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Viewpoint

The three frontlines against COVID-19: Brain, Behavior, and Immunity

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ABSTRACT

The pandemic outbreak of coronavirus disease 2019 (COVID-19) is raising global anxiety and fear of both real and perceived health threat from the virus. Overwhelming evidence shows infected patients experiencing neuropsychiatric complications, suggesting that the “psychoneuroimmunity” model might be beneficial in understanding the impact of the virus. Therefore, this Special Issue on “Immunopsychiatry of COVID-19 Pandemic” was launched immediately after the pandemic was declared, with the first paper accepted on the March 25th, 2020. A total of ninety-three papers were accepted, the last one was on the July 10th, 2020 when the initial acute phase started declining. The papers of this Special Issue have illuminated the social impact, psychopathology, neurological manifestation, immunity responses, and potential treatments and prevention on COVID-19. For example, anxiety disorders, mood disorders, and suicidal ideation are most common psychiatric manifestations. COVID-19 infection can have central and/or peripheral nervous system symptoms, including headache, sleep disorders, encephalopathy, and loss of taste and smell. A “three-steps” Neuro-COVID infection model (neuro-invasion, clearance and immune response) was established. The current therapeutic interventions for COVID-19 include supportive intervention, immunomodulatory agents, antiviral therapy, and plasma transfusion. Psychological support should be implemented, improving the psychological wellbeing, as well as to enhance psychoneuroimmunity against COVID-19.

The pandemic outbreak of coronavirus disease 2019 (COVID-19) is raising global anxiety and fear about the real and perceived health threat from the virus. Overwhelming evidence shows infected patients experiencing neuropsychiatric complications on top of the predominant target of respiratory system (Kim and Su, 2020), suggesting the psychoneuroimmunity model might be beneficial (Lazzari et al., 2020). As the awareness and preparedness against the COVID-19 is now at fullest deployment, early on there was an insufficient understanding of how to mitigate morbidity issues, like autoimmune, neurocognitive, and mental health needs (Vindegaard and Benros, 2020). Therefore, we made an immediate call for the Special Issue of *Brain, Behavior, and Immunity* on the “Immunopsychiatry of COVID-19 Pandemic”, covering from the biopsychosocial impacts to patients and the care providers, as well as the basic and clinical research.

The COVID-19 caused government lockdown the city to control the

pandemic; accurate screening and diagnosis tool for medical staff were urgently needed, as well as the sufficient mental support. The researchers have illuminated the social impact, psychopathology, neurological manifestation, immunity responses of COVID-19, trying to find the potential treatment and prevention. Therefore, this Special Issue on “Immunopsychiatry of COVID-19 Pandemic” was launched immediately after the pandemic was declared, with the first paper accepted on the March 25th, 2020. A total of ninety-three papers were accepted, the last one was on the July 10th, 2020 when the initial acute phase started declining. In this editorial, we reviewed and summarized all the published articles related to this special issue, connecting the efforts of all researchers who have contributed to COVID-19 research.

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1. Lockdown

Is lockdown a necessary measure and what is the immunopsychiatry impacts? During the lockdown, emulation suicides, economic crisis, and recession, all had negative psychological impact on individuals, increasing the suicide rate and depressive features, further worsening stigma (Guo et al., 2020, Hao et al., 2020, Mamun and Ullah, 2020, Meda and Slongo, 2020). Furthermore, Zhu et al., recommended that centralized isolation was not only convenient to get timely treatment and interventions, but effective to cut off transfection (Zhu et al., 2020a). Controversially, a relative high prevalence of mental illnesses was found in the quarantined individuals, due to the impacts on daily life, rather than the control measure of quarantine (Zhu et al., 2020b), and social isolation strategies decreased the likelihood of clinically dysfunctional coronavirus anxiety, even when the individuals were under stressful event (Milman et al., 2020).

