*Int. J. Morphol.*,
*41(5)*:1310-1316, 2023.

# Structural Brain Alterations in Individuals Post-COVID-19: A Systematic Review

## Alteraciones Estructurales Cerebrales en Individuos Post COVID-19: Una Revisión Sistemática

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**MORALES-VERDUGO, J.; LOZANO-LOZANO, J. A.; PÉREZ-ROJAS, F.; MENDEZ-REBOLLEDO, G.; CARREÑO VÁSQUEZ, A.** Structural brain alterations in individuals post-COVID-19: a systematic review. *Int. J. Morphol., 41(5)*:1310-1316, 2023.

**SUMMARY:** Although COVID-19 is primarily considered a respiratory pathology, it has been observed to impact other bodily systems, including the nervous system. While several studies have investigated anatomical changes in brain structures, such as volume or thickness post-COVID-19, there are no comprehensive reviews of these changes using imaging techniques for a holistic understanding. The aim of this study was to systematically analyze the literature on brain changes observed through neuroimaging after COVID-19. We conducted a systematic review according to PRISMA guidelines using Web of Science, Scopus, Medline, Pubmed, Sciencedirect, and LitCOVID. We selected studies that included adult patients during or after COVID-19 development, a control group or pre-infection images, and morphometric measurements using neuroimaging. We used the MSQ scale to extract information on sample characteristics, measured anatomical structures, imaging technique, main results, and methodological quality for each study. Out of 1126 identified articles, we included 19 in the review, encompassing 1155 cases and 1284 controls. The results of these studies indicated a lower volume of the olfactory bulb and variable increases or decreases in cortical and limbic structures' volumes and thicknesses. Studies suggest that brain changes occur post-COVID-19, primarily characterized by a smaller olfactory bulb. Additionally, there may be variations in cortical and limbic volumes and thicknesses due to inflammation or neuroplasticity, but these findings are not definitive. These differences may be attributed to methodological, geographical, and temporal variations between studies. Thus, additional studies are required to provide a more comprehensive and quantitative view of the evidence.

**KEY WORDS: Coronavirus; COVID-19; Neuroimaging; Neurological manifestations; Brain.**

## INTRODUCTION

COVID-19 is primarily considered a respiratory pathology, but its impact on other systems, including the nervous system, has been observed (Petersen *et al*., 2020). Neurological symptoms have been reported in patients with COVID-19, ranging from mild symptoms such as headaches and anosmia, to severe symptoms such as neurovascular events and cognitive impairment (Harapan & Yoo, 2021). Additionally, it has been suggested that these neurological symptoms may increase the risk of developing neurodegenerative conditions (Fotuhi *et al*., 2020).

Various mechanisms have been proposed to explain how SARS-CoV-2 can affect the nervous system (Pouga *et al*., 2021), which are similar to those of other neurotropic viruses, such as MERS-CoV and SARS-CoV-1 (Bohmwald *et al*., 2018). According to Pouga *et al*. (2021), the severity of the infection and the immune system's response play a crucial role in determining the extent of the virus's impact. The virus can cause meningeal irritation or invade the central nervous system through the olfactory nerves via axonal transport or hematogenous route by disrupting the blood-brain barrier. Animal studies (Jiao *et al*., 2021; Seehusen *et al*., 2022) have identified SARS-CoV-2 genetic material in areas of the olfactory pathway, such as the olfactory bulb, trigone, entorhinal cortex, and hippocampus, indicating that the virus can invade the central nervous system through axonal transport and cause neuro-inflammation in these regions (Pantelis *et al*., 2020; Jiao *et al*., 2021; Seehusen *et al*., 2022).

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This research was funded by the Fondo Nacional de Desarrollo Científico y Tecnológico FONDECYT Regular, CONICYT, Chilean government (ref. no. 1190945)

Received: 2023-06-05 Accepted: 2023-07-14

The impact of COVID-19 on the central nervous system has been investigated using human neuroimaging techniques (Choi & Lee, 2020; Parsons *et al*., 2021). A recent systematic review examined the anatomical distribution of neurological events, such as thrombosis or hemorrhages in COVID-19 patients, identifying primarily affected regions in the superior temporal gyrus, precentral gyrus, thalamus, corticospinal tract, and corpus callosum (Parsons *et al*., 2021). However, few neuroimaging studies have focused on changes in brain structures such as volume, thickness, or depth post-COVID-19 without the occurrence of such neurological events (Lu *et al*., 2020; Altunisik *et al*., 2021; Griffanti *et al*., 2021). To date, we have not found any reviews that analyze these changes and offer a comprehensive overview of the existing scientific evidence. Therefore, the objective of this study was to systematically analyze the literature on brain morphometric changes in post-COVID-19 patients using neuroimaging techniques.

