

Review

Inflammation as a Neurobiological Mechanism of Cognitive Impairment in Psychological Stress

Şengül Kocamer Şahin^{1,*}, Esra Aslan²¹Department of Psychiatry, Health Science University, Adana City Health Research and Application Center, 01230 Adana, Turkey²Department of Psychiatry, Aksaray University, Aksaray Training and Research Hospital, 68200 Aksaray, Turkey*Correspondence: snglkcmr@hotmail.com (Şengül Kocamer Şahin)

Academic Editor: Rafael Franco

Submitted: 18 October 2023 Revised: 12 January 2024 Accepted: 15 January 2024 Published: 15 May 2024

Abstract

The feeling of emotional tension, restlessness, pressure, and inability to relax is referred to as psychological stress. Although it is unclear how psychological stress affects neurobiological processes, several factors are thought to be involved, including central and peripheral neuroinflammation, structural degeneration in the prefrontal cortex and hippocampus, alterations in fear neurocircuitry, and neuroplasticity. Aside from data relating cognitive impairment to chronic low-grade inflammatory stress, there is growing evidence linking mental stress, oxidative stress, and systemic inflammation to the development of psychological disorders. After chronic and acute illnesses, insomnia, depression, anxiety, posttraumatic stress disorder, and cognitive impairment were reported. Cognitive impairment is exacerbated by systemic and central inflammatory processes. There is uncertainty about the potential mechanisms causing these symptoms, although they are likely complex, with systemic inflammation playing a significant role. Therefore, this review aims to investigate the role of inflammation in stress-induced cognitive impairment. Depicting the inflammatory mechanisms of cognitive impairment is critical for understanding and treating illnesses, such as chronic stress exposure and anxiety disorders.

Keywords: neuroinflammation; cognition; cognitive impairment; stress; inflammation

1. Introduction

Stress is a condition of impaired homeostasis that occurs in response to an actual or perceived threat. Stress responses help us adapt to our environment and respond appropriately to threats [1,2]. However, the stress response mechanism that protects the organism must also be terminated. A prolonged alarm condition would cause the system to become unstable. Stress has a negative impact on various aspects of brain function when it is sustained or repeated. In particular, uncontrollable, prolonged stress leads to neuropsychiatric disorders [3,4]. Moreover, chronic stress is associated with life-threatening conditions, such as cancer, insulin sensitivity, and cardiovascular disease [5,6].

This review focuses on psychological stress. Emotional tension, mental discomfort, and pressure are symptoms of psychological stress. It may be caused by work stress, exposure to traumatic events, disappointment, unhappiness in marriage, confronting unanticipated negative situations, failure to meet basic needs, and caregiving burden. The psychological stress mentioned in this review is different from mechanical stress. A stress response is triggered when tissue integrity is disrupted, as in bone fractures and burns. This is referred to as mechanical stress. Mechanical stress causes processes, such as psychological stress, and is associated with oxidative stress. However, it was not considered in this review [7].

Traumatic stress affects neurocognitive functions. One of the best examples of how stress affects cognitive

functions is posttraumatic stress disorder (PTSD). If PTSD is revealed, neurocognitive functions are impaired with deficiencies in attention, executive function, and memory [8]. Moreover, when we review the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria, negative cognitive alterations and difficulties concentrating are some of the criteria for the diagnosis of PTSD [9]. Inflammatory diseases also affect cognitive functions. The relationship between inflammatory diseases and impaired cognition has been investigated for a long time. Some immune modulators, such as cytokines and microglia that increase inflammation, affect cognitive functions [10,11]. In this review, the role of inflammation in stress-induced cognitive impairment is discussed in the following order: stress-induced subclinical inflammation, followed by inflammation-induced cognitive impairment.

2. How Stress Induces Subclinical Inflammation

Stress has long been thought to be associated with inflammation because depressive symptoms are common in individuals with autoimmune and inflammatory diseases, such as diabetes and fibromyalgia. An increasing number of studies on this subject have been conducted [12]. Inflammation and increased pro-inflammatory cytokines have been associated with PTSD, depression, and various psychopathologies [13,14]. This has prompted more research into the cause-and-effect relationship and mecha-





Fig. 1. Representation of microglial activation via the SNS and HPA axis in a diagrammatic form. SNS, sympathetic nervous system; HPA, hypothalamic–pituitary–adrenal; TNF- α , tumor necrosis factor- α ; IL-6, interleukin-6; TGF- β , transforming growth factor- β ; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotrophic hormone; NF- κ B, nuclear factor kappa B; TNF- α , tumour necrosis factor α .