To improve mental health during the lockdown, Chen et al., used the online questionnaire and reported physical exercise might be beneficial (Chen et al., 2020a), while a family-centered approach might have the potential benefits to optimize the psychological management (Liu et al., 2020a). In addition, Ren and his colleagues' found that it is necessary to make the information open, transparent and timely (Ren et al., 2020), although the intensity of exposure to media COVID-19 information was positively associated with the individuals' distress (Yao, 2020). Applying health belief such as encouraging lifestyle modification also helped stress appraisal and coping strategies (Mukhtar, 2020).

2. Screening, diagnosis and medical staff

Screening tools or effective diagnostic instruments are urgently needed, because the COVID-19 pandemic and mitigation efforts carry a mental health toll among medical staff, patients, and general population (Ransing et al., 2020). It is very important to continue tracking the development of vicarious traumatization in medical staff as well as the general public (Ghaffari et al., 2020, Li et al., 2020b). For example, Joob et al., reported that traumatization was caused among the Thailand medical staff by high workload, lack of protective devices, non-effective infection control system, and direct insult by patients (Joob and Wiwanitkit, 2020). In addition, the impact of COVID-19 on different people such as African Americans, individuals with low cognitive function, and elite athletes, suggested that the COVID-19 is a heterogeneous disease; therefore, a standard screening tool is urgently needed (Ajilore and Thames, 2020, Batty et al., 2020, Lassale et al., 2020, Mehrsafari et al., 2020, Sominsky et al., 2020).

The medical staff, as well as the volunteer medical staff, were at high risk of mental health problems during the COVID-19 pandemic, and the majority of mental health workers lacked professional training for psychological crisis intervention (Li et al., 2020a). Non-infectious disease specialists have experienced varying, but increased levels of depression, anxiety and insomnia during this COVID-19 pandemic, which could be reduced by sufficient levels of protective equipment and workplace training (Liu et al., 2020b). The targeted psychological intervention measures should be developed to improve the mental health of non-medical workers on the front-line of COVID-19 epidemic, especially the females and younger individuals (Fang et al., 2020). Thus, expanding the availability of well-prepared mental health professionals is needed (Yang et al., 2020), and all medical staff must have complete and accurate knowledge on COVID-19; using telepsychiatry for practice (Kinoshita et al., 2020) and the internet and television for public health education is helpful (Ko et al., 2020). Rapid mental health interventions could improve the medical staff's mental health and physical health perceptions (Kang et al., 2020). In the United States, a National Suicide Prevention Lifeline was activated (Montemurro, 2020).

3. Psychopathology

The first longitudinal study on the mental health of general population was reported by Wang et al., during the COVID-19 pandemic in China; they focused on mental illnesses and the impact of quarantine and lockdown, suggesting that governments should focus on effective methods of disseminating COVID-19 knowledge and teaching correct containment methods (Wang et al., 2020). Then, the first data available on the Italian population showed that affective temperament and attachment style predict psychological impact during the COVID-19 pandemic (Moccia et al., 2020).

Anxiety disorders, mood disorders, and suicidal ideation were the most common psychiatric manifestations during the COVID-19 pandemic (Nalleballe et al., 2020); even the convalescent COVID-19 patients had high self-reported depression (Yuan et al., 2020). Too much or repetitive COVID-19 thinking could induce anxiety and cause clinical dysfunction (Lee, 2020). Poor sleep quality among COVID-19 patients was also associated with a slow recovery and an increased need for intensive care (Zhang et al. 2020a). Among patients with mental disorders, the COVID-19 pandemic appeared to disrupt daily routines, cut social ties, and increase financial worries and fears of the future (Frank et al., 2020).

The predictive models created by Gonzalez-Sanguino et al., showed that the greatest protector was spiritual well-being, while loneliness was the strongest predictor of mental illnesses (Gonzalez-Sanguino et al., 2020); physical health, mental health, and job satisfaction of healthcare staff were other potential predictors (Zhang et al., 2020b). Geographical variation was also present: compared with China, Jahanshahi et al., reported that the Iranian adults have more distress (Jahanshahi et al., 2020); in Croatia, during the earthquake co-occurring with COVID-19 pandemic, more people showed mental illnesses than the infection; furthermore, mental illnesses might impede recovery process (Marko et al., 2020). Timely identification of psychological distress and precise classifying of the mental health needs will facilitate development of targeted psychological interventions (Zhang et al., 2020c).

