

## ARTICLE REVIEW

## Neurobiological aspects of the development of psychopathologies in health professionals while coping with the SARS-CoV-2 pandemic

### *Aspectos neurobiológicos do desenvolvimento de psicopatologias nos profissionais de saúde durante o enfrentamento à pandemia do SARS-CoV-2*

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Silva GC, Santos MJMN, Magalhães PRDM, Bem Junior LS. Neurobiological aspects of the development of psychopathologies in health professionals while coping with the SARS-CoV-2 Pandemic / *Aspectos neurobiológicos do desenvolvimento de psicopatologias nos profissionais de saúde durante o enfrentamento à pandemia do SARS-CoV-2*. Rev Med (São Paulo). 2021 Jan-Feb;100(1):49-56.

**ABSTRACT:** *Introduction:* The SARS-CoV-2 pandemic, although recent, has impacted the healthcare systems globally, resulting in a tremendous psychological overload for healthcare professionals who are actively coping with this disease. The exposure to stressing factors has triggered diverse neuro-biochemical alterations that propitiate the development of psychopathologies, as anxiety, depression, Post-Traumatic Stress Disorder, and Burnout Syndrome. *Objective:* This article seeks to understand the neurobiological alterations that occur in healthcare professionals working in the pandemic, due to chronic stressors, as well as psychological problems related to such changes, through an integrative literature review. *Method:* Integrative bibliographic review, utilizing the PubMed and SciELO databases. *Results:* The healthcare professionals who cope with Covid-19 are subjected to acute and chronic stressing situations, bringing about the triggering of reactions, as abnormalities in the APH axis alterations in the monoamines; increased inflammation; as well as diminished neurogenesis and neuroplasticity, that bring about the development of psychological disorders. *Conclusion:* It was concluded that stressful situations faced by these professionals who work in coping with Covid-19; cause the result of neurobiological alterations, as well as the appearance of more propitious psychopathological conditions.

**Keywords:** Neurobiology; Mental health; Healthcare personnel; Coronavirus.

**RESUMO:** *Introdução:* A pandemia do SARS-CoV-2, apesar de recente, impactou os sistemas de saúde em todo o mundo, resultando em grande sobrecarga psicológica para os profissionais da saúde atuantes no enfrentamento desta doença. A exposição a fatores estressores desencadeia diversas alterações neurobioquímicas que propiciam o desenvolvimento de psicopatologias como a ansiedade, depressão, Transtorno do Estresse Pós-Traumático e Síndrome de Burnout. *Objetivo:* o presente artigo busca, através de uma revisão integrativa da literatura, compreender as alterações neurobiológicas que ocorrem em profissionais da área de saúde atuantes na pandemia, devido aos estressores crônicos, bem como os problemas psicológicos associados a tais mudanças. *Método:* Revisão bibliográfica integrativa, utilizando-se as bases de dados PubMed e SciELO. *Resultados:* Os profissionais de saúde que atuam no enfrentamento da Covid-19 estão submetidos a situações de estresse agudo e crônico, acarretando no desencadeamento de reações como anormalidades no eixo HPA alterações nas monoaminas; aumento da inflamação; além da diminuição da neurogênese e neuroplasticidade, o que leva ao desenvolvimento de distúrbios psicológicos. *Conclusão:* Conclui-se que a situação de estresse vivenciada por estes profissionais que atuam no enfrentamento da Covid-19, leva ao desenvolvimento de alterações neurobiológicas, bem como ao aparecimento de quadros mais propícios de psicopatologias.

**Palavras-chave:** Neurobiologia; Saúde mental; Pessoal de saúde; Coronavírus.

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## INTRODUCTION

The new coronavirus pandemic began in December 2019, associated with the development of pneumonic conditions and deaths. It started in China and subsequently spread worldwide<sup>1</sup>. The Pandemic caused by SARS-CoV-2, despite recent, was capable of abruptly modifying diverse aspects of life in society. Due to this context, different society sectors have had to adapt to countless necessities that have emerged in just a few months<sup>2</sup>.

Thus, those who are in charge of coping with the pandemic, as the class of healthcare professionals has been one of the most affected by the sudden instauration of the pandemic, have been obliged to overload their work schedules. They are being exposed to contamination by the circulating virus and insufficiency of resources for treating all those who have been affected by the infection. They constitute stressful factors present in these professionals' lives, and therefore they are coupled to negative repercussions in their mental health<sup>2,3,4</sup>.