nism. Stress systems transmit threats throughout the body and stimulate inflammatory mechanisms [8]. The stress response adapts quickly to risks, such as increased blood sugar, blood pressure, and heart rate. However, the systems also stimulate the inflammatory response by producing inflammatory cytokines in the blood via the sympathetic branch of the autonomic nervous system (Fig. 1). This initial response is mediated by the hypothalamic–pituitary–adrenal (HPA) axis and the final hormone cortisol on this axis [15]. This acute stress is called “subthreshold” because it does not trigger increased inflammatory responses [16]. However, this article discusses other factors that may cause long-term sensitivity. Cortisol has a wide range of effects on the body and brain and is assumed to play essential roles in daily cognitive and behavioral functions. Chronic stress, such as depression, causes glucocorticoids resistance in the HPA axis, enabling pro-inflammatory signaling pathways to bypass the typical feedback inhibition [17]. Cortisol has various effects on the brain. One of these is increased cognitive deterioration associated with improved neuroinflammatory processes. Cortisol over production primes microglia for an enhanced pro-inflammatory response to stress, which boosts levels of neurotoxic cytokines [18].

The vagus nerve is another mechanism in the link between inflammation and stress. The circuits underlying the symptoms of stress-related psychiatric diseases are regulated by the vagus nerve. Vagus nerve stimulation binds to the α -7 subunit of the cholinergic receptor, activating T cells that produce acetylcholine and inhibiting nuclear factor kappa B (NF- κ B), interferon-gamma (IFN- γ) [19–21]. In some cases, vagal nerve stimulation has even been shown to target immune function modification in the treatment of psychiatric diseases associated with stress [21–23].

The stress response involves the sympathetic system as well as the HPA axis, in the axis of “nervous, endocrine

and immune” mechanisms. The adrenal medulla secretes more norepinephrine (NE) and epinephrine (E) into the bloodstream as a result of the quick reaction brought on by S-Adenosil metiyonin (SAM) activation. Sympathetic nerves also secrete more NE, which raises NE levels in the brain [24]. The organism becomes more vigilant and responds quickly to environmental cues when NE is released. Chronic stress causes locus coeruleus (LC) neurons to become hyperactive, which may be a factor in stress-related depression disorders. Chronic stress may have a mediating effect on microglia through catecholamines. According to recent research, microglia probably take part in the neuroinflammatory response that results from stress, partly via noradrenergic transmission [25]. It has been proposed that NE can upregulate the transcription of the proinflammatory immune response genes interleukin-1 (*IL-1*), tumor necrosis factor (*TNF*), and interleukin-6 (*IL-6*) and decrease the transcription of antiviral type I interferon (*IFN*) genes [26,27].

As a result, chronic subclinical inflammation causes a sustained systemic increase in inflammatory immune mediators. That sustained inflammation is associated with cell damage. Various transcription factors or inflammasomes may play a role in this case, as explained in the following sections.

2.1 Stress Induced Immunomodulators

Combined with cortisol release, the adrenal glands respond by releasing glucocorticoids and catecholamines. Catecholamines (e.g., norepinephrine) are released when the sympathetic nervous system is activated and functions directly on the primary and secondary lymphoid tissues. Glucocorticoids and catecholamines speed up monocyte synthesis, maturation, and release into circulation [16]. These monocytes enter the brain and become enriched in

the hippocampus, prefrontal cortex, and amygdala. However, after microglial activation, the M1 phenotype produces pro-inflammatory cytokines. Therefore, it is plausible that the inflammatory reaction caused by microglial activation may be a factor in brain pathology including cognitive decline [28]. Moreover, activated microglia is able to secrete large amounts of glutamate and increased glutamate release may contribute to excitotoxicity [29]. Extremely motile, microglial processes directly connect with synapses that rely on continuing neuronal activity in part. Recent data demonstrated the critical role NE signaling plays in mediating these dynamic relationships [25,30]. Thus, chronic stress causes an increase in NE signaling. This implies that chronic stress-induced microglial overactivation may result in a reduction in microglia-neuron connections, which could have a negative impact on synaptic plasticity and possibly neural connectivity [25]. Another reason why cognitive functions in the brain are affected may be inflammasomes. Inflammasomes are a multiprotein complex that intensifies inflammatory responses against endogenous activators, not only in response to pathogens but also in response to psychological stress [31]. The most extensively studied inflammatory complex of these is the Nod-like receptor pyrin domain-containing 3 (NLRP3) inflammasome. Research has demonstrated that autophagy and inflammasomes are mutually controlled. The intracellular process of autophagy is critical for both the removal of intracellular pathogens and the recycling of damaged proteins and organelles. Through hyperinflammation and excessive activation of inflammatory cells, autophagy failure can result in inflammatory disorders [32,33].

