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Examining neuropsychological differences in adults afflicted by COVID-19 with and without anosmia

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ABSTRACT

This study presents the outcomes of a research endeavor aimed at comparing the neuropsychological functioning of two distinct groups: one comprising individuals with both COVID-19 and anosmia, and the other without anosmia. A comprehensive neuropsychological assessment, involving ten tests, was administered to 60 participants, divided equally into two groups of 30. The group exhibiting anosmia displayed lower scores in lexical access, inhibitory control, strategy switching, visuoconstructive praxis, nonverbal memory, and verbal fluency functions. The effect sizes for these differences generally ranged from low to medium. Overall, the identified impairments strongly indicate deficits in executive functioning. Certain theories even propose that the frontal lobes may be the primary target of SARS-CoV-2 within the brain. To enhance our comprehension, future research could delve into the specific mechanisms through which the virus interacts with the prefrontal cortex, thereby illuminating the intricacies of COVID-19-related cognitive impairments.

Keywords: anosmia; COVID-19; neuropsychology; executive functions; prefrontal cortex

1. Introduction

Reports of anosmia in asymptomatic individuals have prompted exploration of its potential as an early indicator of SARS-CoV-2 infection (Hopkins et al., 2020). Anosmia is recognized as a significant neurological manifestation of COVID-19 (Divani et al., 2020; Niazkar et al., 2020) and is characterized as a quantitative olfactory pathology leading to a complete loss of odor detection. The most common type is post-viral or post-infectious anosmia with a sensorineural etiology. Olfactory neurons, located in the nasal cavity where the viral load is notably high (Zou et al., 2020), are particularly susceptible to damage. Histological analysis of the olfactory epithelium in affected individuals revealed the absence of cilia and a reduced number of olfactory sensory neurons, replaced by metaplastic squamous epithelium (Han et al., 2020).

Previous studies have observed retrograde transport of the virus from the nasal mucosa to the brain in the case of SARS-CoV-1, suggesting that SARS-CoV-2 may similarly cross the lamina cribrosa to bind to neurons in the olfactory bulb (Fotuhi et al., 2020). Although there is a lack of clarity regarding the specific pathways or neurobiological mechanisms involved in the infection of the central nervous system by the peripheral nervous system, it is evident that upon binding to angiotensin-converting enzyme 2 in respiratory epithelial cells, SARS-CoV-2 triggers the formation of a cytokine storm, leading to a marked increase in the levels of certain interleukins and tumor necrosis factor (Mehta et al., 2020).

Both interleukins and tumor necrosis factor can breach the blood-brain barrier, thereby activating microglia and astrocytes. This activation leads to an upsurge in quinurenine, quinolinic acid, and glutamate. Consequently, there is a decline in specific neurotransmitters, disrupting normal neuronal communication. The disturbance in neurotransmission, coupled with the excitotoxic effects of elevated glutamate and hypoxic injury, contributes to neuronal dysfunction and loss. This cascade of neurobiological events creates a neurotoxic environment capable of inducing neuropsychiatric alterations (Boldrini et al., 2021).

Some studies have documented cognitive alterations linked to inflammation levels in individuals with COVID-19. Zhou et al. (2020) observed a correlation between the ability to sustain attention and the level of C-reactive protein. Higher inflammation was associated with longer attentional reaction times, and individuals who had experienced COVID-19 exhibited prolonged reaction times compared to a control group. Nuber-Champier et al. (2023) found that elevated plasma levels of TNFα in the acute phase of COVID-19 predicted anosognosia for long-term memory deficits and were linked to changes in connectivity in the hippocampus, temporal pole, nucleus accumbens, amygdala, and cerebellum. Additionally, Mazza et al. (2021) reported that systemic inflammation was correlated with impaired

neurocognitive performance in domains such as executive functions (information processing, verbal fluency, and working memory) and psychomotor coordination three months after recovering from the disease.