As stress is the response to adverse stimuli, it is capable of altering the physiological balance. Since the capacity to deal with stressful factors is the differential factor for developing psychopathologies or not. Such adverse conditions generate an adaptive response from the human organism, seeking to preserve its stability, which occurs in various aspects of the human organism, such as the emotional, cognitive, behavioral, and biological factors. It is estimated that when it is exposed to critical levels of stress, homeostatic mechanisms can fail<sup>5</sup>.

Thence, studies were performed on rodents to demonstrate how chronic psychosocial or environmental stress can correlate with the development of synaptic deficits in neural plasticity, as well as the deregulation of neurotransmitters culminating in depressive-like behavior. Furthermore, there are indications that inflammatory processes are related to physiopathology present in disorders similar to depression, as seen in a study that reported on cancer patients who were administered cytosine immunotherapy (interferon alfa and Interleukin- 2) who suffer from an increased risk of developing depressive symptoms, or in studies that have revealed increased levels of pro-inflammatory cytokines, a tumor necrosis factor, or interleukin 6 in patients subjected to chronic stress<sup>6</sup>.

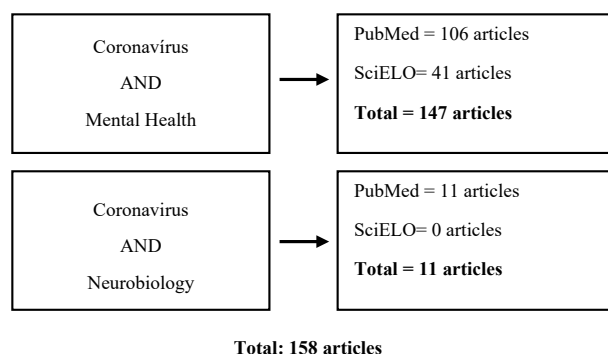
Thereby, diverse neurobiological mechanisms can be related, according to research studies, on developing psychological disorders, as further research is necessary to broaden the perception of such a process. Consequently, it is appropriate to emphasize some mechanisms that can be related to the development of psychopathologies as noradrenergic, serotonergic, dopaminergic alterations, increased inflammations, abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, as well as decreased

neurogenesis and neuroplasticity<sup>7,8,9</sup>

Such disorders are related to these professionals' various problems, as developing depressive symptoms, anxiety, and Burnout syndrome, which can be observed in the pandemic period<sup>8,10</sup>. Thus this article endeavors, through an integrative literature review, to understand the neurobiological alterations that may occur in healthcare professionals coping with the pandemic due to chronic stressors, as well as psychological problems related to such changes.

## METHODS

The literature review has been performed in an integrative nature, carried out by reviewing domestic and international literature on this specific subject. The bibliographic survey was searched online in the PubMed and Scientific Electronic Library Online (SciELO) databases. The inclusion of other databases was limited due to poor results present when the research was performed in June 2020. The study was conducted employing the following indexed descriptors in the "Descritores em Ciências da Saúde" (Health Science Descriptors) (DeCS) combined the "AND" Boolean operator: *Coronavirus AND mental health, and Coronavirus AND neurobiology*. The articles were published in Portuguese and English dating from 2015 to 2020 and pertinent to the defined subject. Irrelevant items to the addressed issue were excluded, and studies concluded with inconclusive results.



Source: Silva GC, et al., 2020.

**Fluxogram 1** - The combined selected articles x frequency

## RESULTS

A total of 158 articles were identified utilizing the descriptors, databases, and the pre-established publication period. After the critical reading of the titles and abstracts and using the pre-established inclusion and exclusion criteria, 14 articles were selected for integrative review. A scientific research analysis chart was prepared (Chart I), reporting the main retrieved results.

In a descriptive and comparative analysis regarding

the methodological designs that utilized the selected research findings, there was a large percentage of observed cross-sectional studies performed through the validated electronic questionnaires (A4, A5, A6, A7, A8, A10, and A13). Among the sampling characteristics, participants' variation was noticed, ranging from 371 (A10) to 14,825

interviewed (A4). Physicians and nurses in China performed all the above-mentioned cross-sectional studies. The remaining studies addressed original articles (A2, A3, A11, and A14) and literature reviews (A1, A9, and A12) performed in Brazil (A1, A12), England (A2), and the United States (A3, A11).