2.1.1 Proinflammatory Cytokines

During M1 activation, microglial cells secrete pro-inflammatory molecules, such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), superoxide radicals, glutamate, and nitric oxide (NO). Thus, it clears infections and repairs tissues. Alternatively, M2 activation is associated with an anti-inflammatory release [28]. However, glucocorticoids increase the expression of anti-inflammatory cytokines (e.g., IL-10 and TNF- β) while decreasing the expression of various pro-inflammatory cytokines, such as IL-6 and TNF- α (Fig. 1) [19]. In this process, the involvement of the previously stated inflammasomes emerges. They improve NLRP3 inflammasome function by increasing IL-1 β secretion in response to adenosine tri phosphate [34]. When pro-inflammatory cytokines, such as IL-1 and IL-18, perceive external and internal danger signals, multiprotein complexes known as inflammasomes break them into mature cytokines [35].

2.1.1.1 Interleukin-1 β (IL-1 β). IL-1 β is a bidirectional mediator between the central nervous and immune systems [36]. Zefferino *et al.* [36] claimed that IL-1 is the primary cause of negative stress outcomes and the primary

biomarker of these effects. This hypothesis is based on the following: it causes an increase in noradrenaline, which has a cascading impact on melatonin and cortisol, affecting the immune system and IL-1 β .

2.1.1.2 Interleukin-8 (IL-8). IL-8 is a pro-inflammatory cytokine produced by various cell types, notably macrophages and microglia. Its pro-inflammatory activities include promoting neutrophil adhesion, chemotaxis, and lysosomal discharge [37]. Clinically, IL-8 is essential in various inflammatory and autoimmune disorders. There have been reports of increased IL-8 production in the peripheral systems of patients suffering from various inflammatory diseases, autoimmune disorders, infections, and cancers [38,39]. Notably, IL-8 appears early in the inflammatory cascade and may persist for extended periods, unlike most other inflammatory cytokines, typically produced and cleared within a few hours [40]. This unique persistence suggests that IL-8 may have a role in chronic inflammatory changes, particularly in neurodegenerative and neuropsychological changes in the brain [41].

2.1.1.3 Interleukin-6 (IL-6). IL-6 is a pro-inflammatory cytokine that stimulates the production of inflammatory acute-phase proteins [42]. These proteins majorly affect vascular permeability, lymphocyte activation, and antibody synthesis. IL-6 was the predominant cytokine in mouse models that can only be induced by acute stress [43]. This stress-induced cytokine is produced from brown adipocytes via the beta-3-adrenergic receptor. One of its functions is to mediate hyperglycemia in the “fight or flight” response via hepatic gluconeogenesis. The cost of this adaptation is increased mortality from a subsequent inflammatory challenge [44]. Within the central nervous system (CNS), IL-6 can function as an indirect immunosuppressive factor by strongly stimulating the pituitary–adrenal axis, producing adrenocorticotrophic hormones [45]. As a result of this hormone release, the adrenal gland increases the synthesis of glucocorticoids.

2.1.1.4 Tumor necrosis factor- α (TNF- α). TNF- α is a well-known molecule that functions as a pleiotropic cytokine and as the primary regulator of the immune system. This adaptable molecule is generated by various cell types and participates in a wide range of pathological processes [46]. Several research groups have highlighted the varied effects of TNF- α and its involvement in various physiological inflammatory pathways [47]. TNF- α has been identified as a critical participant in the field of neurodegenerative central nervous system disorders, which includes Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS), and several other conditions [48].

2.1.2 Anti-Inflammatory Cytokines

2.1.2.1 Interleukin-4 (IL-4). In numerous experimental CNS disease models, interleukin-4 has been suggested as a neuroprotective and regeneration-inducing agent. While most studies have focused on myeloid cells, research on the neuronal IL-4 receptor (IL-4R) signaling pathway suggests that it directly affects neurons. The pleiotropic cytokine IL-4 is important in modulating immune responses. It has an effect when it interacts with high-affinity receptor complexes found in hematopoietic and non-hematopoietic cells [49].

2.1.2.2 Interleukin-10 (IL-10). Interleukin-10, a well-known anti-inflammatory cytokine, is essential in modulating multiple immune functions in response to inflammation. Its significance becomes apparent during the resolution phase. There is an increase in IL-10 expression inside the brain in cases of CNS pathology. This up regulation helps preserve neuronal and glial cells while suppressing inflammatory responses via various signaling pathways [50]. IL-10, initially known as a cytokine synthesis inhibitory factor, inhibits the production of pro-inflammatory cytokines and reduces inflammation by reducing cytokine receptor expression and preventing their activation [50].