4. Neurological manifestation

COVID-19 infection can have a wide variety of central and/or peripheral nervous system symptoms, including headache, sleep disorders, encephalopathy, seizures, acute cerebrovascular disease, impaired consciousness, dizziness, loss of taste and smell neuroleptic malignant syndrome and anti-NMDA receptor encephalitis (Kajani et al., 2020, Nalleballe et al., 2020, Panariello et al., 2020), as well as neuropsychiatric sequelae such as mood changes, psychosis, neuromuscular dysfunction, or demyelinating processes (Troyer et al., 2020). COVID-19 patients frequently presented with subjective neurological symptoms in their early stage of the disease; cutaneous hyperesthesia was also reported (Krajewski et al., 2020, Liguori et al., 2020). Several COVID-19 cases with delirium or meningoencephalitis were also reported (Duong et al., 2020, Hosseini et al., 2020), and the COVID-19 virus was detected in cerebrospinal fluid by PCR in a case with encephalitis (Duong et al., 2020, Huang et al., 2020).

In some cases, the central and/or peripheral nervous system dysfunction by COVID-19 was similar to Guillain-Barré syndrome; thus, plasma therapy was applied in severely affected patients. Several COVID-19 patients with pneumonia had fair clinical response to plasma therapy; however, among COVID-19 patients with Guillain-Barré syndrome, the effect of plasma therapy has not yet been reported (Coen et al., 2020, Gupta et al., 2020).

5. Immunity, biochemistry and physiology

COVID-19 is highly contagious because most persons lack immunity against this novel virus. Horn et al., proposed an immunopsychiatry model of COVID-19 (Horn et al., 2020). To link the neurological

complication and the immunopsychiatry model, Wu et al., reviewed the possible neuro-invasion mechanisms among COVID-19 and other coronaviruses infections (Sun et al., 2020, Wu et al., 2020a), suggesting matrix metalloproteases and the host proteases might involve in this neuroinvasion (Bongetta et al., 2020, Vavougiou, 2020a). In addition, gastrointestinal dysfunction, such as diarrhea, as well as olfactory and gustatory impairments, might be caused by neuroinvasion by COVID-19 (Esposito et al., 2020, Vavougiou, 2020b). Furthermore, massive infiltration of immune cells in the olfactory epithelium and lamina propria of infected animals in the early stage of infection was found (Bryche et al., 2020), indicating why anosmia could be an early indicator (De Santis, 2020). The above findings support that the virus enters the brain through axons of olfactory bulb neurons and the angiotensin converting enzyme 2 (ACE2) receptor may play an important role in this (Bostancikliglu, 2020). Furthermore COVID-19 may induce potential pain sensation (Su et al., 2020). However, currently no obvious pathological evidence was found to support viral infection in nerve tissue, and only short-term effects of COVID-19 on nervous system were reported (Wu et al., 2020b). A potential “three-steps” Neuro-COVID infection model (neuroinvasion, clearance and immune response) was also proposed (Panciani et al., 2020).

From a neurological point of view, the hypercoagulation and aneurysm instability partially due to systemic COVID-19 inflammation might induce severe brain hemorrhage, with a case with concomitant subarachnoid hemorrhage and COVID-19 reported (Muhammad et al., 2020), and the physicians and medical staff should pay attention to potential risk of thromboembolic complications among COVID-19 patients (Mongan et al., 2020). The COVID-19 patients could present with cerebrovascular accidents to minimize their mortality and morbidity; therefore, timely assessment and hyperacute treatment should be performed (Avula et al., 2020).