**Chart 1** – The selected studies' characterization according to the title; author/country/year; magazine; and main results. Recife, PE, Brazil, 2020

N.	Title	Author/Country/ year	Journal	Main results
A1	Mental illness in the general population and health professionals during Covid-19: a scoping review.	Moreira et al. <sup>1</sup> Brazil 2020	Texto e Contexto Enfermagem	The Sars-CoV-19 pandemic increased anxiety, depression, stress, and post-traumatic stress disorder in the general healthcare professional population.
A2	The mental health of healthcare workers in the COVID-19 era.	Greenberg <sup>22</sup> England 2020	Nature Reviews Nephrology	Healthcare professionals providing care during the pandemic are exposed to a greater risk of suffering mental health damages. The team giving care need access to adequate psychosocial support.
A3	COVID-19, mental health, and suicide risk among health care workers: looking beyond the crisis.	Reger et al. <sup>21</sup> United States 2020	Journal of Clinical Psychiatry	The challenges faced while directly combating Covid-19 impact the mental health of physicians. Psychosocial support must be provided during the crisis and afterward.
A4	Mental health status of medical staff in emergency departments during the Coronavirus disease 2019 epidemic in China.	Song et al. <sup>10</sup> China 2020	Brain, Behavior, and Immunity	The study demonstrates the immediate need for psychological intervention for the medical class coping with the pandemic.
A5	Impact on mental health and perceptions of psychological care among medical and nursing staff in Wuhan during the 2019 novel coronavirus disease outbreak: A cross-sectional study.	Kang et al. <sup>29</sup> China 2020	Brain, Behavior, and Immunity	A large portion of healthcare professionals in the city of Wuhan-China is suffering from a range of mental health disorders. Specialized psychological support must be invested for these professionals and future professionals who work in the medical field to prevent the mental impact caused by diverse existing unexpected situations in these professionals' lives.
A6	Screening for Chinese medical staff mental health by SDS and SAS during the outbreak of COVID-19.	Liang et al. <sup>23</sup> China 2020	Journal of Psychosomatic Research	During the unexpected health crisis caused by COVID-19, health professionals are exposed to a great deal of psychological pressure. These professionals' mental health must not be neglected, and it must be intervened daily, with adequate training and psychological support. It is crucial to maintain the mental health of these professionals who are actively coping with this crisis.
A7	The social-psychological impact of the COVID-19 pandemic on medical staff in China: a cross-sectional study.	Dong et al. <sup>27</sup> China 2020	European Psychiatry	Around a fourth of the participating medical professionals participating in this study have faced psychological problems during the Sars-CoV-19 pandemic. It is necessary to provide psychological support to these actively coping professionals.
A8	Psychological status of medical workforce during the COVID-19 pandemic a cross-sectional study.	Lu et al. <sup>24</sup> China 2020	Psychiatry Research	Physicians who provide care in the pandemic face the highest degree of fear, anxiety, and depression. The professionals who actively cope with the front line face twice a greater risk of developing anxiety and depression. Supportive strategies must be established for these individuals.

*Continue*

**Chart 1** – The selected studies' characterization according to the title; author/country/year; magazine; and main results. Recife, PE, Brazil, 2020 *continuation*

N.	Title	Author/Country/ year	Journal	Main results
A9	Mental health and psychological interventions during the new coronavirus pandemic (COVID-19).	Schimdt et al. <sup>2</sup> Brasil 2020	Estudos de Psicologia	The Covid-19 pandemic is considered one of the largest public emergencies suffered this century. That fact contributes to the increase of psychological problems that affect the population and health professionals. Thus, it is necessary to provide increased psychological support to the entire population during this period.
A10	Post-traumatic stress symptoms of health care workers during the coronavirus disease 2019	Yin et al. <sup>25</sup> China 2020	Clinical Psychology and Psychotherapy	The article analyzed 377 healthcare professionals who worked during the Covid-19 pandemic in China. They presented post-traumatic stress symptoms and decreased sleep quality.
A11	Preserving mental health and resilience in frontline healthcare workers during COVID-19	Santarone et al. <sup>4</sup> Estados Unidos 2020	American Journal of Emergency Medicine	Healthcare professionals who work during the pandemic are exposed to chronic stress, which is harmful to their mental and physical health. Thus, mental well-being and resilience must occur through various measures provided by PPEs and psychological support whenever necessary.
A12	When health professionals look death in the eye: the mental health of professionals who deal daily with the 2019 coronavirus outbreak	Neto et al. <sup>3</sup> Brazil 2020	Psychiatry Research	Healthcare professionals have been exposed to various stressor agents due to the Covid-19 pandemic, contributing to high levels of anxiety and psychological exhaustion observed in these professionals.
A13	Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019	Lai et al. <sup>26</sup> China 2020	JAMA Network Open	The article reports a study performed on 1257 healthcare professionals who have been coping with Covid-19 in China. Such professionals have reported anxiety and depression symptoms, especially among female nursing professionals.
A14	Recommended psychological crisis intervention response to the 2019 novel coronavirus pneumonia outbreak in China: a model of West China Hospital	Zhang et al. <sup>28</sup> China 2020	Precision Clinical Medicine	An interaction model was created seeking to harness technology to help healthcare professionals psychologically, aiming at decreasing psychological problems related to Covid-19.