Anosmia has been linked to a diminished ability for emotion recognition in individuals who experienced moderate SARS-CoV-2 infection (hospitalization without respiratory support) (Voruz et al., 2022). Pirker-Kees et al. (2021) discovered that patients with moderate COVID-19 who experienced olfactory disturbances also exhibited cognitive dysfunction, as assessed by the Montreal Cognitive Assessment (MoCA). Ruggeri et al. (2023) found that anosmia served as a reliable predictor of memory functioning, with individuals who had COVID-19 and anosmia displaying a temporo-mesial amnestic profile after recovering from the disease. Mahali & Coolidge (2023) were able to confirm that higher degrees of anosmia were correlated with elevated levels of neurocognitive impairment.

Some authors propose that the cognitive deficits and neuropsychological alterations following COVID-19 may be attributed to depression. According to this perspective, changes in cognitive functioning would be more a consequence of the altered emotional state rather than a direct effect of the infection on the brain. Poletti et al. (2022) reported that depression emerged as the most significant predictor of working memory functioning, verbal fluency, information processing speed, and executive functions in individuals who had experienced COVID-19 six months earlier. Additionally, Brown et al. (2022) found a positive association between depression and cognitive impairment following COVID-19 infection, particularly with lower performance in verbal fluency, attention, and delayed recall.

The aim of this study was to conduct a comprehensive comparison, using a wide array of neuropsychological tests, between individuals who had experienced COVID-19 with and without anosmia. To mitigate the potential negative impact of depression on cognitive functioning, we systematically screened for psychopathological symptomatology to control for this variable. Investigating the relationship between neuropsychological functioning and olfactory alterations in individuals who had COVID-19 aims to enhance our comprehension of the link between olfaction and cognition. Moreover, these studies will contribute to a deeper understanding of the effects of SARS-CoV-2 on the brain, potentially improving the assessment and neuropsychological intervention for individuals experiencing cognitive sequelae after recovering from the disease.

2. Method

2.1 Design

A descriptive-comparative, cross-sectional, non-experimental quantitative study was carried out.

2.2 Sample

Participants were recruited by convenience sampling in two Colombian clinics. A total of 60 people (N = 60) who had COVID-19, diagnosed through a positive Immunoglobulin M (IgM), Immunoglobulin G (IgG) or Polymerase Chain Reaction (PCR) test, were included. Only adults between 27 and 59 years of age were included. In all cases, four or more weeks had passed after diagnosis. None of the participants reported any neurological, psychopathological, or neuropsychological history. Nor did they have a history of olfactory impairment prior to infection. Participants did not receive any compensation for their involvement. Two groups were created. One group (N = 30) of participants who had anosmia after COVID-19 diagnosis and one group (N = 30) with people who did not have anosmia. Anosmia was clinically diagnosed by a neurologist. As can be seen in Table 1, the groups were very similar in terms of their sociodemographic and medical characteristics. Mostly, they were women aged between 30 and 49 years, with university or postgraduate education, right-handed, without hospitalization during COVID-19, nor hypertension, diabetes, fatigue, or smoking.

Table 1. Sample sociodemographic and medical data

		Group			
		With anosmia		Without anosmia	
		f	%	*f*	%
Sex					
	Male	9	30.0	7	23.3
	Female	21	70.0	23	76.7
Age					
	27-29	4	13.3	4	13.3
	30-39	9	29.9	17	56.5
	40-49	13	43.2	5	16.6
	50-59	4	13.3	4	13.2
Schooling					
	Elementary	2	6.7	0	0
	High School	4	13.3	2	6.7
	Technical	10	33.3	5	16.7
	University	9	30.0	15	50.0
	Postgraduate	5	16.7	8	26.7
Laterality					
	Right	27	90.0	25	83.3
	Left	3	10.0	5	16.7
Hospitalization					
	Yes	1	3.3	3	10.0
	No	29	96.7	27	90.0
Hypertension					
	Yes	7	23.3	2	6.7
	No	23	76.7	28	93.3
Diabetes					
	Yes	5	16.7	2	6.7
	No	25	83.3	28	93.3
	Fatigue				
	Yes	8	26.7	8	26.7
	No	22	73.3	22	73.3
	Current smoking				
	Yes	2	6.7	1	3.3
	No	28	93.3	29	96.7
	Past smoking				
	Yes	5	16.7	5	16.7
	No	25	83.3	25	83.3

