





# Correlation Between COVID-19 Recovery, Executive Function Decline, and Emotional State

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**Objective:** The aim of this study was to determine whether there is a relationship between the time since recovery from coronavirus disease 2019 (COVID-19) and alterations in executive functions. We also evaluate the emotional state of post-COVID-19 patients.

**Patients and Methods:** We assessed patients between 18 and 50 years old, who had a history of COVID-19 with mild, moderate, or severe illness. We used the Batería Neuropsicológica de Funciones Ejecutivas y Lóbulos Frontales-3 (BANFE-3), Mini-Mental State Examination (MMSE), and Mini-International Neuropsychiatric Interview (MINI), in addition to a semi-structured interview. Spearman's correlation coefficient was used, with a  $p$  value  $<0.05$  indicating significance.

**Results:** We evaluated 67 patients with a mean age of  $34.6 \pm 9.6$  years, most of whom had  $\geq 13$  years of schooling ( $n=55$ , 82.1%). Among them, 52 (77.6%) reported persistent symptoms after resolution of the condition, with fatigue being the most frequent ( $n=20$ , 29.9%). Most participants had an adequate score on the MMSE ( $n=60$ , 89.6%). However, 19 (28.4%) showed alterations in the BANFE-3 total score, with mental flexibility as the most affected function ( $n=25$ , 37.3%). In participants from the first COVID-19 wave, a negative correlation was observed between the standardized orbitofrontal area scores and the time since recovery from the infection ( $r=-0.841$ ,  $p=0.016$ ), suggesting a pattern of deterioration over time, mainly in stimulus inhibition ( $r=0.880$ ,  $p=0.021$ ). Regarding emotional state, 45 subjects (67.2%) exhibited emotional alterations, with anxiety symptoms being the most frequent ( $n=33$ , 49.3%). Furthermore, individuals with depressive symptoms ( $n=32$ , 47.8%) were more likely to experience executive function impairment after COVID-19 (ExpB 0.302, 95% CI 0.098–0.933,  $p=0.038$ ).

**Conclusion:** COVID-19 could lead to alterations in executive functions, probably resulting from progressive damage to orbitofrontal area functions, mainly in stimulus inhibition. However, the generalizability of these findings is limited, highlighting the need for further research with robust methodology. Furthermore, depression appears to be an indicator of cognitive impairment in individuals recovering from COVID-19. Therefore, cognitive rehabilitation and psychological support are essential for patients affected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.

**Keywords:** coronavirus infection, cognition, executive function, affective symptoms

## Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 causes respiratory, digestive, and cardiovascular symptoms, as well as olfactory and gustatory alterations and hallucinations, which were not seen with previous viruses such as SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-CoV). These symptoms could be caused by an affinity between SARS-CoV-2 and the central nervous system (CNS).<sup>1</sup>

In addition, COVID-19 patients experience neurological symptomatology in the second week after the onset of symptoms; for example, confusion, agitation, alterations in the corticospinal tract, inattention, disorientation, and poorly organized movements in response to command post-discharge.<sup>2</sup> Furthermore, patients may experience enhancement in leptomeningeal spaces, bilateral frontotemporal hypoperfusion, ischemic strokes,<sup>2</sup> and altered consciousness.<sup>3</sup>

The neurological symptoms could be the result of SARS-CoV-2 reaching the CNS through the peripheral nerves (olfactory or trigeminal)<sup>4</sup> or via the systemic circulation, which could damage the blood–brain barrier.<sup>5</sup> They could also be caused by the immune system attack resulting from the cytokine storm;<sup>6</sup> or a reduction of the oxygen supply to the brain, which will result in cognitive impairment.<sup>7</sup>

In Mexico, we had five different COVID-19 waves. A wave is a period of increased incidence of cases, compared to a previous period, due to an increase in generalized transmission. The first wave occurred between epidemiological week (EW) 8 and 29 of 2020, the second wave between EW 40 of 2020 and EW 15 of 2021, the third wave between EW 23 and 42 of 2021, the fourth wave between EW 51 of 2021 and EW 9 of 2022, and the fifth wave between EW 22 and 33 of 2022.<sup>8</sup>

After infection, 10–20% of cases had persistent symptoms.<sup>9</sup> These symptoms, which may or may not have been present in the early part of the infection, appear within 3 months of the onset of COVID-19, last for at least 2 months, and cannot be explained by an alternative diagnosis.<sup>10</sup> This condition is known as the post-COVID-19 condition.<sup>10,11</sup> Fatigue and “mental fog” (problems with concentration and memory) are the key features of this condition.<sup>9,11</sup>

Previous research has reported cognitive alterations, evaluated by the Montreal Cognitive Assessment (MoCA),<sup>12,13</sup> Mini-Mental State Examination (MMSE),<sup>12,13</sup> Trail Making Test part B (TMT-B),<sup>7</sup> and other objective tests.<sup>7,13–24</sup> These alterations were present in the acute phase and from the first month after infection to 6 months. However, they were more commonly encountered in the long term.<sup>9,20</sup>

The most frequent dysfunctions in the post-acute phase include problems with working memory,<sup>14,15</sup> attention,<sup>13,14,20,25</sup> abstraction,<sup>13</sup> verbal fluency,<sup>15</sup> learning and memory,<sup>20,21</sup> and executive functions.<sup>16–18,20,25</sup>

Executive functions are the most elevated cognitive processes, located in the frontal lobe. This area is one of the last areas to complete the myelination process and is the most developed. It is also one of the most susceptible to alterations due to environmental factors, such as infections.<sup>26</sup> The executive functions involve the control of mental activity, emotional response, and behavior.<sup>27,28</sup> In addition, they encompass a set of skills, including problem solving for goal achievement, organization, inhibition of actions, interference management, hypothesis generation, planning, abstraction, mental flexibility, decision making, and self-awareness.<sup>26,27,29</sup>