6. Massive inflammation and related neuropsychiatric manifestations

Almost all individuals with COVID-19 present with lung involvement; the clinical immune responses of COVID-19 are similar to SARS-CoV and MERS-CoV. Higher levels of inflammatory markers were found in blood, and the serum levels of several inflammatory cytokines are positively associated with disease severity; moreover, the severe COVID-19 cases are more likely to have hyperinflammation and/or cytokine storm (Chen et al., 2020b, Zhou et al., 2020). COVID-19 affects central and/or peripheral nervous system both directly and indirectly (Jasti et al., 2020). Early studies from Wuhan showed neutrophilia, lymphopenia, and increased systemic inflammatory proteins such as Interleukin 6 and C-Reactive protein are associated with severe COVID-19 infection and unfavorable outcomes (Chen et al., 2020c). COVID-19 directly binds to ACE2 and induced anosmia, ageusia, and central respiratory failure. Through the massive inflammation, The COVID-19 indirectly induced stroke, toxic-metabolic encephalopathy, acute inflammatory demyelinating polyneuropathy/Guillain Barre syndrome, and other neuropsychiatric manifestations, such as psychosis, insomnia, and mood changes (Oxley et al., 2020, Xiang et al., 2020, Zhao et al., 2020).

7. Treatment and prevention

The Special Issue described potential therapeutic interventions for COVID-19, including supportive intervention, immunomodulatory agents, antiviral therapy, and convalescent plasma transfusion (Chen et al., 2020d, Zhang et al., 2020d). Immunomodulatory medications for rheumatoid arthritis and other targets, such as CCL2, CCR5 or EGFR inhibitors, may have the potential to treat severe COVID-19 patients (Ray et al., 2020). Immunoglobulin A vaccination inducing a local protective immunity within the mucosa where pathogenic infection is initiated may have potential benefit (Chao et al., 2020). Cannabinoids

was found as a plausible option to be added as an adjunct on COVID-19 patients with lung inflammation (Byrareddy and Mohan, 2020). Supportive intervention such as Ayurveda could positively influence immunity (Golechha, 2020, Rajkumar, 2020); recognizing the uniqueness of each individual would also help them adapt and promote mental health (Zhai and Du, 2020). Moreover, Qiu et al., summarized the recent systemic supportive interventions to maintain mental wellness in public population, isolated patients, and frontline medical staff (Qiu et al., 2020).

The internet media such as Facebook, Google, and Twitter have been growing rapidly in the past decade and have become relevant to potential disease prevention. Google related methods were performed to investigate the population interest and the COVID-19 disease spreading, suggesting the importance of public awareness of “hand washing”, “COVID-19 symptoms”, “social distancing” and “lock down” and medical therapeutic direction (Lin et al., 2020, Springer et al., 2020a, Springer et al., 2020b). More online information seeking was related to insomnia, rather than depression and suicide (Misiak et al., 2020). In Twitter, Bhat et al., performed sentiment analysis, and found that even though users are quarantined, yet they are hopeful (Bhat et al., 2020).

An unhealthy lifestyle was identified as a risk factor for COVID-19 hospitalization, suggesting that adopting simple lifestyle changes can have potential benefit (Hamer et al., 2020); physical activity could also help maintain emotional stability, counteract the negative effects of isolation, and improve immune competency (Simpson and Katsanis, 2020). Healthy foods and eating habits might have the potential to reduce susceptibility to severe complications (Butler and Barrientos, 2020). Specific nutritional interventions (e.g. omega-3 polyunsaturated fatty acids) have immunomodulation effects and may potentially improve the immunity to counteract both physical and mental impact of COVID-19 (Chang et al., 2020). In addition, Tan et al., found that the psychoneuroimmunity prevention measures in China had the potential to maintain the low prevalence of psychiatric symptoms among the workforce who returned to work (Tan et al., 2020).

The history of face mask and its related information was reviewed (Goh et al., 2020); face mask restrictions have the potential to protect against the COVID-19 and increase the level of perceived self-protection, as well as the level of social solidarity, improving mental health well-being (Szczesniak et al., 2020).

