Brain, Behavior, & Immunity - Health 26 (2022) 100569

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Connecting the dots from east to west

ARTICLE INFO

Keywords
Depression
Inflammation
Psychoneuroimmunology
East-west global research collaboration

ABSTRACT

Clinical depression and anxiety are not just national health issues. They are significant global health problems, with a worldwide prevalence of clinical depression amounting to nearly 4%. Moreover, its prevalence is certainly underreported, particularly since the beginning of the COVID19 pandemic. This suggests that at least 26 million people are sad, fatigued, do not enjoy life, struggle with weight changes and experience suicidal thoughts. This Special Issue provides cutting-edge, new information from laboratories around the world about inflammation and depression. It consists of four review articles and five original research articles.

1. Introduction

The global mental health crisis brought on by the COVID-19 pandemic, characterized by an estimated increase of 27.6% and 25.6% in major depressive disorder and anxiety disorders (Santomauro et al., 2021), has highlighted the need for new and diverse perspectives in the field of psychoneuroimmunology (PNI). This Special Issue showcases the latest works from laboratories around the world that are investigating mechanisms and treatments that reveal underlying links between inflammation and the myriad of symptoms that characterize clinical depression with a focus on issues related to Eastern medicine. This Commentary summarizes the main results of six papers published in *Brain, Behavior, and Immunity – Health* as well as three papers from another related collection. These contributions include pre-clinical studies focusing on the molecular mechanisms by which social stress and immune activation alter behaviors relevant to depression such as reward motivation and social interaction (Cuomo-Haymour et al., 2022; DiSabato et al., 2022). Additionally, the role of stress, circadian rhythms, and microbiome–gut–immune–brain interactions were explored in the context of medical illnesses that have strong PNI components including high rates of comorbid depression and anxiety (Amoroso et al., 2021; Su et al., 2022; Maltz et al., 2022). Clinical studies in this Special Issue also reflect a growing focus on personalized and/or nuanced approaches in PNI including consideration of specific depressive symptoms, neural circuit dysfunction, and EEG-defined microstates associated with inflammatory dysregulation, as well as moderation of the association between inflammation and depression by race and ethnicity (Wijaya et al., 2022; Zhao et al., 2022; Toussaint et al., 2022). These narratives were then enriched through a historical context of PNI discoveries on inflammation and depression in China (Wang et al., 2022).

2. History of PNI research in China

Professors Wang and Lin at the Chinese Academy of Sciences in Beijing, Professor Chen at Jinan University in Guangzhou and Professor You at the University of Electronic Science and Technology of China in Chengdu published the lead review article. Between 1987, when *Brain, Behavior, and Immunity* was first published, through 2016, there were fewer than 100 papers that appeared from Chinese laboratories. Just four years later, the number of submissions increased four-fold (Fig. 1). More importantly, since 2008, the number of citations to papers from China has increased linearly. During the past 5 years, two of the most cited original research papers published in *Brain, Behavior, and Immunity* were from Chinese authors (awards-lectures" title="https://www.pnirs.org/awards-lectures">https://www.pnirs.org/awards-lectures). Yet, other than a brief overview of PNI research in China (Kelley et al., 2020), Western scientists are generally not familiar with contributions of Chinese scientists to early PNI research. Wang et al. (2022) have now remedied this situation with their historical summary of PNI research published by Chinese scientists. This is an important contribution, as summarized in one sentence by Professor Kuan Pin Su in Taichung, Taiwan, “Psychoneuroimmunology has been long stemmed in ancient medicine” (Su, 2019). His statement is supported and expanded in this article because the authors summarized historical advances made by Chinese scientists in PNI, particularly in the areas of conditioned immune responses, inflammation and depression and emotional stress and immunity.

3. Circadian rhythms, depression and cancer

The 2017 Nobel Prize in physiology or medicine was awarded to Professors Jeffrey C. Hall, Michael Rosbash and Michael W. Young “for their discoveries of molecular mechanisms controlling the circadian rhythm” (Anonymous, 2017). Their discoveries and recognition have led to numerous investigations into the role of circadian rhythms in

https://doi.org/10.1016/j.bbih.2022.100569
Received 25 November 2022; Accepted 26 November 2022
Available online 5 December 2022