2.1.2.3 Transforming Growth Factor- β (TGF- β). Distinguishing itself from other cytokines, the transforming growth factor- β (TGF- β) superfamily is characterized by the multifaceted functions exhibited by its component members. This superfamily encompasses TGF- β , activins, and bone morphogenetic proteins, which activate particular serine/threonine kinase receptors to transmit intracellular signals via Smad proteins [51]. Activins are most often considered memory regulators. TGF- β proteins have an important role in neuronal plasticity, contributing to the development of the nervous system and its continuous adaptability in the adult brain [52].

3. How Inflammation Induces Cognitive Impairment

The consequences of this subclinical inflammation stimulated by long-term psychological stress will also be seen in the brain. Significant evidence points to the role of inflammatory cytokines in directing the brain's inflammatory responses, eventually resulting in injury to its cellular components in neurodegenerative disorders, such as cognitive impairments [53].

The hippocampus is a critical brain region that is the focal point for learning and memory processes. Dysfunction of the hippocampus is important in altering cognitive abilities. Early-onset hippocampal inflammation is a hallmark event in the progression of neurodegenerative disorders, potentially leading to long-term changes in brain function during its developmental phases. Prolonged changes in hippocampal function caused by inflammation signifi-

cantly impact brain excitability, which is associated with various neurological dysfunctions [54]. There is a precursor form of IL-18 in brain neural cells, and its absence causes hippocampal dysfunction and a depressive-like phenotype. As a result, IL-18 has been associated with immunological function, psychiatric traits, including depression, and neurological function [55].

The subsequent content introduces several significant theories regarding the involvement of key molecules in the dynamics of psychological stress.

3.1 Brain-Derived Neurotrophic Factor (BDNF)

A member of the neurotrophic factor family found in the brain is called brain-derived neurotrophic factor (BDNF). It is associated with psychological resilience. It remains one of the most studied molecules in psychiatry and is a common hereditary risk locus for mental disease. Stress, a risk factor for several psychopathologies, targets BDNF in disease-related brain circuits and regions. BDNF plays a complex and underappreciated role in each of these processes as a target and regulator of stress hormone transmission in the brain. Stress hormones affect brain homeostasis by interacting with endogenous BDNF–Tropomyosin receptor kinase B (TrkB) signaling [56]. Additionally, BDNF is acutely recruited by glucocorticoid signaling to promote the development of fear memory [57]. BDNF was found to be required for the pro-neurogenesis effects of IL-4-induced microglia. Microglia activated by IL-4 in the hippocampus have been shown to help protect against depressive-like symptoms by inducing BDNF-dependent neurogenesis in response to chronic stress [58, 59]. In animal studies, pubertal trauma has been associated with increased corticosterone and reduced BDNF levels in the dorsal hippocampus [55]. According to Ferrer *et al.* [60], single nucleotide polymorphisms (SNPs), methylation status, and interactions with modifying variables in the BDNF gene can affect cognition.

Brain-derived neurotrophic factor alters the synaptic plasticity. Synaptic plasticity, or the ability of brain connections to become stronger or weaker over time, underlies cognitive functions, such as memory development and recall [61]. BDNF controls memory processing on several molecular levels, including cation (Na^+/K^+) and ligand-gated channels N-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and protein synthesis via transcription and translation [62]. There is emerging evidence that some aspects of cognition are affected by the level of BDNF-linked neurogenesis and neuroprotection [63]. BDNF has long been associated with cognitive and structural advantages in the brain [64]. According to a meta-analysis by Du *et al.* [65] (2018), peripheral BDNF levels in AD patients were significantly lower than in healthy controls.

3.2 Parvalbumin (PV)

The precise synaptic connections formed between inhibitory interneurons and their excitatory counterparts are critical to adequately operating neural circuits. Inhibitory interneurons, which account for 10%–20% of the neuronal population, are responsible for modulating the activities of excitatory neurons [66]. Parvalbumin (PV) interneurons, a predominant category of inhibitory interneurons, are critical in maintaining the balance of excitation and inhibition within neural circuits [67]. Research showed that inflammation reduces the expression of PV interneurons, eventually leading to PV interneuron dysfunction and cognitive impairment [68].

3.3 Sirtuin 1 (SIRT1)

Sirtuin 1 (SIRT1), a well-known member of the Sirtuin family, is essential for various cellular physiological and biochemical operations, including managing aging-related senescence and inflammation [69]. SIRT1 deficiency appears to have a role in developing cognitive abnormalities in the context of neurodegenerative diseases within microglia, possibly through epigenetic modulation of IL-1 β [70]. Structural abnormalities in microglia have been seen in areas associated with cognitive function, memory formation, and memory processing (e.g., the hippocampus and prefrontal cortex) in several psychopathologies (e.g., depression, anxiety, and PTSD) [71,72].