Alterations in executive function may lead to initiation disorders, memory disorders, hyperactivity or global hypoactivity, adaptation problems, or behaviors that do not follow social conventions (irresponsible or impulsive behaviors). In addition, cognitive deficits and dysregulation of motivational and emotional aspects sometimes precede the development of dementia in patients with neuroinflammatory and neurodegenerative diseases.<sup>30</sup> For these reasons, it is necessary to identify cognitive and emotional sequelae after COVID-19, and, if they exist, to establish what happens over time. Our hypothesis is that there is a correlation between time since COVID-19 recovery and the executive function score. The aim of this study was to determine the correlation between time since recovery from SARS-CoV-2 with the executive function scores.

## Material and Methods

### Design

This observational, prospective, correlation study was conducted in two cities in Guanajuato state, Mexico, from October 2021 to September 2022.

### Participants

The study evaluated 67 patients with a previous diagnosis of COVID-19, who had recovered from the acute phase of the illness, whether it had been mild, moderate, or severe, were between 18 and 50 years old, with a minimum educational level of high school, and had no previously diagnosed prefrontal syndrome, attention deficit hyperactivity disorder (ADHD), history of substance abuse, or epilepsy.

The sample size was calculated with  $r=0.34$ ,  $\alpha=0.05$ , and  $\beta=0.20$ . The result was 67 patients.<sup>31</sup>

The recruitment process followed two main approaches. Eligible patients at the High Specialty Medical Unit HE1 CMN Bajío, IMSS, were invited to participate in the project. In addition, hospital staff, administrative personnel, professors, and students of the University of Guanajuato were recruited through information disseminated via e-mail, posters, and university newsletters.

## Procedure

A single researcher, a psychologist with 3 years of experience in administering psychometric tests, including the Mini-Mental State Examination (MMSE),<sup>32</sup> conducted all evaluations. Specific training for the Bateria Neuropsicológica de Funciones Ejecutivas y Lóbulos Frontales-3 (BANFE-3)<sup>33</sup> was provided by a psychologist with 6 years of experience, while additional training for the Mini-International Neuropsychiatric Interview (MINI)<sup>34</sup> was given by another investigator, with 14 years of experience.

The assessments took place in an office at the IMSS, in a private cubicle in a public library, or a suitable space at the University of Guanajuato. The evaluation process lasted between 45 and 75 minutes, and included the signing of informed consent, an identification form, developed by the authors, and application of the instruments: MMSE, MINI and, after a short break, BANFE-3. The study was conducted entirely in Spanish with Spanish-speaking individuals.

All participants were provided with information about places offering free emotional support and post-COVID rehabilitation (at the University of Guanajuato). Cases of severe emotional disturbances were referred to the IMSS psychology department for follow-up care. In addition, approximately 2–3 months after the evaluation, participants were provided with a report of their results and personalized recommendations to strengthen their cognitive skills.

## Variables

The diagnostic date was the day of a positive test result or the onset of symptoms, whichever came first. All participants had a positive test result by a positive polymerase chain reaction (PCR) or an antigen test. Information on the symptoms in the acute phase and after COVID-19 was self-reported by the participants.

The COVID-19 resolution date was defined by the WHO criteria,<sup>35</sup> the severity level used the IMSS criteria,<sup>36</sup> and the definition of COVID-19 waves followed the epidemiological weeks of the Mexican Ministry of Health.<sup>8</sup>

## Ethics

The study complied with the Declaration of Helsinki, was of minimal risk, and was approved by the Institutional Ethics Committee of the High Specialty Medical Unit HE1 CMN Bajío, IMSS (institutional registration number: R-2021-1001-052). Informed consent was requested from each participant. None of the participants received any financial compensation.

## Instruments

### Bateria Neuropsicológica de Funciones Ejecutivas y Lóbulos Frontales-3 (BANFE-3)

BANFE is an instrument developed by Flores, Ostrosky-Solís, and Lozano. BANFE-3 is the third edition. It has an inter-applicator agreement of 0.8 and a reliability of 0.8. It consists of 15 tests divided according to anatomical–functional criteria: orbitofrontal cortex, medial prefrontal cortex, dorsolateral prefrontal cortex, and anterior prefrontal cortex. This test was standardized in Mexico in subjects between 6 and 90 years of age with schooling level from 3 years old. It provides standardization tables according to age and educational level. The scores obtained can be classified as a high normal level (116 and above), normal (85–115), mild–moderate alteration (70–84), and severe alteration (60 or less).<sup>33</sup>

### Mini-Mental State Examination (MMSE)

MMSE, by Folstein (1975),<sup>32</sup> is a screening test. It has a Cronbach's alpha of 0.78 and the application time is approximately 15 minutes. It is used to detect cognitive deficits. It measures 11 categories: temporal orientation, spatial orientation, attention and calculation, memory, nomination, repetition, comprehension, reading, writing, and drawing. Scores of 30–27 points mean adequate cognitive status, 26–25 points possible cognitive impairment, 24–10 points mild to moderate cognitive impairment, 9–6 points moderate to severe cognitive impairment, and less than 6 points severe cognitive impairment.<sup>32</sup>

### Mini-International Neuropsychiatric Interview (MINI)

MINI<sup>34</sup> is a brief diagnostic structured interview, with standardized information from the ICD-10 criteria. It has an application time of about 15 minutes, and asks about the main psychiatric disorders of axis I of the DSM-IV and ICD-10, with yes/no answers.<sup>34</sup>

## Statistical Methods

SPSS 26.0 statistical software was used for statistical analysis of the data. Qualitative variables were expressed as frequency and percentage; and quantitative variables, according to their distribution, were expressed as means and standard deviation, or median and interquartile range. The chi-squared test or Fisher's exact test was run, when appropriate. In addition, single-factor ANOVA or Kruskal–Wallis was used to compare variables between the different groups, since the sample was divided according to the wave in which the patient had COVID-19. Finally, Spearman's correlation coefficient and logistic regression were used.