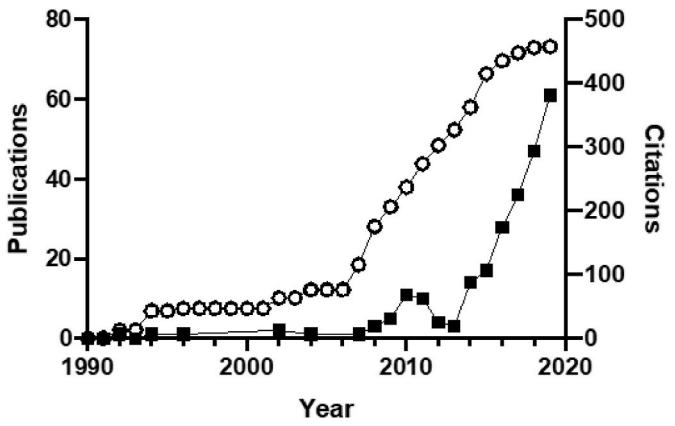

Fig. 1. Thirty-two year summary of the number of submissions to *Brain, Behavior, and Immunity* and subsequent citations to these publications. Reprinted from Kelley, K. W., Peng, Y. P., Liu, Q., et al. Psychoneuroimmunology goes East: Development of the PNIRS**China** affiliate and its expansion into PNIRS**Asia-Pacific**. Brain Behavior, and Immun, 2020, 88, 75, https://doi.org/10.1016/j.bbi.2020.04.026 with permission from Elsevier.

regulating a variety of physiological functions. An important outcome of some of these reports is the role that circadian rhythms play in in cancer. The master regulator of the circadian clock is the suprachiasmatic nucleus in the hypothalamus, although all cells, including cancer cells, display circadian rhythms. Su et al. (2022) summarized the three major biochemical events that regulate animal and human clocks: transcription/translation feedback loops, post-translational modifications and metabolic loops. They go on to describe how a broken circadian clock links cancer to depression, how cancer disrupts the circadian clock to promote depression and the ability of depression to rewire the circadian clock in a way that promotes cancer. They suggest that new chemical and behavioral approaches that restore a normal circadian clock might break the connection between depression and cancer that is linked to jet lag, night light, shift work and behavioral disruptions.

4. Inflamed and depressed patients

The association between inflammation and depression has been a prominent topic in PNI research for at least two decades. Wijaya et al. (2022) from the University of Hong Kong and colleagues at Chinese Academy of Sciences and the Southern Medical University in Guangzhou update new developments in this field. The authors make it clear that not all depressed patients display increased inflammation and that depressed patients with high inflammation show different inflammatory and symptom profiles. They go on to highlight how this heterogeneity is associated with region-specific vulnerabilities in the brain, severity of symptoms, treatment outcomes and how best to identify the subgroup of inflamed depressed patients. Wijaya et al. (2022) conclude that an inflamed major depressive disorder is a distinct subtype. They then offer solid suggestions for new approaches to better understand this subgroup of patients.

5. Vaccination for depression?

With growing recognition of the emerging field of immunopsychiatry, an obvious question is whether some new type of vaccination approach can successfully treat mental health disorders such as depression and anxiety. We are a long way from answering that question, but it is already well-established that both acute and chronic stress contribute to immune dysregulation and stress-related psychiatric disorders. Amoroso et al. (2021) revisit the "Old Friends Hypothesis" that proposes exposure to commensal microbiota early in life promotes proper development of the immune system. These authors review two harmless microorganisms, *M. vaccae* NCTC 11659 and *M. vaccae* ATCC 15483T, that exert significant immunoregulatory effects to promote stress resilience. This excellent comprehensive historical review establishes the major beneficial immunoregulatory property of both subcutaneous and intragastric administration of *M. vaccae* NCTC 11659 is caused in large part by an induction of regulatory T cells (Tregs).

6. Extracellular vesicles as a pathway for communication between the body and brain

Extracellular vesicles consist of a lipid bilayer and carry a variety of cargos. One of these are micro RNAs (miRNA), which are short single-stranded non-coding RNAs that play a role in inflammation by regulating the polarization of macrophages (Li et al., 2021). Cuomo-Haymour et al. (2022) from the Department of Psychiatry, University of Zurich, isolated extracellular vesicles from the blood of mice exposed to either lipopolysaccharide (LPS) or chronic social stress. Both treatments changed composition of the extracellular vesicles. When injected into naïve recipients, both types of extracellular vesicles targeted immune genes in the spleen and brain. There was no effect on motivation for sucrose. However, motivation for sucrose increased across days post-treatment, suggesting recovery from a prolonged, mild state of sickness and a return to homeostasis. These results are important because they contribute to the growing awareness of extracellular vesicles as another mode of communication between the body and the brain.