2.3 Measures

2.3.1 Montreal Cognitive Assessment (MoCA)

Montreal Cognitive Assessment (Nasreddine et al., 2005) is a screening test designed to detect mild cognitive impairment. It is a highly sensitive and specific instrument. It is composed of 19 tasks that assess six cognitive domains: memory, executive functioning, attention, language, visuospatial and orientation. It includes tasks of alternate path tracing, visuoconstructive skills (cube and clock drawing), animal picture naming, recall of a list of words, forward and backward digits, vigilance, calculation, sentence repetition, verbal fluency, recall, abstraction, and orientation. Its administration takes approximately 10 minutes. The test has a standardization for Spanish-speaking population (Ojeda et al., 2016). It has shown good psychometric properties in Colombian adults (Pedraza et al., 2017).

2.3.2 Boston Naming Test (BNT)

Boston Naming Test (Kaplan et al., 1983) is a test created to assess the ability to access the lexicon through naming by visual confrontation using 60 plates containing pictures. The sheets contain drawings with increasing difficulty, from simple and high frequency vocabulary (tree) to rare words (abacus). This test is standardized for the Colombian population (Arango-Lasprilla et al., 2022).

2.3.3 Five Digit Test (FDT)

Five Digit Test (Sedó, 2007) is a test constructed to measure processing speed and aspects related to attention (control, focus and orientation) and executive functioning (response inhibition). The test is based on the Stroop effect but uses digits and asterisks instead of colors and words. Stimuli are presented on sheets for the person to perform one of four tasks: reading, counting, choosing, or alternating.

2.3.4 Wisconsin Card Sorting Test (WCST)

Wisconsin Card Sorting Test (Grant & Berg, 1948) is one of the main tests designed for the assessment of executive functions, especially the assessment of concept formation, mental flexibility and strategy change in problem solving. The test contains a series of 64 cards in which three attributes are combined: shape (triangle, star, cross and circle), color (red, blue, green, and yellow) and number (one, two, three or four shapes). The person must deduce the criteria that the evaluator uses to classify the cards. This test is standardized for the Colombian population (Arango-Lasprilla et al., 2022).

2.3.5 Clock Drawing Test (CDT)

Clock Drawing Test (Goodglass & Kaplan, 1972): is a screening test that allows a quick and reliable assessment of memory, verbal comprehension, visuospatial skills, planning, abstract thinking, and concentration. The test consists of drawing a clock (on verbal command and a copy) that has certain established parameters: it must have all the numbers and must point to eleven and ten o'clock with its hands.

2.3.6 Rey-Osterrieth Complex Figure (ROCF)

Rey-Osterrieth Complex Figure (Osterrieth, 1944; Rey, 1941) is a widely used test in neuropsychological assessment that provides a measure of visuoconstructive praxia and nonverbal memory. The test has two parts. In the first, a drawing with 18 items must be copied. In the second, after 30 minutes, the memory of the figure must be evoked to draw it. This test is standardized for the Colombian population (Arango-Lasprilla et al., 2022).

2.3.7 Hopkins Verbal Learning Test-Revised (HLVT-R)

Hopkins Verbal Learning Test-Revised (Benedict et al., 1998) is one of the most widely used verbal learning and memory tests. It has a high sensitivity and specificity for detecting cognitive impairment associated with dementia. It consists of a list of 12 words that must be listened to, in three immediate learning trials, and then evoked in a free recall trial that is performed 20 minutes after the last learning trial. A recognition test is also performed. This test is standardized for the Colombian population (Arango-Lasprilla et al., 2022).

2.3.8 Trail Making Test (TMT)

Trail Making Test (Reitan, 1958) is a test of visual attention and task switching that also provides information on visual search speed, selective attention, processing speed, mental flexibility, and executive functioning. It consists of two sheets on which numbers and letters are drawn between circles. In part A there are only numbers, and the person must join them in order by means of a continuous line. In part B, there are numbers and letters, and the person must join them by means of a continuous line interspersed with numbers and letters in increasing alphabetical order. This test is standardized for the Colombian population (Arango-Lasprilla et al., 2022).

2.3.9 Control Oral Word Association Test (COWAT)

Control Oral Word Association Test (Lezak et al., 2012) is a task included in the evaluation battery for aphasia to measure verbal fluency. It evaluates the ability to produce, in a period of one minute, words beginning with letters ("F", "A" and "S"). This test is standardized for the Colombian population (Arango-Lasprilla et al., 2022).