SIRT1 is important in managing the biological condition known as oxidative stress. This vital function includes regulating key transcription factors, such as nuclear erythroid factor 2-related factor 2 (Nrf2), which causes the transcription of antioxidant enzymes, influencing the cellular redox equilibrium. As a redox-responsive transcription factor, Nrf2 acts as a mediator for various cytoprotective [70] elements, including heme oxygenase-1 (HO-1) and antioxidant enzymes, such as superoxide dismutase. In addition, through deacetylation, SIRT1 inhibits the mammalian target of rapamycin (mTOR) and triggers autophagy. Thus, autophagy activities break down and remove α -synuclein clumps and damaged mitochondria [73].

3.4 Neuropeptide Y (NPY)

One of the most prevalent peptides in the body is Neuropeptide Y (NPY). Its effects on the peripheral nervous system and central nervous system are extensive. The brain's hypothalamus, septum, nucleus accumbens, periaqueductal gray, and locus coeruleus have particularly high levels of NPY expression. Numerous physiological processes, including circadian rhythm, anxiety, memory, fear, and stress, are regulated by NPY. NPY has anti-stress properties. In brain areas linked to stress, it alters neurotransmission [74,75]. By suppressing the secretion of IFN- γ and TNF- α and stimulating the secretion of IL-4 and TGF- β , NPY causes a shift in the Th1/Th2 balance in favor of the Th2 phenotype [76].

4. Conclusion

Brain function depends on the coordinated activity of presynaptic and postsynaptic signals generated by neurons and non-neuronal components, such as glial cells. Inflammation via mediators, such as cytokines, affects neuronal differentiation and synapse transmission. Although there is evidence for many reasons why stress causes inflammation and subsequently impacts cognitive functions, we are still far from fully understanding the underlying molecular and cellular mechanisms. This review examines the possible mechanisms of stress-induced inflammation, focusing on the relationship between inflammation and cognitive functions. Understanding how stress regulates inflammation and cognitive functions may lead to identifying novel targets for human attention, learning, memory, cognition, and, eventually, treating psychiatric diseases.

Author Contributions

ŞKŞ conceptualized and designed the study. ŞKŞ and EA collected, analyzed literatures. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] McEwen BS, Akil H. Revisiting the Stress Concept: Implications for Affective Disorders. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2020; 40: 12–21.
- [2] O'Connor DB, Thayer JF, Vedhara K. Stress and Health: A Review of Psychobiological Processes. *Annual Review of Psychology*. 2021; 72: 663–688.
- [3] Bagot RC, Labonté B, Peña CJ, Nestler EJ. Epigenetic signaling in psychiatric disorders: stress and depression. *Dialogues in Clinical Neuroscience*. 2014; 16: 281–295.
- [4] Saccaro LF, Schilliger Z, Dayer A, Perroud N, Pigué C. Inflammation, anxiety, and stress in bipolar disorder and borderline personality disorder: A narrative review. *Neuroscience and Biobehavioral Reviews*. 2021; 127: 184–192.
- [5] Dar T, Radfar A, Abohashem S, Pitman RK, Tawakol A, Osborne MT. Psychosocial Stress and Cardiovascular Disease. *Current Treatment Options in Cardiovascular Medicine*. 2019; 21: 23.