## MATERIAL AND METHOD

**Design of the Review:** The current systematic review was registered in PROSPERO (registration CRD42022380245) and conducted in adherence to the "Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Page *et al*., 2021). The current study did not require ethical approval.

**Criteria for Study Inclusion:** The inclusion criteria were: i) Population or patients of interest: over 18 years (e.g, studies with a population of children or animals were excluded); ii) Exposure: SARS-CoV-2 infection; iii) Comparison: patients without COVID-19, or neuroimaging of participants prior to pathology; iv) Outcome: morphometric parameters of brain structures using structural neuroimaging. The exclusion criteria were: i) Participants with pre-existing neurological infections or pathologies; ii) Studies without primary data (e.g., systematic reviews or meta-analyses); iii) Without access to full text (e.g., conference proceedings); and vi) Duplicate studies.

**Search Strategy:** The search was conducted in September 2022. We employed a combination of controlled descriptors extracted from medical subject headings (MeSH), and free-text terms derived from the specific language used in the subject area. Each keyword included in our study was specifically chosen to address all relevant components of the PECO (Patients, Exposure, Comparison and Outcomes) question format (Morgan *et al*., 2018). The search was conducted by topic (title, abstract, and keywords) in multiple databases, including Web of Science, Scopus, PubMed, ScienceDirect, and LitCOVID. The following combination of keywords and Boolean terms were used: (("COVID-19") OR ("COVID19") OR ("SARS-CoV-2") OR ("SARS COV 2")) AND (("Brain") OR ("central nervous system") OR ("CNS") OR ("cerebral")) AND (("Magnetic resonance") OR ("MRI") OR ("computerized tomography") OR ("neuroimage") OR ("neuroimaging")) AND (("Morphology") OR ("Morphometry") OR ("Morphometrics") OR ("Volume") OR ("Thickness") OR ("anatomy")). This search strategy was used for the databases Medline, Scopus, PubMed, LitCOVID, and Web of Science. To accommodate the lower limit of Boolean terms in ScienceDirect, we utilized the search strategy: (("COVID-19") OR ("SARS-CoV-2")) AND (("Central nervous system") OR ("Brain")) AND (("Neuroimage") OR ("Neuroimaging")) AND (("Morphometry") OR ("Volume") OR ("Neuroanatomy")). Furthermore, a comprehensive examination of the reference lists of all chosen articles was performed to identify any additional studies which could be included in the review.

**Study Selection:** The selection process was independently conducted by two researchers (JMV and JLL). In the event of any disagreement during the process, a consensus was reached or a third researcher (FPR) was consulted. To assess the agreement between coders, Cohen's Kappa coefficients were calculated. The interpretation of Cohen's Kappa score was as follows: scores ≤ 0 indicated no agreement, [.01-.20] indicated slight agreement, [.21-.40] indicated fair agreement, [0.41-0.60] indicated moderate agreement, .61-.80 indicated substantial agreement, and [.81- 1] indicated almost perfect agreement (McHugh, 2012). During the screening stage, titles and abstracts were assessed to determine which studies could potentially meet the eligibility criteria for a full-text review, and duplicates were removed after identifying the relevant studies.

**Data Extraction:** The study characteristics, population, exposure, and main outcomes were independently extracted from the published articles by the same two researchers previously identified. To obtain additional information, the authors of the articles were contacted when deemed necessary. To enable careful examination and interpretation of the analyzed studies, we applied the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

**Quality Assessment:** Additionally, a methodological quality assessment was conducted for the included studies using the Methodological Quality Scale (MQS) (Chacón-Moscoso *et al*., 2016, 2023), which has been reported to have high reliability. The 10-items MQS (See10-items MQS https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1217661/full) measures external validity (items 1-4), internal validity (items 5-8), and construct validity (items 9-10). Additionally, it allows for obtaining a global score. For each type of validity, a score < 0.5 is interpreted as low, values between [0.5 - 0.75] as medium, and > 0.75 as high. Finally, a qualitative analysis was conducted to compare the imaging measurements of the studies, as well as their moderating and methodological variables, to draw conclusions about the available literature.