2.3.10 Digits Subtest Weschler Intelligence Scale (WAIS-IV)

Digits Subtest Weschler Intelligence Scale (Wechsler, 2013) is a subtest included in the WAIS-IV that has three forms: direct digits, inverse digits and digits sequencing. In general, it provides a measure of immediate auditory memory and working memory. It is also a measure of attention and concentration ability. In the direct digit task, a series of numbers is read, and the person must repeat them in the same order. In the inverse digit task, the person must repeat them in reverse order. In the sequencing task, the person must say them in numerical order.

2.3.11 The Symptom Checklist-90-R

The Symptom Checklist-90-R (Derogatis, 2011) is a self-report that contains a list of 90 psychopathological symptoms of various levels of severity. The person must answer how much each symptom has affected him/her (not at all, a little, moderately, quite a lot, extremely) during the week prior to the assessment. Its structure contains nine factors: somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychotic symptoms.

2.4 Procedure

Individual neuropsychological assessments were carried out during three-hour sessions, divided into two parts, each lasting one and a half hours. There was a 30-minute break between the two parts. The assessments took place in a medical office, ensuring optimal lighting and sound conditions. In the initial phase, screening, attention, and memory tests were conducted, while the subsequent phase involved assessments of executive functioning, language, and psychopathology.

Two psychologists in their second year of a master's degree in clinical neuropsychology performed the assessments. All participants provided their informed consent by signing a form prepared in accordance with Law 1090 of 2006 (Code of Ethics for Psychologists in Colombia), Resolution 8430 of 1993

(Health Research Regulations in Colombia), and the Declaration of Helsinki (World Medical Association). The research received approval from the Bioethics Committee of Pontificia Universidad Javeriana - Cali, Colombia.

2.5 Data analysis

Data were analyzed in SPSS. v. 28. Summary statistics were calculated for all variables and the normality of the data was evaluated using the Shapiro-Wilk test. Since the distribution was nonparametric, the Mann-Whitney U test was used to compare the means of the variables and to determine if there were statistically significant differences ($p < .05$). In addition, the effect size (d) was calculated (Sullivan & Feinn, 2012).

3. Results

The assessment of psychopathological symptomatology with The Symptom Checklist-90-R revealed that none of the participants had emotional disturbances such as depression or anxiety. Neither did they show problems of hostility, phobic anxiety, paranoid ideation, psychotic symptoms, or interpersonal difficulties. Only one participant (3.3%) in the group with anosmia showed somatization symptoms and another participant in the same group showed obsessive-compulsive symptoms (3.3%). In the group without anosmia, only one participant (3.3%) showed somatization symptoms.

Table 1 provides an overview of the sociodemographic and medical characteristics of the sample, organized by group. Remarkably, both groups exhibit pronounced similarities in these aspects. Most participants were women, aged 30 to 39, with a college education, right-handed, not hospitalized during the COVID-19 infection, devoid of hypertension, diabetes, or fatigue, and non-smokers.

Table 2 shows the mean, standard deviation and statistical significance value when applying the Mann-Whitney U test to compare the means of the two groups. The only neuropsychological functions in which there were no statistically significant differences in any of their variables were: Screening, Learning and verbal memory; Visual attention and task switching; and Immediate auditory memory and working memory. In all other functions there were differences in at least one of the variables.