7. Recovery from colitis, stress and anxiety

Maltz et al. (2022) studied the role of social disruption in mice following recovery from colitis. The social disruption stressor did not exacerbate recovery from colitis but did increase anxiety-like behaviors and these correlated with an increase in interleukin (IL)-17A in both blood and brain. The more important contribution was their use of network analyses to explore changes in inflammatory proteins in the colon, mesenteric lymph nodes, serum and brain (hippocampus and amygdala). Social disruption reduced inducible nitrous oxide (iNOS) in the colon but increased it as well as IL-17A and interferon (IFN)γ in mesenteric lymph nodes. All three of these molecules in both brain tissues were related to serum and hippocampal IL-17A. The loss of iNOS in the gut that was followed by an increase in IFNγ in draining lymph nodes led the authors to conclude that iNOS in the colon is likely to protect against extra-colonic inflammation and serve as a link between the gut and brain. Their data also indicated that hippocampal IL-17A is an important marker of anxiety-like behavior.

8. EEG-defined microstates link inflammatory proteins to depression

Microstates are semi-stable, transient patterns of an electroencephalogram that persist from milliseconds to seconds. Analyzing microstates is a relatively new but promising field for studying neuropsychiatric disorders. Given the recent characterization of depression as a pro-inflammatory state (Osimo et al., 2020), Zhao et al. (2022) at the China Academy of Chinese Medical Sciences measured serum IL-2, tumor necrosis factor (TNF)-α and high sensitivity C-reactive protein (hs-CRP) in 24 patients with major depressive disorder and 24 control subjects. All three pro-inflammatory proteins were significantly elevated in depressed patients. The authors then categorized electroencephalograms into four different microstates. The duration, occurrence and coverage of one of these, microstate D, were negatively related to serum levels of all three pro-inflammatory proteins. These data are exciting because they are among the first to use electroencephalogram microstates to establish a clear relationship between pro-inflammatory signaling and functional brain networks in depressed patients.

9. Race, inflammation and depression

Race and ethnicity often lead to unfair differences in access to mental health care as well as the quality of mental health care that is offered. Furthermore, risk for depression may vary by race such that race moderates the association between inflammation and depression. By using CRP to index systemic inflammation, Toussaint et al. (2022) investigated the extent to which inflammation and symptoms of depression vary by race. The data were derived from over 3000 community-dwelling adults in the Chicago Community Adult Health Survey, of which 610 subjects provided blood samples. The authors found in multivariate models that Black and Hispanic Americans exhibited higher CRP levels than White Americans, and Black Americans had higher depression symptom levels than White Americans. Notably, inflammation was associated with depressive symptoms among Black Americans only, with 8% of the variance in depressive symptoms being accounted for by CRP. Although this report did not investigate the underlying physiological pathways responsible for these race-related effects, these data make it clear that there is much more to learn about the causes for these differences by race and ethnicity.

10. Glutamatergic neuronal IL-1 receptor required for stress sensitization

A variety of stressors, ranging from chronic psychological stress to trauma, often lead to a phenomenon known as stress-sensitization. This process is defined as displaying increased responses to subsequent stressors. DiSabato et al. (2022) from Ohio State University and Florida Atlantic University explored the fundamental mechanisms for neuronal stress sensitization. They had previously established that IL-1 receptor-1 (IL-1R1) expression in the hippocampus increases after six cycles of social defeat. In this report, they subjected wild-type and transgenic mice with the IL-1R1 deleted selectively in glutamatergic neurons to six rounds of social defeat. Thirty days later, the mice were acutely stressed with one exposure to social defeat. DiSabato et al. found that the neuronal IL-1 receptor was required for defeat-induced neuronal activation, as assessed by deltaFosB and pCREB, in the hippocampus of stress-sensitized mice. Absence of the IL-1R1 on glutamatergic neurons ameliorated the effect of the acute stress on both social interaction and Y-maze tasks. Hippocampal administration of AAV2-IL1RA to block the IL-1R1 in stress-sensitized mice blocked the increase in deltaFosB but not pCREB and reduced social exploration but not working memory (spontaneous alternation in a Y-maze). These experiments extend their previous findings in an important way by demonstrating that the IL-1 receptor on glutamatergic neurons is required for neuronal-sensitization and social withdrawal.

11. Conclusion

The strength of the Special Issue lies in its incorporation of diverse perspectives from around the world. These new data bridge mechanistic animal model studies to clinical findings on the role of inflammation in the pathophysiology of depression while considering complex interplays of lifestyle, environmental, co-morbid medical and sociodemographic factors. Taken together, these articles reflect the continued focus of the PNI field on understanding the mechanisms and devising new treatments for depression and anxiety through multi-faceted and nuanced approaches.

