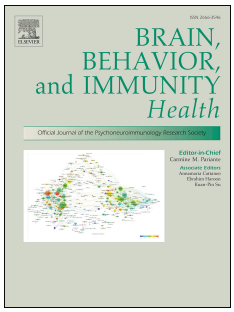

THREE INSIGHTS ON PSYCHONEUROIMMUNOLOGY OF MOOD DISORDERS TO BE TAKEN FROM THE COVID-19 PANDEMIC

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THREE INSIGHTS ON PSYCHONEUROIMMUNOLOGY OF MOOD DISORDERS TO BE TAKEN FROM THE COVID-19 PANDEMIC

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It is well known that depression and some domains of depressive psychopathology such as anhedonia and suicidal behavior exhibit seasonal variation. Factors that may be implicated in this association include variations in light exposure and the incidence of viral infections, such as influenza. Replicated data from ecological studies show a seasonal peak of suicide in the spring (Postolache et al., 2010), which is even more pronounced in individuals with a history of mood disorders. It is also largely recognized the existence of an overlap between the peak of viral respiratory infections and the suicide rates, but methodological caveats prevent definitive cause-effect conclusions.

In recent months, the world was taken by surprise by the outbreak of a coronavirus (SARS-CoV-2) pandemic (COVID-19). Coronaviruses have been recognized as a respiratory and neurotropic virus with the ability to penetrate the Central Nervous System (CNS) via the olfactory neural pathway. Viral infections may be associated with psychiatric symptoms as a direct result of the virus infection in the brain but most often due to activation of a powerful immune-inflammatory response (Cheng et al., 2004). Coronavirus infection has recently been implicated in the onset of psychosis (Severance et al., 2009), major depression and bipolar disorder (Okusaga et al., 2011).

However, the COVID-19 pandemic is a unique opportunity to advance the understanding of the association of neurotropic respiratory viruses with mood disorders and suicide. It is necessary not only because mood disorders are highly prevalent, but also because the use of anti-inflammatory interventions is a promising but still underexplored treatment strategy. In this point of view, we speculate about some few insights that the COVID-19 pandemic could potentially offer to the scientific community to be further fully explored.

1. **COVID-19 is an opportunity for investigation of the naturalistic association between psychiatric symptoms and viral respiratory infections.**

Although the association between viral infections, mood disorders, and suicide attempts is plausible, there is still a need to systematically examine it. The naturalist observation of the individuals with COVID-19 infection, further use of antidepressants as well as admissions and visits due to suicide attempts offers a unique opportunity to go from the ecological designs to cohort studies, which are much more methodologically powerful. Furthermore, as one could speculate that the immune response to viruses may create a vulnerability to mood episodes in some subpopulations, the assessment of serum titters for COVID-19 might be an important tool to be integrated into research in neuropsychoimmunology of depression, in the same way it was recently done with cytomegalovirus.

2. **If the hypothesis of immunosenescence is correct, COVID-19 response in individuals with mood disorders will be similar to elderly people.**

One of the hypotheses for the persistent and longstanding activation of inflammatory response in individuals with mood disorders in linked to a theory that those who suffer from depression and bipolar disorder present on average a premature aging of different body systems including the immune system. Data supporting this view came from the documentation of increase of subpopulations of senescent T lymphocytes, a predominance of memory cells, the relative lack of naïve T cells, an increase in pro-inflammatory cytokines and shortening of telomeres in individuals with mood disorders (Rizzo et al., 2018). One of the strategies for investigating the immune system function in individuals with mood disorders is to observe their response to injected antigenic substances such as endotoxin. The outbreak of a viral infection is a

unique opportunity to investigate the impact of an acute immune challenge on different domains of the psychopathology of mood disorders.

3. If COVID-19 and mood disorders are associated, it is possible that anti-SARS-CoV-2 medications have a therapeutic utility in mood disorders.

Although there is no approved specific medication to treat COVID-19, the antimalarials hydroxychloroquine and chloroquine have been investigated due to their immunomodulatory and anti-inflammatory activity. Chloroquine has shown to have antiviral activity in vitro and hydroxychloroquine was effective in reducing the viral carriage on day 6 of treatment (Gautret et al., 2020). In addition, azithromycin added to hydroxychloroquine was even more efficient for reduction of the amount of virus (Gautret et al., 2020). The mechanisms involved in antimalarial immunomodulatory activity have intrigued immunologists for years (Schrezenmeir and Dorner 2020). They act in multiple molecular targets but seem to have a unique property of modulating lysosomal activity and interfering with autophagy. Interestingly, Major Depression Disorder (MDD) has been associated with increased or dysregulated autophagy in some critical regions such as the hippocampi and there is some evidence from animal studies that at least part of the effect of different antidepressants can be exerted by the stabilization of lysosomal activity (Gulbins et al., 2018). Similarly, azithromycin and other macrolides antibiotics also had shown to exhibit anti-inflammatory activity. Interestingly, azithromycin was also very efficient in inhibiting depressive-like behaviors in animal models of inflammation-induced depression, also reducing the levels of classic proinflammatory cytokines (Hao et al., 2013). Together, this evidence suggests that medications potentially useful to modulate the immune system in order to make the organism more resilient to COVID-19 also represent an opportunity to repurpose drugs as antidepressants.

The COVID-19 pandemic is bringing significant challenges to people, families, communities and countries, but is also teaching us several lessons. Historically, every epidemic teaches us more about the immune system, vaccines, medicines, epidemiology, and public interventions to contain its spread. It necessarily invites the scientific community to preserve critical thinking and to keep the capacity to use our resources to understand more about the brain functioning when faced with an immune challenge. It also invites the academic community to endeavor collaborative research in order to translate insights into novel approaches to understand, prevent and treat mood disorders.

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