## Results

We evaluated 68 patients, of whom one was eliminated because he decided not to complete the evaluation process. The total sample consisted of 67 patients, with a mean age of  $34.6 \pm 9.6$  years. Forty-nine patients (73.1%) were women. Thirteen subjects (22.4%) were studying for bachelor's degrees and two for master's degrees (3%), and 39 subjects (58.3%) had attended psychological therapy (Table 1).

The most common symptoms in the acute phase were fatigue, cough, and body pain, which were experienced by 43 (64.2%), 41 (61.2%), and 39 subjects (58.2%), respectively. Only four participants (6%) had been hospitalized, of whom one had been in the ICU (1.5%). In terms of severity, 54 (80.6%) had mild illness. The median time from COVID recovery was 235 (34–370) days. In 52 subjects (77.6%), symptoms persisted after resolution of the condition. The most frequent symptoms were fatigue ( $n=20$ , 29.9%), concentration problems ( $n=14$ , 20.9%), memory problems ( $n=12$ , 17.9%), and insomnia ( $n=10$ , 14.9%).

**Table 1** Characteristics of patients with a history of COVID-19 (N=67)

|                           | Total<br>(n=67) | First Wave<br>(n=6) | Second Wave<br>(n=24) | Third Wave<br>(n=7) | Fourth Wave<br>(n=30) | p†    |
|---------------------------|-----------------|---------------------|-----------------------|---------------------|-----------------------|-------|
| Gender, n (%)             |                 |                     |                       |                     |                       | 0.852 |
| Female                    | 49 (73.1%)      | 4 (66.7%)           | 18 (75%)              | 6 (85.7%)           | 21 (70%)              |       |
| Male                      | 18 (26.9%)      | 2 (33.3%)           | 6 (25%)               | 1 (14.3%)           | 9 (30%)               |       |
| Age, n (%)                |                 |                     |                       |                     |                       | 0.427 |
| ≤30 years                 | 25 (37.7%)      | 1 (16.7%)           | 7 (29.2%)             | 3 (42.9%)           | 14 (46.7%)            |       |
| ≥31 years                 | 42 (62.7%)      | 5 (83.3%)           | 17 (70.8%)            | 4 (57.1%)           | 16 (53.3%)            |       |
| Educational level, n (%)  |                 |                     |                       |                     |                       | 0.10  |
| ≤12 years                 | 12 (17.9%)      | 2 (33.3%)           | 6 (25%)               | 3 (42.9%)           | 1 (3.3%)              |       |
| ≥13 years                 | 55 (82.1%)      | 4 (66.7%)           | 18 (75%)              | 4 (57.1%)           | 29 (96.7%)            |       |
| Occupation, n (%)         |                 |                     |                       |                     |                       | 0.010 |
| UG student                | 15 (22.4%)      | 1 (16.7%)           | 5 (20.8%)             | 1 (14.3%)           | 8 (26.7%)             |       |
| Docent                    | 8 (12.1%)       | 1 (16.7%)           | 0                     | 0                   | 7 (23.3%)             |       |
| IMSS employee             | 7 (10.4%)       | 1 (16.7%)           | 6 (25%)               | 0                   | 0                     |       |
| Healthcare worker         | 6 (9%)          | 0                   | 1 (4.2%)              | 1 (14.3%)           | 4 (13.3%)             |       |
| Medical resident          | 6 (9%)          | 0                   | 4 (16.7%)             | 0                   | 2 (6.7%)              |       |
| General worker            | 15 (22.4%)      | 2 (33.3%)           | 7 (29.2%)             | 2 (28.6%)           | 4 (13.3%)             |       |
| Entrepreneur              | 3 (4.5%)        | 1 (16.7%)           | 0                     | 0                   | 2 (6.7%)              |       |
| UG worker                 | 1 (1.5%)        | 0                   | 0                     | 0                   | 1 (3.3%)              |       |
| Unemployed                | 6 (9%)          | 0                   | 1 (4.2%)              | 3 (42.9%)           | 2 (6.7%)              |       |
| Current disease, n (%)    |                 |                     |                       |                     |                       | 0.174 |
| Hypertension              | 3 (4.5%)        | 0                   | 3 (12.5%)             | 0                   | 0                     |       |
| Diabetes                  | 5 (7.5%)        | 1 (16.7%)           | 2 (8.3%)              | 1 (14.3%)           | 1 (3.3%)              |       |
| Cancer                    | 2 (3%)          | 0                   | 0                     | 1 (14.3%)           | 1 (3.3%)              |       |
| Hypothyroidism            | 3 (4.5%)        | 0                   | 0                     | 0                   | 3 (10%)               |       |
| Polycystic ovary syndrome | 3 (4.5%)        | 0                   | 0                     | 0                   | 3 (10%)               |       |
| Other <sup>a</sup>        | 6 (9%)          | 1 (16.7%)           | 4 (16.8%)             | 0                   | 1 (3.3%)              |       |
| None                      | 45 (67.2%)      | 4 (66.7%)           | 15 (62.5%)            | 5 (71.4%)           | 21 (70%)              |       |

