immunization.[38] Visuospatial processing deficits after COVID-19 have been associated with alterations in inflammatory biomarkers,[6] and strategies aimed at reducing neuroinflammation, such as prior vaccination, may help mitigate the cognitive impairments observed in this study, potentially explaining the differences found between vaccinated and unvaccinated individuals.

The findings are consistent with recent meta-analyses indicating the protective effect of vaccination against the development of post-COVID conditions, including cognitive deficits,[13,39] especially when infection occurs after the administration of the second dose.[39] For instance, Chau et al. (2024)[40] found that individuals vaccinated prior to infection had a reduced risk of developing neuropsychiatric symptoms. However, most studies assessing the impact of vaccines on the risk of post-infection cognitive deficits rely on subjective measures, leaving a significant gap in understanding the mitigating role of vaccination on cognition,[41] as subjective measures reflect patients' perceived cognitive difficulties rather than cognitive performance directly.

The number of doses appears to be crucial for mitigating post-COVID conditions, with one vaccine dose offering a smaller protective effect compared to two doses. [13,39] Furthermore, immunization with three doses prior to infection has shown an even greater protective effect than two doses,[42] reinforcing the importance of booster dose adherence in countries where third-dose coverage remains low, such as the United States (36%), Indonesia (25%), and India (17%).[43]

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Although many individuals report specific preferences for certain vaccines,[44] no statistically significant differences in ROCFT copy performance were observed among participants vaccinated with CoronaVac, AstraZeneca, or Pfizer. The findings of the present study support previous research that also found no statistically significant differences between different vaccine technologies in mitigating post-COVID conditions.[12] However, given the small sizes of the vaccine subgroups, these results should be interpreted cautiously, and further studies with larger samples are needed to investigate possible differences between vaccine manufacturers or technologies.

Many studies have investigated the cognitive profiles of individuals who chose to be vaccinated or not, associating the decision not to vaccinate with personality traits[45] and educational level,[46] for example. In contrast, the present study is less likely to be affected by this decisional bias, since most unvaccinated participants were infected before the beginning of the national vaccination campaign, when vaccines were not yet broadly available. In addition, the 25 participants infected after the start of the vaccination campaign, although unvaccinated at the time of infection, were subsequently vaccinated. This reduces potential confounding variables in interpreting the results. No previous studies were found in the literature that used objective cognitive measures to compare vaccinated and unvaccinated individuals without the bias of voluntary vaccine refusal,[41] which further highlights the importance, relevance, and uniqueness of the present study.

Saperia and colleagues (2023)[47] published a study in which they found no differences in objective cognitive performance between vaccinated and unvaccinated individuals against COVID-19. However, in the original study from the same research group,[48] the authors specify that all participants were infected before being vaccinated. Thus, rather than investigating the preventive role of vaccination against cognitive deficits, the authors examined its effect on the course of symptoms. The impact of vaccination on the trajectory of post-COVID conditions has been previously reported,[49] with most individuals reporting no noticeable improvement in already established symptoms.

In contrast, the findings of the present study suggest a protective role of vaccination administered prior to infection in reducing post-infection visuospatial deficits. Individuals who were unvaccinated at the time of infection showed

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poorer performance on the Rey-Osterrieth Complex Figure Test (Copy) when compared to those infected after receiving at least two doses of the COVID-19 vaccine.

The results reinforce the importance of public health policies aimed at increasing vaccination coverage, particularly in countries where booster dose uptake remains low. The findings highlight the relevance of vaccination not only in reducing severe cases and hospitalizations, but also in mitigating the long-term effects of the disease. An important point is that all participants in the clinical group: both vaccinated and unvaccinated, experienced only mild symptoms of COVID-19. Thus, the better performance observed in the vaccinated group cannot be attributed to differences in disease severity, since all participants in both groups had mild cases.

The use of a historical control group assessed in 2015-2016 should be considered when interpreting the present findings, as the COVID-19 groups were assessed between 2020 and 2023. Some social, behavioral, and environmental changes across this period may have influenced neuropsychological performance and cannot be completely controlled retrospectively. However, the main finding involved ROCFT Copy, a measure characterized by a restricted score range and ceiling effects in healthy individuals[32]. Moreover, metanormative data derived from multiple studies have shown close correspondence with previously established normative values for the ROCFT Copy[32,50,51]. These characteristics may limit the extent to which upward secular gains in cognitive performance, such as those associated with the Flynn effect, would be detectable on this measure. Nevertheless, residual confounding related to temporal and cohort differences cannot be completely excluded, and the findings should therefore be interpreted with appropriate caution.