**Data Synthesis**: Once the included studies were extracted and synthesized, they were grouped into ad hoc summary tables. These tables included i) general characteristics of the studies (author, year, sample size, and sample characteristics); ii) imaging assessment characteristics (technique, sequence, measurement type, and measured brain structures); iii) results of general brain volume measurements; iv) results of measurements of regional cortical thickness; v) results of measurements of regional gray and white matter.

## RESULTS

**Search Results:** The search strategy applied to the databases yielded 1,126 articles. After removing duplicates (n=292), title and abstract screening was conducted (n=834), leading to the exclusion of 792 articles. Out of the remaining articles (n=42), a full-text review was conducted on 39 to apply eligibility criteria, resulting in the exclusion of 20 studies for various reasons: 10 studies did not employ morphometric measurements of brain structures; 6 studies did not report the use of healthy controls or previous images as a comparator; 2 studies included subjects with previous neurological conditions; 1 study was a review article; and 1 study had unavailable measurement values. Ultimately, 19 articles were included. The steps of the search strategy are illustrated in Figure S1 (See Supplementary Material FS1 https://osf.io/wjq8f).

The intercoder agreement indices were very good for both the study selection process based on title and abstract (Kappa = 0.968; p < 0.001; 95% CI, .931-1), and the full-text analysis (Kappa = 0.952; p < 0.001; 95% CI, 0,860-1).

**Characteristics of the included studies:** The process of selecting studies yielded a total of 19 included in the analysis (See Supplementary Material TSI and TSII https://osf.io/wjq8f).

The total sample size was 2433, with 1155 patients (557 males and 598 females) and 1278 controls. Ten studies specified the severity level of COVID-19, using different criteria such as symptoms, hospitalization, admission to intensive care units, or the severity criteria defined by the World Health Organization. The remaining 9 studies did not

Table I. Clinical aspects of included study participants.

| First Author (year) | Symptoms | Severity | Time after infection |
|---|---|---|---|
| Altunisik (2021) | Olfactory dysfunction, headache, ageusia, vertigo | NS | 2-8 Weeks |
| Besteher (2021) | Depression symptoms, lower MoCA test score | Mild, Moderate, and Severe | 2-16 Months |
| Bhagavan (2021) | Action tremor | Severe | 1 month post-hospital discharge |
| Burulday (2021) | Anosmia | NS | 3 Days |
| Cattarinussi (2022) | Headache, hyposmia, hypogeusia, depressive symptoms, and extrapyramidal symptoms | NS | 0-9 Months |
| Cecchetti (2022) | Headache, hyposmia, dysgeusia, confusion, asthenia, depressive symptoms, impairment of memory, executive functions, and visuospatial skills | NS | 0-2 Months |
| Chiu (2020) | Anosmia | NS | 2 Months |
| Chung (2021) | Anosmia | Mild | NS |
| Douaud (2022) | Greater time to perform numerical tests | Inpatients and outpatients | NS |
| Frosolini (2022) | Headache, hyposmia, hypogeusia | NS | NS |
| Gore (2022) | NS | NS | NS |
| Griffanti (2021) | Anosmia, headache, impairment of visuospatial abilities | Moderate, and Severe | 2-3 Months |
| Hafiz (2022) | Fatigue, anosmia, headache, respiratory symptoms | NS | 2 Weeks post-hospital discharge |
| Lu (2020) | Memory dysfunction, anosmia | Mild, Moderate, and Severe | 3-4 Months |
| Petersen (2021) | Asymptomatic | Mild and Moderate, | 9 Months |
| Qin (2021) | Fatigue, headache | Mild, and Severe | Acute phase and 3 months |
| Raman (2021) | Headache, impairment of visuospatial abilities | Moderate, and Severe | 2-3 Months |
| Tian (2022) | Fatigue, Headache | Mild, and Severe | 3-19 months post-hospital discharge |
| Tsivgoulis (2020) | Anosmia, Ageusia, Headache | NS | NS |

(NS) Not specified. (MoCA) Montreal Cognitive Assessment.