(Continued)

Table 1 (Continued).

|   | Total<br>(n=67) | First Wave<br>(n=6) | Second Wave<br>(n=24) | Third Wave<br>(n=7) | Fourth Wave<br>(n=30) | p†    |
|---|-----------------|---------------------|-----------------------|---------------------|-----------------------|-------|
| Personal psychological antecedents, n (%) |                 |                     |                       |                     |                       |       |
| Grief                                     | 4 (6%)          | 0                   | 1 (4.2%)              | 2 (28.6%)           | 1 (3.3%)              | 0.174 |
| Eating disorder                           | 2 (3%)          | 0                   | 0                     | 1 (14.3%)           | 1 (3.3%)              | 0.353 |
| Depression                                | 12 (17.9%)      | 0                   | 6 (25%)               | 1 (14.3%)           | 5 (16.7%)             | 0.671 |
| Anxiety                                   | 13 (19.4%)      | 0                   | 4 (16.8%)             | 3 (42.9%)           | 6 (20%)               | 0.325 |
| OCD                                       | 1 (1.5%)        | 0                   | 0                     | 0                   | 1 (3.3%)              | 1     |

Notes: †Fibromyalgia, asthma, hypophysial adenoma, dermatographism, achondroplasia, HVP, vasopressor dysautonomia, chronic kidney disease. †Fisher's exact test.

Abbreviations: UG, Universidad de Guanajuato; IMSS, Instituto Mexicano del Seguro Social; OCD, obsessive-compulsive disorder.

Table 2 presents the results of the tests applied. Anxiety disorders were the most prevalent (n=33, 49.3%), with significant difference between waves, as well as depressive symptoms. No association was found between the participants' psychological history and alterations on the MINI ( $p=0.74$ ).

The majority of subjects demonstrated an adequate level on the MMSE (n=60, 89.6%). Similarly, 48 participants (71.6%) scored within the normal range on the BANFE-3, one participant (1.5%) scored in the high normal range, while three patients (4.5%) exhibited severe alterations and 16 patients (23.9%) presented mild to moderate alteration.

Likewise, the scores obtained on the BANFE-3 specified which skills were impaired. Mental flexibility, metamemory, and risk-benefit balance were the most frequently altered, in 25 (37.3%), 23 (34.3%), and 19 patients (28.4%), respectively (Table 3).

Table 2 Results of MINI, MMSE, and BANFE-3

|                                       | Total<br>(n=67) | First Wave<br>(n=6) | Second Wave<br>(n=24) | Third Wave<br>(n=7) | Fourth Wave<br>(n=30) | p             |
|---------------------------------------|-----------------|---------------------|-----------------------|---------------------|-----------------------|---------------|
| MINI                                  |                 |                     |                       |                     |                       |               |
| Diagnostics, n (%)                    | 45 (67.2%)      | 4 (66.7%)           | 15 (62.5%)            | 7 (100%)            | 19 (63.3%)            | 0.277†        |
| Depressive symptoms <sup>a</sup>      | 32 (47.8%)      | 2 (33.3%)           | 9 (37.5%)             | 7 (100%)            | 14 (46.7%)            | <b>0.027†</b> |
| Anxious symptoms <sup>b</sup>         | 33 (49.3%)      | 4 (66.7%)           | 10 (41.7%)            | 7 (100%)            | 12 (40%)              | <b>0.023†</b> |
| State of post-traumatic stress        | 4 (6%)          | 1 (16.7%)           | 2 (8.3%)              | 1 (14.3%)           | 0                     | 0.238†        |
| Eating behavior disorder              | 1 (1.5%)        | 0                   | 1 (4.2%)              | 0                   | 0                     | 0.611†        |
| MMSE: Qualitative and quantitative    |                 |                     |                       |                     |                       |               |
| Normal, n (%)                         | 60 (89.6%)      | 5 (83.3%)           | 21 (87.5%)            | 5 (71.4%)           | 29 (96.7%)            | 0.229†        |
| Quantitative scores, median (Q1–Q3)   | 29 (28–30)      | 28.5 (27.5–30)      | 29 (28–30)            | 29 (26–30)          | 29 (27.8–30)          | 0.964§        |
| BANFE-3: Qualitative and quantitative |                 |                     |                       |                     |                       |               |
| Total score                           |                 |                     |                       |                     |                       |               |
| Normal, n (%)                         | 48 (71.6%)      | 3 (50%)             | 18 (75%)              | 4 (57.1%)           | 23 (76.7%)            | 0.455†        |
| Standardized score, average (SD)      | 92 (12.6)       | 87.8 (11.3)         | 93.9 (15.4)           | 85.1 (14.9)         | 93 (9.4)              | 0.341†        |
| Orbitofrontal area                    |                 |                     |                       |                     |                       |               |
| Normal, n (%)                         | 47 (70.1%)      | 2(33.3%)            | 18 (75%)              | 4 (57.1%)           | 23 (76.7%)            | 0.149†        |
| Standardized score, median (Q1–Q3)    | 100 (81.5–106)  | 82.5 (73–102)       | 99.5 (81–107)         | 92 (71–108)         | 101 (86.8–108)        | 0.895§        |
| Prefrontal area                       |                 |                     |                       |                     |                       |               |
| Normal, n (%)                         | 49 (73.1%)      | 6 (100%)            | 15 (62.5%)            | 6 (85.7%)           | 22 (73.3%)            | 0.246†        |
| Standardized score, average (SD)      | 92.6 (17.5)     | 95.7 (9.8)          | 95.8 (21.3)           | 88.4 (13.3)         | 89.9 (16.2)           | 0.615‡        |
| Dorsolateral area                     |                 |                     |                       |                     |                       |               |
| Normal, n (%)                         | 54 (80.6%)      | 5 (83.3%)           | 20 (83.3%)            | 4 (57.1%)           | 25 (83.3%)            | 0.432†        |
| Standardized score, average (SD)      | 95.42 (11.1)    | 92.8 (12.5)         | 97.7 (11.5)           | 88.4 (13.3)         | 95.8 (9.8)            | 0.252‡        |
| Executive function score              |                 |                     |                       |                     |                       |               |
| Natural score, average (SD)           | 98.2 (15.6)     | 91.2 (14.9)         | 100.5 (16)            | 88.3 (17.2)         | 100.1 (14.4)          | 0.169‡        |