- [6] Dai S, Mo Y, Wang Y, Xiang B, Liao Q, Zhou M, *et al.* Chronic Stress Promotes Cancer Development. *Frontiers in Oncology*. 2020; 10: 1492.
- [7] Yui N, Yudoh K, Fujiya H, Musha H. Mechanical and oxidative stress in osteoarthritis. *The Journal of Physical Fitness and Sports Medicine*. 2016; 5: 81–86.
- [8] Quinones MM, Gallegos AM, Lin FV, Heffner K. Dysregulation of inflammation, neurobiology, and cognitive function in PTSD: an integrative review. *Cognitive, Affective & Behavioral Neuroscience*. 2020; 20: 455–480.
- [9] Forkus SR, Raudales AM, Rafiuddin HS, Weiss NH, Messman BA, Contractor AA. The Posttraumatic Stress Disorder (PTSD) Checklist for DSM-5: A Systematic Review of Existing Psychometric Evidence. *Clinical Psychology: a Publication of the Division of Clinical Psychology of the American Psychological Association*. 2023; 30: 110–121.
- [10] Rosenblat JD, Brietzke E, Mansur RB, Maruschak NA, Lee Y, McIntyre RS. Inflammation as a neurobiological substrate of cognitive impairment in bipolar disorder: Evidence, pathophysiology and treatment implications. *Journal of Affective Disorders*. 2015; 188: 149–159.
- [11] Wichmann MA, Cruickshanks KJ, Carlsson CM, Chappell R, Fischer ME, Klein BEK, *et al.* Long-term systemic inflammation and cognitive impairment in a population-based cohort. *Journal of the American Geriatrics Society*. 2014; 62: 1683–1691.
- [12] Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, *et al.* The relationship of depression and stressors to immunological assays: a meta-analytic review. *Brain, Behavior, and Immunity*. 2001; 15: 199–226.
- [13] Sumner JA, Nishimi KM, Koenen KC, Roberts AL, Kubzansky LD. Posttraumatic Stress Disorder and Inflammation: Untangling Issues of Bidirectionality. *Biological Psychiatry*. 2020; 87: 885–897.
- [14] Majd M, Saunders EFH, Engeland CG. Inflammation and the dimensions of depression: A review. *Frontiers in Neuroendocrinology*. 2020; 56: 100800.
- [15] Rohleder N. Stress and inflammation - The need to address the gap in the transition between acute and chronic stress effects. *Psychoneuroendocrinology*. 2019; 105: 164–171.
- [16] Biltz RG, Sawicki CM, Sheridan JF, Godbout JP. The neuroimmunology of social-stress-induced sensitization. *Nature Immunology*. 2022; 23: 1527–1535.
- [17] Pariante CM. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*. 2017; 27: 554–559.
- [18] Milligan Armstrong A, Porter T, Quek H, White A, Haynes J, Jackaman C, *et al.* Chronic stress and Alzheimer's disease: the interplay between the hypothalamic-pituitary-adrenal axis, genetics and microglia. *Biological Reviews of the Cambridge Philosophical Society*. 2021; 96: 2209–2228.
- [19] Bremner JD, Gurel NZ, Jiao Y, Wittbrodt MT, Levantsevych OM, Huang M, *et al.* Transcutaneous vagal nerve stimulation blocks stress-induced activation of Interleukin-6 and interferon- γ in posttraumatic stress disorder: A double-blind, randomized, sham-controlled trial. *Brain, Behavior, & Immunity - Health*. 2020; 9: 100138.
- [20] Rosas-Ballina M, Olofsson PS, Ochani M, Valdés-Ferrer SI, Levine YA, Reardon C, *et al.* Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. *Science (New York, N.Y.)*. 2011; 334: 98–101.
- [21] Bremner JD, Gurel NZ, Wittbrodt MT, Shandhi MH, Rapaport MH, Nye JA, *et al.* Application of Noninvasive Vagal Nerve Stimulation to Stress-Related Psychiatric Disorders. *Journal of Personalized Medicine*. 2020; 10: 119.