Table 2. Summary measures and comparison of means

Test	Score	Group				Statistics	
		With anosmia		Without anosmia			
		M	*SD*	*M*	*SD*	*p*	*d*
MoCA	Global	26.43	2.48	26.67	4.58	.18	.19
CDT	Global	9.03	1.40	9.40	1.16	.26	.14
BNT	Responses	13.17	2.16	14.17	1.28	.12	.21
	Time	18.67	3.65	16.50	2.54	.01*	.36
FDT	Time-Reading	28.70	20.24	44.33	16.75	.00*	.42
	Time-Counting	26.53	21.08	43.37	23.25	.00*	.42
	Time-Choice	27.60	21.66	46.27	19.79	< .001*	.51
	Time-Alternacy	28.43	25.37	50.37	22.08	.00*	.47
	Inhibition	34.63	28.47	47.30	23.97	.05	.29
	Flexibility	34.37	29.39	50.27	25.22	.03*	.32
	Errors-Reading	1.10	0.54	1.00	.00	.33	.03
	Errors-Counting	1.30	0.91	1.10	.54	.31	.06
	Errors-Choice	2.00	1.17	1.33	.60	.02*	.30
	Errors-Alternacy	1.80	0.84	1.53	.68	.22	.16
WCST	Correct-Responses	45.73	8.94	50.93	3.73	.01*	.35
	Total-Errors	18.20	8.99	13.07	3.73	.02*	.33
	Errors-Perseverative	8.33	6.98	4.07	2.71	.00*	.44
	Non-Perseverative-Errors	9.87	3.530	9.00	2.66	.40	.12
	Conceptual-Responses	40.37	12.88	47.97	5.53	.02*	.33
	Categories-Complete	2.63	1.35	3.77	.77	.00*	.46
ROCF	Score-Copy	34.27	3.92	35.30	1.20	.21*	.16
	Time-Copy	202.53	63.01	172.57	68.40	.04*	.30
	Score-Memory	20.87	6.24	23.72	5.40	.05	.29
	Time-Memory	145.10	77.36	138.13	54.44	.97	.00
HLVT-R	Learning	21.97	4.30	23.80	3.69	.10	.24
	Registration	65.50	24.36	75.33	18.75	.12	.22
	Evocation	67.67	23.22	72.33	19.19	.50	.10
	Recognition	11.30	1.46	12.17	2.15	.06	.19
TMT	A	74.33	16.38	76.00	17.63	.56	.08

	B	70.83	19.30	77.33	13.37	.27	.16
COWAT	F-Words	13.43	3.54	14.93	3.68	.12	.23
	A-Words	12.17	4.13	14.80	3.28	.01*	.36
	S-Words	10.93	3.22	13.57	2.89	.00*	.43
	Animals	19.47	3.87	20.53	3.95	.28	.16
	Fruits	14.73	2.50	16.60	2.59	.00*	.40
WAIS	Digits-Direct	8.40	1.73	8.20	1.18	.69	.05
	Digits-Inverse	7.00	1.57	7.73	1.31	.08	.25
	Digits-Sequence	7.07	2.18	7.37	1.49	.56	.08

* $p < .05$

4. Discussion

The study aimed to compare the neuropsychological functioning of two groups of individuals who had experienced COVID-19: one with anosmia during the disease and one without. The results revealed statistically significant differences in various functions, including lexical access, inhibitory control, strategy switching, visuoconstructive praxia, nonverbal memory, and verbal fluency. The effect sizes for these differences were generally low to medium (ranging between 0.3 and 0.5). Across all variables where differences were observed, the group with anosmia performed less favorably than the group without anosmia. These findings align with previous studies discussed in the introduction, which also reported similar outcomes (Mahali & Coolidge, 2023; Pirker-Kees et al., 2021; Ruggeri et al., 2023; Voruz et al., 2022). In essence, the identified impairments primarily involve executive, praxic, and language functioning, with no significant differences noted in memory, attention, and learning among individuals who experienced anosmia.

Evidence suggests that SARS-CoV-2 can infiltrate the central nervous system from the nasal mucosa into the brain through the olfactory pathway (Butowt & Bilinska, 2020; Butowt & von Bartheld, 2021; Han et al., 2020; Li et al., 2020). The olfactory bulb connects to the brain in the orbitofrontal cortex. One etiological explanation for anosmia in COVID-19 proposes hypofunctionality of the orbitofrontal cortex (Karimi-Galougahi et al., 2020). Individuals with anosmia due to COVID-19 exhibit greater atrophy and indicators of increased tissue damage in the orbitofrontal cortex, as well as other areas and brain regions connected to the primary olfactory cortex (Sollmann et al., 2022). Moreover, it has been suggested that olfactory deficits significantly contribute to volumetric changes in specific brain regions, particularly the dorsolateral prefrontal cortex (Bitter et al., 2010).