Notes: <sup>a</sup>Depression and dysthymic disorder. <sup>b</sup>Generalized anxiety disorder, agoraphobia, social phobia, and panic disorder. †Fisher's exact test.

‡One-way ANOVA. §Kruskal Wallis test. Bold text: significant difference.

Abbreviations: MINI, Mini-International Neuropsychiatric Interview; MMSE, Mini-Mental State Examination; BANFE-3, Bateria Neuropsicológica de Funciones Ejecutivas y Lóbulos Frontales 3.

**Table 3** Qualitative Results of the BANFE-3

| Impaired Functions*      | Total<br>(n=67) | First Wave<br>(n=6) | Second Wave<br>(n=24) | Third Wave<br>(n=7) | Fourth Wave<br>(n=30) | p†           |
|--------------------------|-----------------|---------------------|-----------------------|---------------------|-----------------------|--------------|
| Impaired functions       | 56 (83.6%)      | 6 (100%)            | 20 (83.3%)            | 7 (100%)            | 23 (76.7%)            | 0.411        |
| Working memory           | 15 (22.4%)      | 3 (50%)             | 2 (8.3%)              | 2 (28.6%)           | 8 (26.7%)             | 0.082        |
| Inhibition               | 13 (19.4%)      | 1 (16.7%)           | 6 (25%)               | 3 (42.9%)           | 3 (10%)               | 0.127        |
| Planning                 | 18 (26.9%)      | 2 (33.3%)           | 9 (37.5%)             | 3 (42.9%)           | 4 (13.3%)             | 0.103        |
| Risk–benefit balance     | 19 (28.4%)      | 3 (50%)             | 6 (25%)               | 1 (14.3%)           | 9 (30%)               | 0.554        |
| Mental flexibility       | 25 (37.3%)      | 5 (83.3%)           | 8 (33.3%)             | 2 (28.6%)           | 8 (26.7%)             | <b>0.044</b> |
| Metamemory               | 23 (34.3%)      | 3 (50%)             | 7 (29.2%)             | 2 (28.6%)           | 11 (36.7%)            | 0.778        |
| Follow-up of indications | 13 (19.4%)      | 3 (50%)             | 4 (16.7%)             | 2 (28.6%)           | 4 (13.3%)             | 0.151        |
| Verbal fluency           | 11 (16.4%)      | 2 (33.3%)           | 3 (12.5%)             | 1 (14.3%)           | 5 (16.7%)             | 0.643        |
| Language                 | 4 (6%)          | 6 (100%)            | 2 (8.3%)              | 1 (14.3%)           | 1 (3.3%)              | 0.460        |
| Consecutive subtraction  | 15 (22.4%)      | 2 (33.3%)           | 8 (33.3%)             | 2 (28.6%)           | 3 (10%)               | 0.122        |
| Abstraction              | 8 (11.9%)       | 6 (100%)            | 3 (12.5%)             | 1 (14.3%)           | 4 (13.3%)             | 1            |
| Nomination               | 2 (3%)          | 6 (100%)            | 0                     | 1 (14.3%)           | 1 (3.3%)              | 0.353        |
| Concentration            | 18 (26.9%)      | 3 (50%)             | 7 (29.2%)             | 1 (14.3%)           | 7 (23.3%)             | 0.532        |

**Notes:** \*A function is considered altered for the purposes of this research if, in all the results of the tests that measure each function, the patient obtains a standardized score of 0 or 1. †Fisher's exact test. Bold text: Significant difference.

**Abbreviation:** BANFE-3, Batería Neuropsicológica de Funciones Ejecutivas y Lóbulos Frontales.

It was determined that there is an association between severity level and alteration in the BANFE-3 total score ( $p=0.030$ ). Persistent symptoms, such as fatigue, sleep problems, and agitation, were associated with alterations in the dorsolateral area ( $p=0.031$ ,  $p=0.047$ ,  $p=0.001$ , and  $p=0.035$ , respectively). In addition, sleep problems were associated with alterations in the BANFE-3 total score ( $p=0.006$ ), and the presence of headache and loss of smell during the acute phase were associated with alterations in cognitive functions ( $p=0.018$  and  $p=0.012$ , respectively).

We also found a correlation between the people who had COVID-19 in the first wave and the standardized orbitofrontal cortex score ( $r=-0.841$ ,  $p=0.036$ ). When taking each of the tests that integrate the evaluation of the orbitofrontal area, there was a negative correlation between the percentages of risk cards in the card test, which measures the ability to make decisions in uncertain situations, based on a risk–benefit balance ( $r=-0.812$ ,  $p=0.050$ ). This means that the longer the time elapsed after COVID-19, the lower the percentage and the better the performance.