- [22] Namgung U, Kim KJ, Jo BG, Park JM. Vagus nerve stimulation modulates hippocampal inflammation caused by continuous stress in rats. *Journal of Neuroinflammation*. 2022; 19: 33.
- [23] Bremner JD, Wittbrodt MT, Gurel NZ, Shandhi MH, Gazi AH, Jiao Y, *et al.* Transcutaneous Cervical Vagal Nerve Stimulation in Patients with Posttraumatic Stress Disorder (PTSD): A Pilot Study of Effects on PTSD Symptoms and Interleukin-6 Response to Stress. *Journal of Affective Disorders Reports*. 2021; 6: 100190.
- [24] Chu B, Marwaha K, Sanvictores T, Ayers D. *Physiology, Stress Reaction*. StatPearls Publishing: Treasure Island (FL). 2023.
- [25] Picard K, St-Pierre MK, Vecchiarelli HA, Bordeleau M, Tremblay MÈ. Neuroendocrine, neuroinflammatory and pathological outcomes of chronic stress: A story of microglial remodeling. *Neurochemistry International*. 2021; 145: 104987.
- [26] Cole SW, Arevalo JMG, Takahashi R, Sloan EK, Lutgendorf SK, Sood AK, *et al.* Computational identification of gene-social environment interaction at the human IL6 locus. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107: 5681–5686.
- [27] Grebe KM, Takeda K, Hickman HD, Bailey AL, Embry AC, Bennink JR, *et al.* Cutting edge: Sympathetic nervous system increases proinflammatory cytokines and exacerbates influenza A virus pathogenesis. *Journal of Immunology (Baltimore, Md.: 1950)*. 2010; 184: 540–544.
- [28] Réus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, *et al.* The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience*. 2015; 300: 141–154.
- [29] Dantzer R, Walker AK. Is there a role for glutamate-mediated excitotoxicity in inflammation-induced depression? *Journal of Neural Transmission (Vienna, Austria: 1996)*. 2014; 121: 925–932.
- [30] Liu LL, Li JM, Su WJ, Wang B, Jiang CL. Sex differences in depressive-like behaviour may relate to imbalance of microglia activation in the hippocampus. *Brain, Behavior, and Immunity*. 2019; 81: 188–197.
- [31] Sutterwala FS, Haasken S, Cassel SL. Mechanism of NLRP3 inflammasome activation. *Annals of the New York Academy of Sciences*. 2014; 1319: 82–95.
- [32] Swanson KV, Deng M, Ting JPY. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nature Reviews. Immunology*. 2019; 19: 477–489.
- [33] Biasizzo M, Kopitar-Jerala N. Interplay Between NLRP3 Inflammasome and Autophagy. *Frontiers in Immunology*. 2020; 11: 591803.
- [34] Kim IB, Lee JH, Park SC. The Relationship between Stress, Inflammation, and Depression. *Biomedicine*. 2022; 10: 1929.
- [35] Palazon-Riquelme P, Lopez-Castejon G. The inflammasomes, immune guardians at defence barriers. *Immunology*. 2018; 155: 320–330.
- [36] Zefferino R, Di Gioia S, Conese M. Molecular links between endocrine, nervous and immune system during chronic stress. *Brain and Behavior*. 2021; 11: e01960.
- [37] Huber AR, Kunkel SL, Todd RF, 3rd, Weiss SJ. Regulation of transendothelial neutrophil migration by endogenous interleukin-8. *Science (New York, N.Y.)*. 1991; 254: 99–102.
- [38] Opendakker G, Van Damme J. Chemokines and proteinases in autoimmune diseases and cancer. *Verhandelingen - Koninklijke Academie Voor Geneeskunde Van België*. 2002; 64: 105–136.
- [39] Proost P, Wuyts A, van Damme J. The role of chemokines in inflammation. *International Journal of Clinical & Laboratory Research*. 1996; 26: 211–223.
- [40] Remick DG. Interleukin-8. *Critical Care Medicine*. 2005; 33: S466–S467.
- [41] Tsai SJ. Role of interleukin 8 in depression and other psychiatric disorders. *Progress in Neuro-psychopharmacology & Biological Psychiatry*. 2021; 106: 110173.