Source: Silva GC, et al., 2020.

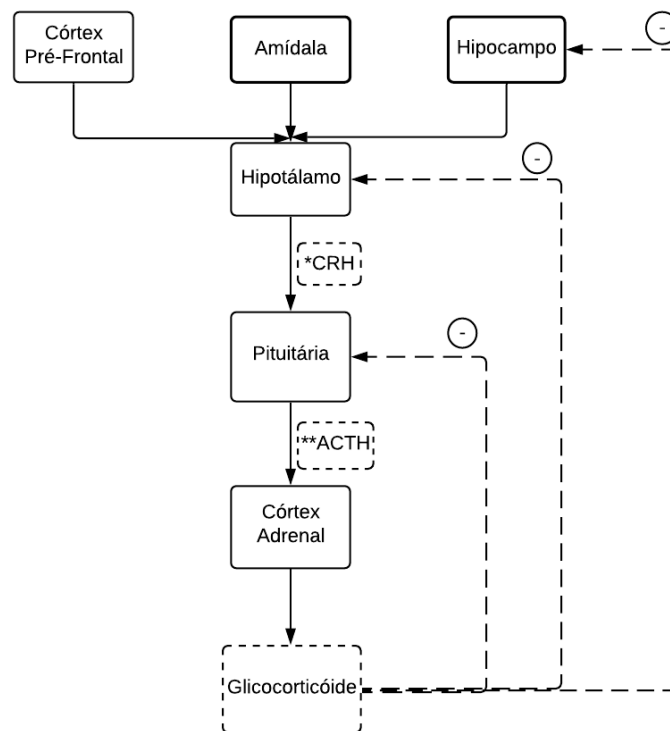
## DISCUSSION

Manifestations from large-scale infectious diseases seem to moreover subject healthcare professionals to a psychological burden. In 2003, during the SARS-CoV epidemic, depression and post-traumatic stress disorders were confirmed, respectively ranging from 28.9% to 31.2% among the population submitted to quarantine<sup>11</sup>. In the healthcare professional population, there are significant stress levels that have been identified in those who work in the emergency departments during the epidemic, moreover physicians and nurses. The primary sources of stress or stressors have been identified as vulnerability, concern for

their health, spreading of the virus, family members' health, changes in work practices, and isolation.

The exposure to psychological stressors, as experienced by healthcare professionals while working and coping with the SARS-CoV-2 Pandemic, is responsible for changes in varied and complex neurobiological complexes. One of these mechanisms that justifies the prevalence of psychopathologies in the medical-class-care providers is related to the APH axis<sup>8,9</sup>.

The APH axis is an essential set of neuroendocrine mechanisms that make up the stress response system, collaborating with the autonomous nervous system, and it releases monoamines<sup>8</sup>.



\*CRH- Hormônio Liberador de Corticotrofina  
 \*\*ACTH- Hormônio Adrenocorticotrófico

Source: Silva GC, et al., 2020.

**Figure 2:** Physiology of the hypothalamic-adrenal axis

The stressor stimulus acts on the subgenual prefrontal cortex, suppressing its inhibitory activity on the hypothalamus, making the APH activity begin<sup>8</sup> (Figure 2). The first mechanism consists of releasing the Corticotrophin-releasing hormone (CRH) by the paraventricular nucleus of the hypothalamus<sup>8</sup>. The CRH is provided access to the pituitary gland by the Hypophysis-portal circulation, where it will stimulate the Adrenocorticotrophic Hormone (ACTH) secretion. Then ACTH will act on the fasciculated area of the adrenals stimulating glucocorticoids' production and secretion. Glucocorticoids are the final product from this series of events, as they promote a series of metabolic alterations, as gluconeogenesis, increased cardiac contractility, insulin resistance, and increased coagulation activity. Once those glucocorticoids are released, they connect to the glucocorticoid receptors (GRs) in the paraventricular nucleus, suppressing the secretion of CRH by negative feedback<sup>12,13</sup>.