specify the severity of the infection. Regarding the neurological symptoms presented by the patients, the most common signs were hyposmia, anosmia, ageusia, hypogeusia, and headache. Fatigue and vertigo were also reported, and five studies indicated a decrease in more complex abilities such as visuospatial skills, memory, and extrapyramidal symptoms. (Lu *et al*., 2020 ; Griffanti *et al*., 2021 ; Cattarinussi *et al*., 2022 ; Cecchetti *et al*., 2022 ; Douaud *et al*., 2022). The post-diagnosis evaluation time for COVID-19 varied from 3 days post-infection (Burulday *et al*., 2021) to 10 months post-infection (Tian *et al*., 2022). The clinical characteristics of these participants are summarized in Table I.

In all studies, magnetic resonance imaging (MRI) was used, for which mostly digital measurement techniques such as voxel-based morphometry, FreeSurfer, or artificial intelligence systems were employed. In six studies, measurements were made manually by experienced radiologists (Chiu *et al*., 2020; Altunisik *et al*., 2021; Burulday *et al*., 2021; Frosolini *et al*., 2022; Gore *et al*., 2022; Tsivgoulis *et al*., 2022). The main measurements that were taken corresponded to global and regional brain volumes, thickness, cortical density, as well as the length and depth of cerebral sulci. Among the regional structural measurements reported in the studies is the olfactory bulb (n=160) (Chiu *et al*., 2020; Altunisik *et al*., 2021; Burulday *et al*., 2021; Chung *et al*., 2021; Frosolini *et al*., 2022; Griffanti *et al*., 2021; Gore *et al*., 2022; Tsivgoulis *et al*., 2022); olfactory tract (n=30) (Altunisik *et al*., 2021); thalamus (n=166) (Besteher *et al*., 2021; Hafiz *et al*., 2021; Qin *et al*., 2021; Tian *et al*., 2022); basal nuclei (n=226) (Lu *et al*., 2020; Besteher *et al*., 2021; Hafiz *et al*., 2021; Qin *et al*., 2021; Tian *et al*., 2022); amygdala (n=477) (Besteher *et al*., 2021; Burulday *et al*., 2021; Douaud *et al*., 2021; Hafiz *et al*., 2021); and various cerebral gyri and tracts (n=678) (Lu *et al*., 2021; Besteher *et al*., 2021; Douaud *et al*., 2021; Griffanti *et al*., 2021; Hafiz *et al*., 2021; Qin *et al*., 2021; Tian *et al*., 2022).

**Global brain measurements:** Eight studies report measurements of global brain volumes (Hafiz *et al*., 2021; Lu *et al*., 2020; Petersen *et al*., 2021; Raman *et al*., 2021; Cattarinussi *et al*., 2022; Bhagavian *et al*., 2022; Cecchetti *et al*., 2022; Douaud *et al*., 2022). Most studies did not identify significant differences in global brain measurements between post-COVID-19 patients and controls. Among the studies that did identify significant differences, Lu *et al*., 2020 reported a higher global volume of gray matter, and Petersen *et al*., 2021 reported an increase in cortical thickness in post-COVID-19 subjects. On the other hand, Douaud *et al*., 2022 observed a lower brain volume to intracranial volume ratio, along with higher cerebrospinal fluid volume and lateral ventricle volume.

**Regional measurements of gray and white matter in the brain:** Nine studies reported significant differences in specific brain regions (Lu *et al*., 2020; Tsivgoulis *et al*., 2020; Altunisik *et al*., 2021; Besteher *et al*., 2021; Burulday *et al*., 2021; Griffanti *et al*., 2021; Qin *et al*., 2021; Douaud *et al*., 2022; Gore *et al*., 2022), with contradictory results for certain structures. On the one hand, Griffanti *et al*., 2021, Qin *et al*., 2021, Douaud *et al*., 2022, and Tian *et al*., 2022, found decreased volume in cortical regions and brain tracts in post-COVID-19 subjects, while Lu *et al*., 2020, and Besteher *et al*., 2021 reported increased gray matter volumes in many of the same regions. Most of the studies that differentiated patients according to severity (Lu *et al*., 2020; Besteher *et al*., 2021; Griffanti *et al*., 2021, Qin *et al*., 2021, Douaud *et al*., 2022, and Tian *et al*., 2022) identified greater differences in more severe cases.