Likewise, there was a strong positive correlation between the number of Stroop A errors and the time since COVID-19 ( $r=0.880$ ,  $p=0.021$ ). That is, the more days, the greater the number of errors in this subsection, which is linked to the inhibition of a highly automated response.

Similarly, regarding functions related to the prefrontal area, it was found that the longer the time since recovery from infection, the fewer positive errors occurred in the metamemory test. That is, the lower the overestimation of the number of words predicted by the subject ( $r=-0.926$ ,  $p=0.008$ ).

In addition, the longer the time since COVID-19, the fewer perseverations were seen in the letter classification test, which implies a probable recovery of the mental flexibility function in patients from the first COVID-19 wave ( $r=0.828$ ,  $p=0.042$ ).

Finally, people with depressive symptoms were 3.3 times more likely to have executive function impairment (ExpB=3.307,  $p=0.038$ , 95% CI 0.098–0.933), compared to those without.

## Discussion

The present observational, prospective, correlation study found that Mexican adults who were infected with COVID-19 during the first wave exhibited lower standardized scores in the orbitofrontal area as more time elapsed after recovery, with a correlation coefficient of  $-0.841$  ( $p=0.036$ ), which implies a strong correlation.<sup>37</sup> However, when analyzing specific cognitive functions, we observed progressive dysfunction in stimulus inhibition, evaluated by the Stroop part A ( $r=0.880$ ,  $p=0.021$ ). Nevertheless, decision making in uncertain situations improved over time, as evidenced by a decrease in the percentage of risk cards in the card test ( $r=-0.812$ ,  $p=0.050$ ).



Cognitive impairments in COVID-19 survivors, including mental flexibility (37.7%), metamemory (34.3%), risk–benefit balance in uncertain situations (28.8%), planning (26.9%), working memory (22.4%), and consecutive subtraction (22.4%), were consistent with those found in previous studies.<sup>13–15,18,38</sup>

From this, we suggest that there is an executive deficit after COVID-19 in different domains, such as verbal fluency, inhibition, cognitive flexibility, and attention, as evaluated in the inverse digit test.<sup>39,40</sup> In addition to memory,<sup>20,21,41</sup> attention and concentration problems,<sup>41</sup> learning, executive function, and perceptual motor problems,<sup>20</sup> which were also found in research with young adults, it is concluded that patients who have recovered from mild or moderate COVID-19 may have neuropsychological deficits.<sup>41</sup>

These cognitive alterations could be explained by neuroanatomical changes due to the infection, such as the loss of gray matter in the left orbitofrontal cortex, left parahippocampal gyrus, and left superior insula, with extension to the anterior cingulate cortex, left supramarginal gyrus, and right temporal pole.<sup>42,43</sup> Many of these areas are related to the primary olfactory cortex,<sup>42,43</sup> explaining the high incidence of olfactory disturbances.<sup>4</sup>

One of the possible entry routes into the CNS is by transneuronal penetration through the olfactory bulb,<sup>4,44</sup> spreading transneuronally to other regions of the brain, and causing inflammation and demyelinating reactions.<sup>44</sup> Persistent inflammation in the olfactory neuroepithelium has been observed 110–119 days after the first COVID-19-related symptoms in patients with persistent olfactory loss.<sup>45</sup>

In our patients, the anosmia in the acute phase was associated with cognitive dysfunction ( $p=0.012$ ), consistent with findings from Almeria et al, who reported associations between loss of smell/taste and impairments in attention, memory, processing speed, and executive function.<sup>14</sup> Similarly, Cysique et al associated cognitive impairment with objectively tested anosmia, and with a lower work capacity.<sup>46</sup>

Other affected areas in COVID-19 patients have connections with the frontal lobe and therefore influence executive functions. The hippocampus, anterior cingulate cortex, and orbitofrontal cortex play key roles in memory and emotional regulation,<sup>47</sup> and in the processing and regulation of emotional and affective states, as well as behavior regulation.<sup>33</sup>

When discussing the expected recovery pattern in COVID-19 patients who experienced cognitive impairments, the literature shows that in non-hospitalized patients (mean patient age=45.7, SD=10.4 years) there were significant improvements in the domains of learning, memory, and executive function at 6 months after the baseline assessment.<sup>20</sup> Similarly, Ferrucci et al found that while attention, processing speed, and verbal memory tended to improve, visuospatial memory did not appear to improve at 5 and 12 months after hospital discharge (mean patient age=56.2, SD=12 years).<sup>22</sup> Conversely, another study reported significant improvements in visual memory, verbal and declarative memory, processing speed, executive function, and naming at 6 months after the first evaluation (mean patient age=49.1, SD=7.7 years).<sup>24</sup> However, patients who initially had no cognitive complaints but developed them at 6 months did not show these improvements, and exhibited lower performance compared with the group with no cognitive complaints.<sup>24</sup>

A survey of individual symptom trajectories over time revealed that reports of cognitive dysfunction increased during the first 3 months, followed by a slight decline in subsequent months. Regarding memory symptoms, these increased during the first few months and persisted for up to 6 months.<sup>48</sup> In addition, a study with a mean participant age of 45.37 (SD=20.98) years found that with a longer time since infection, patients had improvements in symptoms related to sleep, gastrointestinal and neuroendocrine pain, but progressive dysfunction in neurocognitive aspects, mainly in the ability to form words and in concentration.<sup>39</sup>

Similarly, research with follow-up at 2, 4, and 12 months post-infection in patients with mild to moderate COVID-19 found that cognitive performance was different from the normative reference at all assessment points, and that cognitive performance declined over time. The impairment profiles varied, with some patients being impaired at all of the follow-up visits (0.9%) and others showing impairment at specific time points, 2 and 12 months (2.4%), 4 and 12 months (2.4%), 2 and 4 months (3.9%), or at just one of the visits (8.7%, 13.4%, and 15% at 2, 4, and 12 months, respectively).<sup>46</sup>