The APH axis faces the first relationship with psychopathologies through the GR activity<sup>13,14</sup>. The linking protein controls that to FKBP 51 gene, codified by the FKBP5 gene<sup>13</sup>. Some studies suggest that this gene's epigenetic alterations are related to chronic stress, displaying deregulation in the APH axis operation,

culminating in the development of psychopathologies as Depressive Disorder<sup>8,13,14</sup>.

It has been observed that alterations of the APH axis are not involved in the most commonly studied depressor or even focused on the generalized treatment of psychopathologies. There are even reports on unsuccessful monotherapy seeking to treat these alterations, despite some indications that such treatments could benefit small and specific groups<sup>15</sup>.

Another mechanism triggered by stressor factors and intimately related to alterations in the APH axis is associated with altering the level of circulating monoamines<sup>7</sup>. Such monoamines modulate the brain network, protruding to the midbrain nuclei and the brainstem (dopamine in the ventral tegmental area, serotonin in the dorsal raphe in the periaqueductal gray area, and the norepinephrine in the locus coeruleus). It was also noticed that these neurotransmitters interfere reciprocally in their concentrations in the brain, therefore being interrelately<sup>16</sup>.

It has been observed that this related noradrenaline (NA) neurotransmitter noradrenaline is associated with regulating the mood of depressive patients. Chronic stress is a factor that stimulates the production and release of NA, causing increased secretion of the corticotropin from



the hypothalamus that in turn triggers the release of ACTH by the pituitary gland that stimulates the adrenal gland to release NA and cortisol. Such elevations in the cortisol and NA levels substantially increase the sympathetic impulse and release of cytokines, which impose reciprocal effects on the PPH axis and neurotoxins<sup>7</sup>.

Furthermore, exposure to stressor stimuli triggers a neuroinflammatory response, propitiating a vicious cycle involving stress, inflammation, and depression<sup>7</sup>. Psychological stress promotes a sterile pro-inflammatory response that occurs in the absence of any pathogens. Endogenous receptors activate the sterile inflammatory route for molecular patterns associated with damage (DAMPs), which are non-microbial molecules that elevate the response to physical and pathological stress. The DAMPs group involves diverse molecules, such as S100 proteins, unique acids, and adenosine triphosphate<sup>17</sup>.

The pro-inflammatory cytokines released in response to DAMPs by the route dependent on the  $\kappa$ B factor (NF- $\kappa$ B), like IL-6, TNF- $\alpha$ , are actively transported by epithelial and endothelial cells through the blood-brain barrier, and IL-1 $\beta$  is transduced by the vagus nerve<sup>7,18</sup>. The DAMPs activate the microglia, the CNS's innate immune cells through Toll-like microglial receptors (TLRs), and Receptor for Advanced Glycation Endproducts (RAGE), promoting the release of inflammatory mediators<sup>18</sup>. Stress promotes hyperactivity of TRL2 and TRL4, generating an exacerbated pro-inflammatory response<sup>17,18</sup>.

The neuroinflammatory factors derived from microglia contributed to alterations in neuroplasticity and behavioral deficits<sup>18</sup>. Neuroinflammatory mediators, moreover IL-1 $\beta$ , reduce the neurogenesis and neuronal differentiation in the hippocampus. The pro-inflammatory cytokines released by the microglia induce neuronal molecular changes, generating, in specific regions, changes in the expression of the neurotrophins as BDNF<sup>19</sup>.

BDNF stimulates survival and neuronal differentiation, as this is important for the homeostasis of neuroplasticity mechanisms<sup>19</sup>. It is expressed in the amygdalae, prefrontal cortex, and hippocampus, and it acts through the tyrosine kinase receptors-B-BDNF (BDNFTrkB)<sup>18,19</sup>. Diverse studies have demonstrated a reduction of the serum levels in patients submitted to chronic stress and depression, suggesting the role of BDNF in the physiopathology of depression, anxiety, and post-traumatic stress disorder<sup>7</sup>.

Besides that, there is astrocyte stimulation that amplifies the pro-inflammatory signalization initiated by the microglia<sup>18</sup>. In psychological stress situations, the microglia remains in an active state, producing cytotoxic molecules as pro-inflammatory cytokines and glutamate, resulting in insufficient levels of neurotrophic support and decreased neurogenesis, decreased brain volume, and neuronal atrophy in the hippocampus and prefrontal cortex<sup>17,18</sup>.