Regarding olfactory structures, five studies identified statistically significant differences in their measurements (Lu *et al*., 2020; Tsivgoulis *et al*., 2020; Altunisik *et al*., 2021, Burulday *et al*., 2021; Gore *et al*., 2022). Lu *et al*. 2020 identified a greater volume of gray matter in the olfactory cortex of post-COVID-19 subjects compared to controls, while the rest of the studies agreed that there is a lower volume (Altunisik *et al*., 2021, Burulday *et al*., 2021; Gore *et al*., 2022) or height (Tsivgoulis *et al*., 2020) of the olfactory bulb.

In Table II, the statistically significant findings of the measurements performed in the different studies are summarized.

**Assessment of the risk of bias of primary studies:** In terms of the overall score of the MQS scale, 2 out of the 19 studies analyzed (Bhagavan *et al*., 2021; Chiu *et al*., 2020) had a low (scores of .3), while the remaining studies had a medium overall score (scores between .56 and .75). Moreover, 17 of the studies showed high external validity (scores between .88 and 1), while 2 (Bhagavan *et al*., 2021; Chiu *et al*., 2020) had medium external validity (scores between .67 and .75). These studies did not provide explicit criteria for the inclusion and exclusion of the study units and did not perform cross-group comparisons.

All the analyzed studies exhibit low internal validity (scores between .13 and .38), as eighteen of them employed a pre-experimental design, with only one utilizing a quasi-experimental design (Chung *et al*., 2021). In addition, only four studies conducted follow-up assessments between 3 to 10 months after the initial evaluation (Chung etal., 2021; Cecchetti *et al*., 2022; Douaud *et al*., 2022; Qin *et al*., 2021; Tian *et al*., 2022), while only one study (Chung *et al*., 2021) conducted at least two measurements of the same dependent or outcome variable.

Table II. Significant differences in regional measurements in the included studies.

| | Measurement technique | Anatomical structure | SSD |
|---|---|---|---|
| Altunisik (2021) | Manual | Olfactory bulb | - |
| | | Olfactory tract | - |
| Besteher (2021) | Voxel-based morphometry | Middle frontal gyrus, inferior frontal gyrus, insula lobe, posterior orbital gyrus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, fusiform gyrus, postcentral gyrus, angular gyrus, hippocampus, parahippocampal gyrus, ambient gyrus, amygdala, caudate nucleus, putamen, globus pallidus, thalamus | + |
| Burulday (2021) | Manual | Olfactory bulb | - |
| Douaud (2022) | Software: FreeSurfer, Vóxel Wise Maps | Lateral orbitofrontal cortex | - |
| Gore (2022) | Manual | Olfactory bulb | - |
| | | Olfactory sulcus | - |
| Griffanti (2021) | Software: FIRST, FreeSurfer, BIANCA | Superior frontal gyrus, lateral occipital gyrus, middle frontal gyrus, supramarginal gyrus, hippocampus, isthmus of the cingulate gyrus | - |
| | | Transverse Temporal Gyrus | + |
| Lu (2020) | Voxel-based morphometry | Superior temporal gyrus, middle temporal gyrus, inferior parietal lobule, cuneus | - |
| | | Central sulcus operculum, transverse temporal gyrus, hippocampus, insular cortex, olfactory cortex, cingulate gyrus. | + |
| Qin (2021) | Software: ANT, Atropos, Direct, XTRACT | Fasciculus cinguli., corticospinal tract, aslant frontal tract, inferior fronto-occipital fasciculus, superior longitudinal fascicle, inferior longitudinal fascicle, optic radiation. | - |
| Tian (2022) | Software: ANT, Atropos, Direct, XTRACT | Putamen, nucleus accumbens, thalamus, corticospinal tract, aslant frontal tract, major forceps, minor forceps, inferior longitudinal fasciculus, vertical occipital fasciculus. | - |
| Tsivgoulis (2020) | Manual | Olfactory bulb | - |

(SSD) Statistical Significance Direction ($p<0.05$) of the changes observed in cases in comparison to controls.

All studies showed medium construct validity (scores between .5 and .75). Although all the studies used highly standardized instruments that had undergone validity and reliability studies, none of them provided a clear conceptual or empirical definition of their outcome variables. The assessment of the risk of bias is shown in Table SIII (See Supplementary Material TSIII https://osf.io/wjq8f).