A longitudinal imaging study identified greater cognitive decline between two assessment points, suggesting progressive neurodegeneration in some cases (mean patient age=65.4, SD=8.9 years).<sup>43</sup>

These findings underscore the variability in the trajectory of cognitive symptoms over time after COVID-19.<sup>20</sup> Researchers in China have proposed four distinct post-COVID-19 cognitive profiles: early-onset deterioration, late-onset deterioration, progressive deterioration, and stable cognitive status.<sup>49</sup>

A factor that permeates the cognitive profile observed in our patients from the first wave is the fact that no vaccines were available at the time of acute infection. This is supported by research showing a higher risk of memory problems in pre-vaccination studies (RR=4.84, 95% CI 3.28–7.15 vs RR=3.02, 95% CI 1.15–7) and concentration problems in pre-vaccination studies (RR=2.39, 95% CI 0.76–7.47 vs RR=2.14, 95% CI 1.25–3.67). These findings suggest that vaccination could play a protective role in reducing the risk of long COVID.<sup>50</sup> In this way, vaccination was associated with reduced odds of hospitalization, having more than five symptoms in the first week of illness, and a long duration of symptoms after the second dose, meaning that cases were less severe.<sup>51</sup> In addition, it has been found that the risk of long COVID associated with infection by the omicron variant is lower, ie 50% less, compared with the delta variant.<sup>52</sup> It has been suggested that different SARS-CoV-2 variants may induce different long COVID phenotypes.<sup>53</sup>

The progression of cognitive damage could be the result of the viral RNA remaining in the brain tissue for long periods,<sup>4</sup> leading to neuronal loss over time; or due to a prolonged process of neuroinflammation,<sup>9,54</sup> which causes severe hypoxia and, consequently, cerebral vasodilatation, cerebral edema, and ischemia.<sup>44</sup>

It could also be explained by anatomical changes in COVID-19 patients (average 141 days after onset), such as longitudinal differences in the functionally connected regions of the temporal piriform cortex and olfactory tubercle, or by a reduction in gray matter thickness in the left parahippocampal gyrus and lateral orbitofrontal cortex, in comparison with control patients. In addition, atrophy was present in regions such as the limbic area and crus II, with the latter being associated with cognitive decline; and there was a decrease in whole-brain volume, suggesting additional diffuse gray matter loss.<sup>43</sup>

The global gray matter volume (GMV) in COVID-19 patients (3 months after onset) was correlated slightly with lactate dehydrogenase (LDH) concentration; therefore, the decreased GMV in patients with elevated LDH may indicate atrophy due to a severe inflammatory response.<sup>55</sup>

Moreover, there could be an adverse dynamic of hypometabolism over time, which presumably is associated with severity; that is, more severe cases have more glucose disturbance and a longer duration of symptoms.<sup>41</sup> This was identified in our results, where we observed an association between the level of severity and the presence of cognitive impairment ( $p=0.30$ ).

On the other hand, the progressive recovery of functions could be attributed to an improvement in hypometabolism in the bilateral prefrontal area, ie, in the orbitofrontal, dorsolateral, and mesiofrontal cortex. This pattern is consistent with clinical frontal lobe syndrome. Follow-up of the subjects for a median of 5 months showed an improvement in the results of neurological examinations and indicated that the patients were autonomous in their activities of daily living. However, executive deficits were still constant, consistent with emotional diagnoses.<sup>56</sup>

In some patients, cerebral metabolism improved as early as 1 month after the first evaluation, and by 6 months, it had returned to levels comparable to those of the control group. In others, the improvement was moderate.<sup>56</sup> Moreover, in certain cases, even when there was no significant decrease in cerebral metabolism, residual neocortical hypometabolism persisted in COVID-19 patients, particularly in areas that were more affected in the acute phase, so they may take longer to recover.<sup>57</sup>

Thus, further research with more robust methodological designs is needed, including control groups, larger sample sizes, and consideration of COVID-19 waves during sample size calculations, long-term studies with follow-up periods extending beyond 12 months after infection, and the use of objective methodologies to assess cognitive functions. Such research is crucial to be able to draw more robust conclusions.

Moving on to emotional alterations, the most frequent in our subjects were depression and anxiety, as reported in the literature on post-COVID syndrome.<sup>9,21,23,58</sup> These conditions may be attributed to trauma during the infection, social isolation, and/or confinement.<sup>9</sup> In addition, misinformation about the condition, social stigmatization, feelings of uncertainty, and the perception of loss of control could contribute to these disorders.<sup>21</sup>

In this regard, studies on the general Mexican population during the first months of the pandemic reported prevalence rates ranging from 37.7% to 65.2% for symptoms consistent with anxiety, while depression was present in 36.3–51.3% of the subjects.<sup>59,60</sup> In our study, depression was observed in 32 (47.8%) and anxiety-related diagnoses (agoraphobia, anxiety disorder, and generalized anxiety) were present in 33 (49.3%).

Comparing these frequencies with those of the general population prior to the pandemic, National Health and Nutrition Survey (ENSANUT) data from 2018 showed that 17.3% of adults in Mexico experienced depressive symptoms,<sup>61</sup> while anxiety was present in 14.3% of the population in 2003.<sup>62</sup> This highlights an increase in mental



health disorders due to the COVID-19 pandemic and associated lockdowns.<sup>63</sup> In addition to other risk factors, individuals who were unemployed, had low income, lacked physical activity, were women or young adults (<35 years), were elderly, had a history of psychiatric disorders, or worked in healthcare were at a higher risk of experiencing emotional disturbances.<sup>63 64</sup>

Cognitive alterations may also have an emotional cause, as reflected in our results, in which people with depressive symptoms were 3.3 times more likely to have impaired executive function ( $\text{Exp}B=3.307$ ,  $p=0.038$ , 95% CI 0.098–0.933) compared to those without these symptoms.