- [42] Gauldie J, Richards C, Harnish D, Lansdorp P, Baumann H. Interferon beta 2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells. *Proceedings of the National Academy of Sciences of the United States of America*. 1987; 84: 7251–7255.
- [43] Fattori E, Cappelletti M, Costa P, Sellitto C, Cantoni L, Carelli M, *et al.* Defective inflammatory response in interleukin 6-deficient mice. *The Journal of Experimental Medicine*. 1994; 180: 1243–1250.
- [44] Qing H, Desrouleaux R, Israni-Winger K, Mineur YS, Fogelman N, Zhang C, *et al.* Origin and Function of Stress-Induced IL-6 in Murine Models. *Cell*. 2020; 182: 372–387.e14.
- [45] Mastorakos G, Ilias I. Interleukin-6: A Cytokine and/or a Major Modulator of the Response to Somatic Stress. *Annals of the New York Academy of Sciences*. 2006; 1088: 373–381.
- [46] Cheng X, Shen Y, Li R. Targeting TNF: a therapeutic strategy for Alzheimer's disease. *Drug Discovery Today*. 2014; 19: 1822–1827.
- [47] Zelová H, Hošek J. TNF- α signalling and inflammation: interactions between old acquaintances. *Inflammation Research*. 2013; 62: 641–651.
- [48] Chen WW, Zhang X, Huang WJ. Role of neuroinflammation in neurodegenerative diseases (Review). *Molecular Medicine Reports*. 2016; 13: 3391–3396.
- [49] Gessner A, Rölinghoff M. Biologic functions and signaling of the interleukin-4 receptor complexes. *Immunobiology*. 2000; 201: 285–307.
- [50] Strle K, Zhou JH, Shen WH, Broussard SR, Johnson RW, Freund GG, *et al.* Interleukin-10 in the brain. *Critical Reviews in Immunology*. 2001; 21: 427–449.
- [51] Schmierer B, Hill CS. TGF β -SMAD signal transduction: molecular specificity and functional flexibility. *Nature Reviews. Molecular Cell Biology*. 2007; 8: 970–982.
- [52] Diniz LP, Matias ICP, Garcia MN, Gomes FCA. Astrocytic control of neural circuit formation: highlights on TGF- β signaling. *Neurochemistry International*. 2014; 78: 18–27.
- [53] Wang WY, Tan MS, Yu JT, Tan L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Annals of Translational Medicine*. 2015; 3: 136.
- [54] Giovanello KS, Schnyer D, Verfaellie M. Distinct hippocampal regions make unique contributions to relational memory. *Hippocampus*. 2009; 19: 111–117.
- [55] Yamanishi K, Doe N, Mukai K, Hashimoto T, Gamachi N, Hata M, *et al.* Acute stress induces severe neural inflammation and overactivation of glucocorticoid signaling in interleukin-18-deficient mice. *Translational Psychiatry*. 2022; 12: 404.
- [56] Notaras M, van den Buuse M. Brain-Derived Neurotrophic Factor (BDNF): Novel Insights into Regulation and Genetic Variation. *The Neuroscientist: a Review Journal Bringing Neurobiology, Neurology and Psychiatry*. 2019; 25: 434–454.
- [57] Notaras M, van den Buuse M. Neurobiology of BDNF in fear memory, sensitivity to stress, and stress-related disorders. *Molecular Psychiatry*. 2020; 25: 2251–2274.
- [58] Miao Z, Wang Y, Sun Z. The Relationships Between Stress, Mental Disorders, and Epigenetic Regulation of BDNF. *International Journal of Molecular Sciences*. 2020; 21: 1375.
- [59] Zhang J, Rong P, Zhang L, He H, Zhou T, Fan Y, *et al.* IL4-driven microglia modulate stress resilience through BDNF-dependent neurogenesis. *Science Advances*. 2021; 7: eabb9888.
- [60] Ferrer A, Labad J, Salvat-Pujol N, Barrachina M, Costas J, Urretavizcaya M, *et al.* BDNF genetic variants and methylation: effects on cognition in major depressive disorder. *Translational Psychiatry*. 2019; 9: 265.
- [61] Zenke F, Agnes EJ, Gerstner W. Diverse synaptic plasticity mechanisms orchestrated to form and retrieve memories in spiking neural networks. *Nature Communications*. 2015; 6: 6922.
- [62] Bekinschtein P, Cammarota M, Medina JH. BDNF and memory processing. *Neuropharmacology*. 2014; 76: 677–683.
- [63] Walsh EI, Smith L, Northey J, Rattray B, Cherbun N. Towards an understanding of the physical activity-BDNF-cognition tri-umvirate: A review of associations and dosage. *Ageing Research Reviews*. 2020; 60: 101044.
- [64] Leckie RL, Oberlin LE, Voss MW, Prakash RS, Szabo-Reed A, Chaddock-Heyman L, *et al.* BDNF mediates improvements in executive function following a 1-year exercise intervention. *Frontiers in Human Neuroscience*. 2014; 8: 985.
- [65] Du Z, Li Y, Li J, Zhou C, Li F, Yang X. Physical activity can improve cognition in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. *Clinical Interventions in Aging*. 2018; 13: 1593–1603.
- [66] Freund TF, Buzsáki G. Interneurons of the hippocampus. *Hippocampus*. 1996; 6: 347–470.
- [67] Hu H, Gan J, Jonas P. Interneurons. Fast-spiking, parvalbumin⁺ GABAergic interneurons: from cellular design to microcircuit function. *Science (New York, N.Y.)*. 2014; 345: 1255263.
- [68] Ji MH, Lei L, Gao DP, Tong JH, Wang Y, Yang JJ. Neural network disturbance in the medial prefrontal cortex might contribute to cognitive impairments induced by neuroinflammation. *Brain, Behavior, and Immunity*. 2020; 89: 133–144.
- [69] Libert S, Guarente L. Metabolic and neuropsychiatric effects of calorie restriction and sirtuins. *Annual Review of Physiology*. 2013; 75: 669–684.
- [70] Cho SH, Chen JA, Sayed F, Ward ME, Gao F, Nguyen TA, *et al.* SIRT1 deficiency in microglia contributes to cognitive decline in aging and neurodegeneration via epigenetic regulation of IL-1 β . *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 2015; 35: 807–818.
- [71] Deri Y, Clouston SAP, DeLorenzo C, Gardus JD, 3rd, Bartlett EA, Santiago-Michels S, *et al.* Neuroinflammation in World Trade Center responders at midlife: A pilot study using [¹⁸F]-FEPPA PET imaging. *Brain, Behavior, & Immunity - Health*. 2021; 16: 100287.
- [72] Mondelli V, Vernon AC, Turkheimer F, Dazzan P, Pariante CM. Brain microglia in psychiatric disorders. *The Lancet. Psychiatry*. 2017; 4: 563–572.
- [73] Rahimmi A, Tozandehjani S, Daraei M, Khademerfan M. The neuroprotective roles of Dietary Micronutrients on Parkinson's disease: a review. *Molecular Biology Reports*. 2022; 49: 8051–8060.
- [74] Benarroch EE. Neuropeptide Y: its multiple effects in the CNS and potential clinical significance. *Neurology*. 2009; 72: 1016–1020.
- [75] Nahvi RJ, Sabban EL. Sex Differences in the Neuropeptide Y System and Implications for Stress Related Disorders. *Biomolecules*. 2020; 10: 1248.
- [76] Li C, Wu X, Liu S, Zhao Y, Zhu J, Liu K. Roles of Neuropeptide Y in Neurodegenerative and Neuroimmune Diseases. *Frontiers in Neuroscience*. 2019; 13: 869.