## DISCUSSION

The main findings of the included studies indicate that are changes in various cortical and subcortical regions and and tracts based on the severity level. Nevertheless, except for the changes observed in olfactory regions, there is considerable debate surrounding which areas are affected, and which changes correspond to higher or lower parameters such as volume, length, or thickness. Therefore, further research is needed to elucidate the specific regions and parameters affected by the severity of the condition.

The findings of the included studies suggest that the decrease in volume of the olfactory bulb corresponds with other imaging findings, such as changes in magnetic resonance imaging intensity, as well as symptoms like anosmia and ageusia, indicating changes in olfactory areas. Specifically, these changes in volume support prior research indicating the significance of the olfactory bulb in processing olfactory information (Choi & Lee, 2020; Collantes *et al*., 2021; Najt *et al*., 2021).The olfactory tract, sulcus (Altunisik *et al*., 2021), and olfactory cortex (Lu *et al*., 2020) were also found to undergo changes in the other studies included. These studies suggest that SARS-CoV-2 may infiltrate the central nervous system through an axonal transport mechanism via olfactory cells after infection of the olfactory mucosa (Kumari *et al*., 2021; Najt *et al*., 2021).

Although there is some clarity regarding the impact of COVID-19 on the olfactory bulb, the findings of the included studies are contradictory regarding changes in other brain regions. Lu *et al*. (2020) and Besteher *et al*. (2021) report an increase in gray matter volume in structures related to olfactory areas or the limbic system, such as the hippocampus, cingulate gyrus, or insular lobe. Both studies suggest that the differences may be due to possible neuroplastic changes, such as functional compensation following olfactory dysfunction, while also acknowledging other potential causes such as neuroinflammation.

On the other hand, several studies (Griffanti *et al*., 2021; Qin *et al*., 2021; Douaud *et al*., 2022) have reported a decrease in the volume and thickness of various brain structures, including the overall volume of gray matter, the volume of the orbitofrontal cortex (Douaud *et al*., 2022), and the volume of the frontal, parietal, temporal, occipital cortex, hippocampus, and cingulate gyrus (Griffanti *et al*., 2021), as well as a decrease in the volume of the thalamus, basal nuclei, and various association and projection tracts (Qin *et al*., 2021). These findings suggest that neuro-invasion and neuro-inflammation lead to a reduction in several brain dimensions, which is more pronounced in severe cases.

Although studies present contrasting results, they concur on the following aspects: i) the areas involved are directly or indirectly associated with the olfactory and limbic systems, ii) the invasion route is through the olfactory system, which can lead to inflammation, and iii) this can lead to clinical olfactory dysfunction (Altunisik *et al*., 2021), memory impairment (Lu *et al*., 2020), worse performance in visuospatial ability tests (Douaud *et al*., 2022), cognitive tests, or symptoms of depression (Besteher *et al*., 2021). Additionally, there were studies that did not identify significant differences in structural measurements (Cecchetti *et al*., 2022; Raman *et al*., 2022), and studies that observed that differences decreased after neurosensory training (Chung *et al*., 2021) and follow-up (Tian *et al*., 2022). The studies, along with others such as Qin *et al*., Besteher *et al*. (2021), and Griffanti *et al*. (2021), suggest that the noted changes may be rather partially reversible. However, additional molecular, structural, and functional neuroimaging studies are needed to confirm this.

Differences in the results of the included studies may be attributed to several factors, such as the place and timing of infection, the characteristics of the population, and the predominant SARS-CoV-2 variants at each time (Tatsi *et al*., 2021, Seehusen *et al*., 2022). Other aspects to consider include the level of severity, supportive measures, time elapsed since infection, type of imaging technique and measurement methods. Regarding the severity of the infection, which has been shown to impact the changes identified in studies (Qin *et al*., 2021; Griffanti *et al*., 2021; Douaud *et al*., 2021), differences in severity levels among patients may have influenced the results of the included studies. This could be due to possible variations in patients' viral load, which has been associated with greater neuro-invasion and more severe consequences (Pouga *et al*., 2021).