References

Amoroso, M., Langgartner, D., Lowry, C.A., et al., 2021. Rapidly growing Mycobacterium species: the long and winding road from tuberculosis vaccines to potent stress-resilience agents. Int. J. Mol. Sci. 22, 12938 https://doi.org/10.3390/ijms222312938.

Anonymous, 2017. The Noble Prize in Physiology or Medicine, 2017. Press Release. https://www.nobelprize.org/prizes/medicine/2017/press-release/" \o. https://www.nobelprize.org/prizes/medicine/2017/press-release/. https://www.nobelprize.org/prizes/medicine/2017/press-release/.

Cuomo-Haymour, N., Sigrist, H., Ineichen, C., et al., 2022. Evidence for effects of extracellular vesicles on physical, inflammatory, transcriptome and reward behaviour status in mice. Int. J. Mol. Sci. 23, 1028. https://doi.org/10.3390/ijms23031028.

DiSabato, D.J., Yin, W., Biltz, R.G., et al., 2022. IL-1 Receptor-1 on Vglut2+ Neurons in the hippocampus Is Critical for Neuronal and Behavioral Sensitization after Repeated Social Stress. Brain, Behavior, and Immun – Health, 2022, (this issue).

Kelley, K.W., Peng, Y.P., Liu, Q., et al., 2020. Psychoneuroimmunology goes East: development of the PNIRS**China** affiliate and its expansion into PNIRS**Asia-Pacific**. Brain Behav. Immun. 88, 75. https://doi.org/10.1016/j.bbi.2020.04.026.

Li, Y., Tan, L., Miao, Y., et al., 2021. MicroRNA in extracellular vesicles regulates inflammation through macrophages under hypoxia. Cell Death Dis. 7, 285. https://doi.org/10.1038/s41420-021-00670-2.

Maltz, R.M., Marte-Ortiz, P., Rajasekera, T.A., et al., 2022. Stressor-induced increases in circulating, but not colonic, cytokines are related to anxiety-like behavior and hippocampal inflammation in a murine colitis model. Int. J. Mol. Sci. 23 https://doi.org/10.3390/ijms23042000, 2000.

Osimo, E.F., Pillingera, T., Mateos Rodriguez, I., et al., 2020. Inflammatory markers in depression: a meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav. Immun. 87, 901. https://doi.org/10.1016/j.bbi.2020.02.010.

Santomauro, D.F., Mantilla Herrera, A.M., Shadid, J., et al., 2021. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet 398, 1700. https://doi.org/10.1016/S0140-6736(21)02143-7.

Su, K.P., 2019. Are we all the same? The critical role of translational brain, behavior, and immunity research in East Asia. Brain Behav. Immun. 82, 1. https://doi.org/10.1016/j.bbi.2019.07.011.

Su, K., Ud Din, Z., Cui, B., et al., 2022. A broken circadian clock: the emerging neuro-immune link connecting depression to cancer. Brain, Behavior, and Immun – Health, 2022, (this issue).

Toussaint, L.L., Moriarity, D.P., Kamble, S., et al., 2022. Inflammation and Depression Symptoms Are Most Strongly Associated for Black Adults. Brain, Behavior, & Immunity – Health (this issue).

Wang, W., Lin, W., Chen, G., et al., 2022. History and Main Research of Psychoneuroimmunology in China. Brain, Behavior and Immun – Health (this issue).

Wijaya, M.T., Jin, R., Liu, X., et al., 2022. Inflammation Shapes the Clinical Phenotypes of Depression. Brain, Behavior and Immun – Health (this issue).

Zhao, Y.-N., He, J.-K., Wang, Y., et al., 2022. The pro-inflammatory factors contribute to the EEG microstate abnormalities in patients with major depressive disorder. Brain, Behavior, and Immunity – Health. https://doi.org/10.1016/j.bbih.2022.100523.

Keith W. Kelley*

Department of Animal Sciences, College of ACES, University of Illinois at Urbana-Champaign, 212 Edward R. Madigan Laboratory, 1201 West Gregory Drive, Urbana, Il, 61801, USA

Jennifer Felger

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 101 Woodruff Circle, Woodruff Memorial, Building, Suite 4306, Atlanta, GA, 30322, USA

Mandakh Bekhbat

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 101 Woodruff Circle, Woodruff Memorial, Building, Suite 4306, Atlanta, GA, 30322, USA

* Corresponding author.
E-mail address: kwkelley@illinois.edu (K.W. Kelley).