Moreover, the pro-inflammatory cytokines increase the indoleamine activity 2,3-dioxygenase, the essential enzyme through degradation of tryptophan, known as the kynurenine route<sup>17,18</sup>. In stressful situations, this process results in increased quinolinic acid production, generating neurotoxicity and decreased availability of tryptophan. Decreased tryptophan results in a lower production of serotonin in the brain; thus, this means developing depressive disorder and neurodegeneration<sup>18</sup>.

The serotonergic changes were analyzed through research studies that revealed a metabolic decrease of serotonin in the brain of patients who suffer from depressive disorders. The tricyclic antidepressants, whose active mechanism occurs through inhibiting the reuptake of serotonin or serotonin and noradrenaline, are responsible for an increase of these monoamines in patients and thereby resulting in improved mood and well-being<sup>7</sup>. When serotonin is in normal concentrations in the dorsal nucleus raphe, it serves the purpose of reducing fear and decreasing anxiety, as well as activating a portion of the neurons for the corticotrophin release factor (CRF)<sup>20</sup>.

Besides the serotonergic changes, there were also changes observed in dopamine availability, an essential monoaminergic neurotransmitter providing the sensation of reward and motivation in individuals. Diverse studies have revealed that neurovegetative symptoms related to depression include anecdotal and reduced motivation, which are related to malfunctioning of this reward system, demonstrating alterations in the dopaminergic transmission and in the mesolimbic pathway that occur in psychiatric psychopathological disorders, such as depression, post-traumatic stress disorder, and Burnout syndrome<sup>7,21</sup>.

In this context, anxiety and depression are more prevalent psychopathologies in the population after chronic exposure to stress<sup>5</sup>. Thus, anxiety disorders, like post-traumatic stress disorder (PTSD), can originate from situations experienced in troublesome manners that expose people to stressful and traumatic moments. The involved neurochemical mechanisms in both situations are very similar<sup>5,22</sup>.

Therefore, various chronic psychological stressors among healthcare professionals who work coping with this disease are related to the Covid-19 pandemic period. The most significant predominance of psychological symptoms was reported to occur in previous pandemics and epidemics. Recent studies have revealed that the prevalence of depression in healthcare professionals affected 50.7% and symptoms related to stress 70.4% during the pandemic period<sup>23</sup>. Further studies report, in the current pandemic, an increase in the prevalence of post-traumatic stress disorder among healthcare professionals starting in the first month of combating Covid-19<sup>24</sup>, as well as dire fear affecting 70% of the studied medical teams<sup>25</sup>. Another study<sup>26</sup> reported a large quantify of symptoms, as depression (50.4%), anxiety (44.6%), insomnia (34.0%), and anguish (71.5%),

present in these professionals, as there is a need for creating strategies to provide psychosocial support to healthcare professionals, seeking to decrease the risks of psychological suffering, as well as progression to psychopathologies among the professionals in this field<sup>27,28,29</sup>.

## CONCLUSION

There is a growing prevalence in the literature on developing scientific research work proving the impact of psychological stressors in the imbalance of neuro-biochemical homeostasis, neurogenesis, and neuroplasticity and through the activation of the APH axis, releasing CRH, ACTH, increased levels of ANS serum cortisol recruitment, the sterile pro-inflammatory response activated by DAMPs and alterations in the noradrenaline, dopamine, and serotonin. Thus, three routes are related and interconnected, as it is necessary to analyze all these mechanisms to

achieve a better understanding of the psychological aspects facing healthcare professionals coping with the Covid-19 pandemic.

The impacts from the Covid-19 pandemic are understood to include numerous psychological stressors that can favor the appearance of psychopathologies, such as anxiety, depression, Burnout Syndrome, and Post-Traumatic Stress Disorder among healthcare professionals since there have been abrupt changes in their coping while facing stressors, and subjected to diverse mechanisms in response to stress and bringing about significant changes in these healthcare workers. The greatest degree of stress, anxiety, and depression in the pandemic period can be related to such alterations. We, as a result of this, emphasize the necessity for future studies addressing psychic stress experienced by diverse professions coping with the SARS-CoV-2 pandemic, as well as its impacts on the prevalence of these psychopathologies.

**Participation of the authors:** *Gisele Carvalho Silva, Maria Júlia Moura Nascimento Santos, Pedro Renan de Melo Magalhães:* Research and data collection, analysis, and interpretation, manuscript composition, critical review of the manuscript. *Luiz Severo Bem Junior:* Councilor, study idealization, research, and data collection, analysis, and interpretation, manuscript composition, critical review of the manuscript.

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