Regarding the bias assessment of the nineteen included studies, three of them (Cecchetti *et al*., 2022; Douaud *et al*., 2022; Tian *et al*., 2022) achieved a high total score on the scale, while two studies obtained a low score (Bhagavan *et al*., 2021; Chiu *et al*., 2020), and the remaining studies received a medium score. Despite seventeen of the nineteen studies obtaining high scores for external validity, all of them scored low in internal validity due to the absence of randomized experimental designs, lack of repeated measures of the different study groups over time, and no use of masking as a control technique. The urgency of the healthcare context in which they were conducted (Jung *et al*., 2021) may have contributed to these limitations. In addition, all studies showed a medium construct validity despite using highly standardized instruments, none of them provided a clear conceptual and empirical definition of their outcome variables.

The main limitation of this study is that we were unable to conduct a meta-analysis of the results due to the availability of data from a limited number of studies. In the future, when we can include a greater number of studies with greater homogeneity in their measurement techniques and outcome variables, we may be able to perform an analysis of effect size and identify possible moderator variables.

Finally, this review provides a comprehensive overview of the available evidence on imaging-based structural brain changes, the main affected areas, and the reported neurological consequences. This serves as a reference for future studies on functional neuroimaging or the effects of various interventions to prevent or mitigate the consequences of severe COVID-19 infection on the nervous system. Furthermore, this review can help visualize the effects of new variants and evaluate the effectiveness of vaccination treatments for such conditions.

## CONCLUSION

According to available literature, post-COVID-19 brain changes vary depending on disease severity and are characterized by decreased dimensions of the olfactory bulb, as well as possible increases (due to inflammation) or decreases in volumes and thicknesses of cortical, nuclear, and limbic system structures. The variations in findings may be attributed to geographic and temporal context, as well as methodological differences.

Supplementary Materials. The data materials are available upon request from the corresponding author.

**FUNDING.** This research was funded by the Fondo Nacional de Desarrollo Científico y Tecnológico FONDECYT Regular, CONICYT, Chilean government (ref. no. 1190945)

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**MORALES-VERDUGO, J.; LOZANO-LOZANO, J. A.; PÉREZ-ROJAS, F.; MENDEZ-REBOLLEDO, G.; CARREÑO VÁSQUEZ, A.** Alteraciones cerebrales estructurales en individuos post-COVID-19: una revisión sistemática. *Int. J. Morphol., 41(5)*:1310-1316, 2023.

**RESUMEN:** Aunque el COVID-19 se considera principalmente una patología respiratoria, se ha observado que afecta otros sistemas corporales, incluido el sistema nervioso. Si bien varios estudios han investigado los cambios anatómicos en las estructuras cerebrales, como el volumen o el grosor posteriores a la COVID-19, no hay revisiones exhaustivas de estos cambios que utilicen técnicas de imágenes para una comprensión holística. El objetivo de este estudio fue analizar sistemáticamente la literatura sobre los cambios cerebrales observados a través de neuroimagen después de COVID-19. Realizamos una revisión sistemática de acuerdo con las pautas PRISMA utilizando Web of Science, Scopus, Medline, Pubmed, Sciencedirect y LitCOVID. Seleccionamos estudios que incluyeron pacientes adultos durante o después del desarrollo de COVID-19, un grupo de control o imágenes previas a la infección y mediciones morfométricas mediante neuroimagen. Utilizamos la escala MSQ para extraer información sobre las características de la muestra, las estructuras anatómicas medidas, la técnica de imagen, los principales resultados y la calidad metodológica de cada estudio. De 1126 artículos identificados, incluimos 19 en la revisión, que abarca 1155 casos y 1284 controles. Los resultados de estos estudios indicaron un menor volumen del bulbo olfatorio y aumentos o disminuciones variables en los volúmenes y espesores de las estructuras corticales y límbicas. Los estudios sugieren que los cambios cerebrales ocurren después del COVID-19, caracterizados principalmente por un bulbo olfatorio más pequeño. Además, pueden haber variaciones en los volúmenes y grosores corticales y límbicos debido a la inflamación o la neuroplasticidad, pero estos hallazgos no son definitivos. Estas diferencias pueden atribuirse a variaciones metodológicas, geográficas y temporales entre estudios. Por lo tanto, se requieren estudios adicionales para proporcionar una visión más completa y cuantitativa de la evidencia.

**PALABRAS CLAVE: Coronavirus; COVID-19; Neuroimagen; Manifestaciones neurológicas; Cerebro.**

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