Research has found that depressive symptoms are associated with self-reported memory failures, and that their predictive value is higher in patients without olfactory dysfunction, as observed in most of our sample. Emotional symptoms predicted self-reported memory failures in regression models.<sup>65</sup> Furthermore, the cognitive component of fatigue (dysfunctions in processing speed, sustained attention, and executive functions) was most strongly predicted by neuropsychiatric symptoms, such as level of depression and anxiety.<sup>66</sup>

In another study, which used the Depression Anxiety and Stress Scale-21 (DASS-21) to assess anxiety, depression, and stress, these emotional symptoms significantly influenced the majority of neuropsychological test scores, except for Test of Everyday Attention auditory reaction time and Rey figure recall.<sup>23</sup> It has also been reported in the literature that higher scores on anxiety and depression could contribute to the lack of neurocognitive improvement at 6 months.<sup>24</sup>

There is also well-documented comorbidity between depression and cognitive impairment, including evidence that depression disorder includes abnormalities in cognitive functioning and that this mood alteration increases the risk of dementia.<sup>67</sup> During the acute phase of depression, alterations have been observed in processing speed, learning, memory, verbal fluency, and attention. Although these deficits become less pronounced in the remission phase, attention, learning, memory, and working memory deficits may persist.<sup>68</sup>

A lower volume in the insula, superior temporal gyrus, inferior frontal gyrus, amygdala, hippocampus, and thalamus has been identified in patients with major depressive disorder (MDD) and mild cognitive impairment, potentially explaining their longitudinal comorbidity.<sup>67</sup> In addition, inflammation, a factor associated with MDD, is a significant feature of COVID-19, which caused systemic inflammation and may contribute to the development or exacerbation of MDD.<sup>69</sup>

## Limitations

This study has some limitations. First, there was no control group, owing to the high infectivity of the virus and the difficulty in identifying individuals who did not contract it. However, in BANFE-3 we utilized normative tables depending on educational level and age.

Second, the study design may be seen as a limitation. While a long-term study would have been ideal, the chosen design allowed us to identify an initial association between these quantitative variables through the correlation analysis. Third, there is a risk of sampling bias, as the use of non-probabilistic convenience sampling may lead to higher prevalence estimates than those observed in the literature. Nevertheless, the proportion of cognitive impairment observed in our study is consistent with, or even lower than, findings from other studies, which is likely to be due to the younger age of our sample. In addition, we tried to minimize the bias through the inclusion criteria, to ensure a sample with similar characteristics. Fourth, the sample size was too small, and dividing it into groups increased the probability of type II errors. This limitation affected the ability of the study to detect potential differences between groups, highlighting the need for larger sample sizes in future research to ensure sufficient statistical power. Nevertheless, the magnitude of correlation found in this study was high and statistically significant.

One of the main strengths of this research is the use of an evaluation instrument that emphasizes higher cognitive processes in a sample of the Mexican population. Furthermore, the inclusion of emotional aspects as part of the post-COVID patient profile and the control of educational level add significant value to the study. In addition, the consideration of waves during the acute phase of infection provides a way to continue exploring the pattern of cognitive recovery from different COVID-19 variants.

## Recommendations

Cognitive rehabilitation is essential and several therapies have been used for post-COVID patients, including Speed of Processing Training, Instrumental Activities of Daily Living Shaping,<sup>70</sup> and game-based cognitive training,<sup>71</sup> such as the

AKL-T01, a digital therapy provided through a videogame interface, to target attention and executive control. This approach has shown improvements in task-switching, processing speed, and reductions in total fatigue, cognitive fatigue, and anxiety.<sup>72</sup> Other approaches include transcranial direct current stimulation,<sup>73</sup> goal management training, which relies on metacognitive strategies to improve executive attention processes,<sup>74</sup> and an ambulatory program with neuropsychological rehabilitation, which include cognitive treatment, training in compensatory strategies, and emotional intervention,<sup>75</sup> all available through a telerehabilitation platform called Guttman NeuroPersonalTrainer®,<sup>76</sup> which includes personalized computerized cognitive exercises. This treatment has demonstrated improvements in working and verbal memory, verbal fluency, anxiety, and depression.<sup>75</sup>

## Conclusion

COVID-19 can cause alterations in executive functions, the most frequent in mental flexibility. The functions located in the orbitofrontal area, mainly stimulus inhibition, could even worsen over time in patients who contracted the infection during the first wave.

In addition, depression appears to be a potential indicator of cognitive impairment in individuals who recovered from the disease.

However, the absence of a control group, the small sample size, and the lack of patient follow-up limit the generalizability of these findings. Therefore, the conclusions of this study should be interpreted with caution.

Further research is required, with a longitudinal design and a larger sample size, incorporating a control group and groups differentiated by waves or virus variants to more accurately identify the effects of infection on cognition and mental health. Moreover, the use of neuroimaging or biomarker studies is essential to understanding how COVID-19 affects brain function.

Finally, we emphasize the importance of cognitive rehabilitation and psychological support as essential components in the multidisciplinary treatment of patients who have experienced SARS-CoV-2 infection.

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## Disclosure

The authors declare that they have no conflicts of interest.

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