8. Conclusion

We linked the psychoneuroimmunity model to the three frontlines: Brain, Behavior, and Immunity, and described the detail below. Brain involves both psychology and neurology. The medical staff, as well as the general population, felt anxious and low mood under the stress of COVID-19. The direct neuroinvasion of COVID-19 induced headache, sleep disorder, olfactory and gustatory impairments, and more severe encephalopathy. In addition to neuroinvasion, the COVID-19 infection triggered the immunity, causing massive inflammation of lung and brain; the former is the main death cause of COVID-19 and the latter can induce brain hemorrhage. The hypercoagulation and aneurysm instability partially due to systemic COVID-19 inflammation might be the potential cause of mental illnesses. During the COVID-19 pandemic, the individuals performed specific behavioral patterns to relieve stress and anxiety; they were more likely to browse internet to seek health information such as face mask and hand washing. Healthy lifestyle and psychological intervention were recommended to boost the immune system against COVID-19. Furthermore, the government locked down the cities. Though lockdown seems to be positive against COVID-19, it had a deep impact on both the general populations' social interaction and psychological wellbeing. The connection between Brain, Behavior, and Immunity showed in Fig. 1.

COVID-19 therapy involves prevention, symptomatic treatments, and supportive care. Besides the targeted vaccinations that have been made available just recently, a healthy lifestyle and psychological

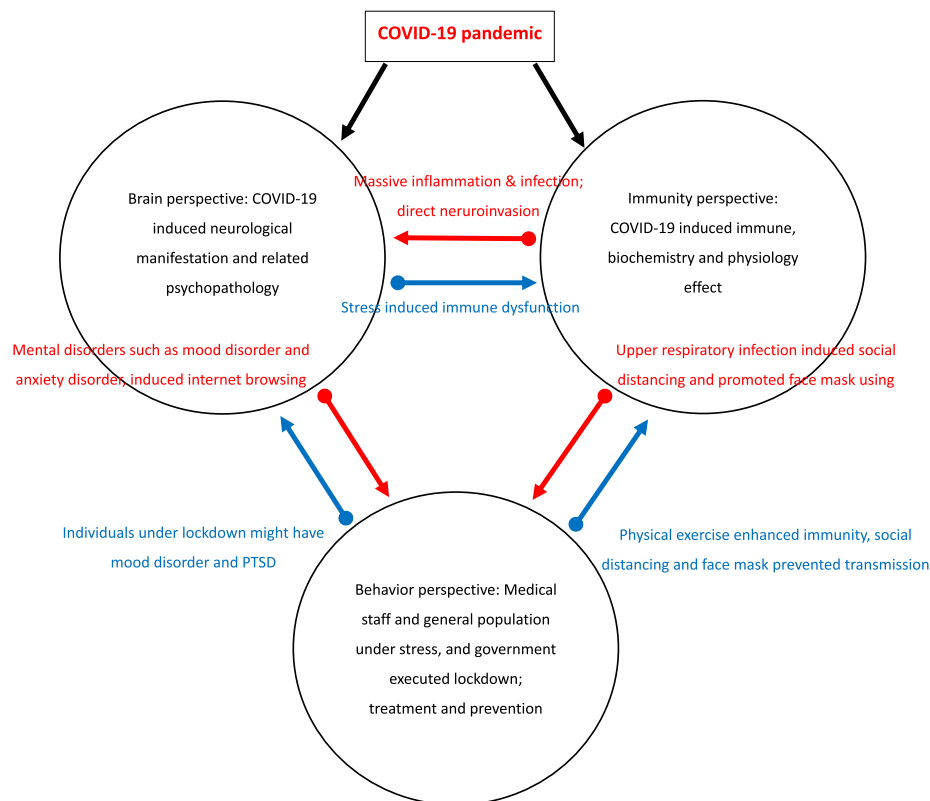


Fig. 1. The connection between the psychoneuroimmunity model and the three frontlines: Brain, Behavior, and Immunity.

interventions have the potential to improve psychoneuroimmunity. Although social distancing or wearing masks might help us to prevent infection, quality interpersonal connection should be fostered not only among the medical staff but also the general population, to improve the psychological wellbeing and also to enhance psychoneuroimmunity against COVID-19.

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