This study has limitations such as the use of a convenience sample which may introduce selection bias, as the educational level of the sample is not representative of the broader Brazilian population. Additionally, the lack of socioeconomic data may be a limitation, since the prevalence of post-COVID symptoms tends to be higher in low-income populations.[52] Although women have been found to have a higher incidence of post-COVID conditions,[3] the high proportion of female participants in the present sample may also represent

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a significant limitation. Another important limitation is the absence of pre-infection cognitive assessments, which prevents determining whether the observed between-group differences reflect cognitive changes occurring after SARS-CoV-2 infection or pre-existing differences in cognitive performance. Therefore, the findings should be interpreted as post-infection between-group differences rather than evidence of within-person cognitive decline, and causal inferences regarding the effects of infection or vaccination should be made cautiously. Another relevant issue is that no genomic sequencing was performed to determine the SARS-CoV-2 variant that infected each participant, although some studies suggest different cognitive outcomes may be associated with different viral variants.[17] Moreover, changes in circulating SARS-CoV-2 variants temporally overlapped with the rollout of COVID-19 vaccination and may therefore have contributed to between-group differences.

Future studies should investigate the mechanisms through which vaccination may mitigate post-COVID cognitive deficits, particularly the interaction between immune responses and cognition. Larger and more representative samples may yield more robust results, and the integration of longitudinal analyses could provide a better understanding of symptom progression differences between vaccinated and unvaccinated groups.

The present study provides important data to advance the understanding of the role of vaccination in mitigating cognitive deficits related to COVID-19 infection. Many individuals continue to experience the impact of persistent post-COVID-19 symptoms, highlighting the need for studies of the underlying mechanisms and the development of effective intervention strategies. Vaccination may play an even more critical role than previously thought, underscoring the importance of including vaccination status as a variable of interest in future studies.

Disclosure

All authors certify that they have no affiliations or involvement with any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Data Availability

The anonymized data that support the findings of this study are available from the corresponding author upon reasonable request. Data will be shared in accordance with applicable ethical approvals and data protection regulations, and only to the extent necessary to preserve participant confidentiality.

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Authors' Contributions

LGS: conception and design of the study; acquisition and analysis of data; drafting of the manuscript. BCDF: acquisition of data; critical revision of the manuscript. JCMO: analysis of data; drafting and critical revision of the manuscript. DVR: acquisition of data; conception and design of the study; drafting and critical revision of the manuscript. DSC: conception and design of the study; drafting and critical revision of the manuscript. DMM: conception and design of the study; drafting and critical revision of the manuscript MARS: conception and design of the study; drafting and critical revision of the manuscript. JJP: conception and design of the study; drafting and critical revision of the manuscript. All authors have read and approved the final version submitted and take public responsibility for all aspects of the work.

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Supplementary material

Supplementary Table S1. Sensitivity analyses adjusting for age and education as continuous covariates

Panel A. Omnibus permutation-based ANCOVA						
	Group effect		**Age effect**		**Education effect**	
Test	**F**	**p**	**F**	**p**	**F**	**p**
ROCFT (Copy)	42.23	<0.001	0.43	0.516	19.49	<0.001
ROCFT Immediate Recall	16.93	<0.001	0.93	0.338	21.81	<0.001
ROCFT Delayed Recall	18.09	<0.001	1.43	0.232	24.65	<0.001
Digit Span Backward	0.86	0.425	0.08	0.783	27.51	<0.001

Panel B. Pairwise comparisons for outcomes with significant omnibus group effects				
Test	**Comparison**	**Adjusted difference***	**P (Permutation)**	**p (Holm)**
ROCFT (Copy)	Control vs. Unvaccinated	1.420	<0.001	<0.001
	Control vs. Vaccinated	1.107	<0.001	<0.001
	Vaccinated vs Unvaccinated	0.313	**0.0375**	**0.0375**
ROCFT (Immediate Recall)	Control vs. Unvaccinated	0.789	<0.001	<0.001

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	Control vs. Vaccinated	0.590	<0.001	<0.001
	Vaccinated vs Unvaccinated	0.199	0.1320	0.1320
ROCFT (Delayed Recall)	Control vs. Unvaccinated	0.792	<0.001	<0.001
	Control vs. Vaccinated	0.609	<0.001	<0.001
	Vaccinated vs Unvaccinated	0.183	0.1519	0.1519

Note: Positive values indicate higher adjusted performance in the first group listed in the comparison. P-values were obtained using the Freedman-Lane permutation procedure with 50,000 permutations. Pairwise p-values were adjusted using the Holm procedure within each outcome. ROCFT = Rey-Osterrieth Complex Figure Test.

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