In our study, individuals with anosmia exhibited lower performance on tasks related to inhibitory control, strategy switching, and information processing speed. These functions rely on specific areas within the prefrontal regions of the brain (Fuster, 2015), including the orbitofrontal cortex and dorsolateral cortex. A recent investigation suggested the potential for mild prefrontal dysfunction associated with olfactory impairment in individuals who had recovered from the infection. Through metabolic and electroencephalographic measurements, Clemente et al. (2023) observed that individuals with hyposmia displayed slightly reduced neuropsychological performance and minor alterations in event-related responses during the Stroop task.

Numerous studies on cognitive impairments associated with COVID-19 have consistently reported executive dysfunctions linked to the prefrontal cortex (Ariza et al., 2023; Manukyan et al., 2022; Pallanti et al., 2023; Velichkovsky et al., 2023). A growing body of clinical, brain imaging, neurochemical, electroencephalographic, and neurobiological evidence has led to the suggestion that the frontal lobes are among the initial targets of SARS-CoV-2 in the brain. Toniolo et al. (2021) proposed that a parainfectious inflammatory process, with a preference for the frontal lobes and/or frontal networks, could be responsible for these observed findings. Additionally, Yesilkaya et al. (2021) suggested a transient alteration in the glutamatergic pathway of the dorsolateral prefrontal cortex due to inflammation.

Regarding visuoconstructive praxia, there are also documented alterations in patients who had COVID-19, but there is no differentiation between those with anosmia and those without. Negrini et al. (2021) reported cases in which severe deficits were observed in executing the two-pentagon copy task of the Mini-Mental State Examination (MMSE). Similarly, Lathouwers et al. (2023) identified issues with complex tracking and visual scanning indicative of apraxia. Specifically, in the Rey Complex Figure copying task, de Paula et al. (2023) observed changes in molecular and structural brain imaging that correlated with the up regulation of peripheral immune markers and visuoconstructive praxia.

Research on the cognitive and neuropsychological effects of COVID-19 has predominantly been conducted without discerning the associated neurological alterations. While neurological symptoms linked to the disease are acknowledged, there is often a lack of detailed analysis, as seen in the case of olfactory disturbances. Only a handful of studies have delved into this specific analysis (Mahali & Coolidge, 2023; Pirker-Kees et al., 2021; Ruggeri et al., 2023; Voruz et al., 2022). Advancements in research suggest that the virus does not consistently reach the brain. Cases of COVID-19 with anosmia are likely more complex neuropsychologically than those without anosmia, as there is a higher risk of direct brain involvement through the olfactory pathway. It is

plausible that a majority of COVID-19 cases exhibiting cognitive deficits or neuropsychological alterations are those with olfactory involvement.

While acknowledging the limitation in sample size, it is not the primary constraint of this study. Given the non-experimental design and the nature of this analysis, it is not feasible to assert that anosmia is solely responsible for the neuropsychological effects identified here. Our objective was confined to comparing two groups (anosmia/no anosmia) while ensuring the absence of depressive symptomatology. Within the context of current research on the connection between olfaction and cognition in viral infections, the results suggest that the neuropsychological effects are more pronounced and exhibit a tendency toward the disruption of functions associated with the prefrontal cortex. Considering the aforementioned, future studies should incorporate larger participant pools and employ diverse analyses to make more robust inferences regarding causality.

Due to the limited number of participants and the nature of the analysis, caution is warranted in generalizing the results. Nonetheless, the observed findings align with those from comparable studies. It's worth noting that while there has been extensive research in the field of neuropsychology related to COVID-19, a more in-depth analysis specifically focusing on cases with anosmia remains somewhat limited. The relevance of this study lies in its focused examination of anosmia.

Data Availability

Due to the nature of the research, supporting data is not available.

Ethic Statement

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was approved by the Pontificia Universidad Javeriana – Cali. Informed consent was obtained from all participants prior to their inclusion in the study. The participants were informed of their right to withdraw from the study at any time without any consequences. Confidentiality and anonymity of the participants were strictly maintained throughout the research process. No identifying information was collected or shared.

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Author's contribution

Jorge Emiro Restrepo-Carvajal: Conceptualization, Formal analysis, Writing - Original Draft, Writing - Review & Editing
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