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The Crossroads of Neurology and Immunology: Exploring the Intricacies of Neuroimmune Interactions

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Abstract

The concept of neuroimmune interactions has shown significant advancements over the years. Modern research has revealed many areas of connection between fields, which were previously viewed as distinct disciplines. For example, the nervous system can sense changes in the external environment and convey these changes through molecules and mediators with receptors in the immune system to modulate immune responses. Neuromediators can act on different receptors in the same group of cells, producing antipodal effects. Identification of the anti-inflammatory role of glucocorticoids highlighted that the body functions properly in an integrated manner. These interactions and crosstalk are not unidirectional, as the immune system can also influence various aspects of the nervous system, such as synaptic plasticity and fever. Strict integration of neuro-immuno-endocrine circuits is indispensable for homeostasis. Understanding these circuits and molecules can lead to advances in the understanding of various immune diseases, which will offer promising therapeutic options.

Keywords

Neuroimmune Interactions, Neuromediators, Synaptic Plasticity, Homeostasis, Immune Modulation

1. Introduction

In the past history of scientific and medical fields, physiological systems were

believed to work independently on their own merit. Particularly, immune and nervous systems were thought to be working separately due to their apparently different functions. The neuronal innervation of lymphoid tissues such as the thymus, lymph nodes, bone marrow, and spleen was recognized by anatomists in the 19th century [1]. However, immunologists conjecture that neuronal input and brain guidance are not crucial for immune response. They claim that "the immune system has its own rules for operation, which it can do perfectly well in a dish" [2]. Over the past few decades, advances in molecular biology tools have paved the way for studying and tracing various molecules generated by different physiological systems to influence others. For instance, fluorescence and single-cell RNA studies in the neuroanatomy of lymphoid organs elucidated the map of neuronal circuits and their effect on the activity and function of lymphoid organs. Proteomic analysis illustrated the function of different molecules, such as neuropeptides and cytokines, as signaling mediators. Additionally, chemicals that were previously regarded to have solely neurological mediators, like norepinephrine and acetylcholine, are now known to have various immunomodulating functions. Cholienrgic role in neuroinflammation was studied using modern areas of optogenetics and chemogenetics [3].

Nonetheless, this era of research is comparatively new, but has been swiftly progressing. This has helped in understanding the communication molecules and signaling pathways that engender boundaries blurring between different physiological disciplines. These molecules, their pathways, and receptors represent the gateway that helps to understand the language of communication between the brain and immune system [4]. Consequently, immunologists finally agreed to accept that the immune system requires nervous system tuning to function and respond appropriately.

Mutually, the immune system influences various nervous system functions like neuronal development in early life besides its regulatory role in neuronal and synaptic plasticity in adulthood in addition to its pyrogenic effects and sickness behaviors [5]. The immune system should be regarded as a sensory organ that conveys information about pathogens to the brain in the same manner that pain receptors send pain signals through the spinothalamic tract to the brain [4]. Consequently, the brain secretes neurochemicals and hormones, which represent efferent response tools that refine immune functions. This leads researchers to conclude that both systems operate in copulas that respond to different external stimuli. Any alteration in brain/immune interactions and communication can lead to many pathological conditions that were previously ascribed to isolated system disorders [6].

2. Neuroimmune Modulation via Autonomic Innervation

Neuroanatomical studies have shown that all lymphoid organs are innervated by packed sympathetic fibers. These fibers accompany the vascular supply and end

at what is called a "neuroeffector junction", in close proximity to the T lymphocytes and plasma cells that occupy the parenchymal part of lymphoid organs [1] [7]. The terminal parts of these neurons secrete different neuropeptides such as substance P and Met-encephalin, in addition to the key neurotransmitter norepinephrine [1]. In contrast, meager parasympathetic innervation is provided to the lymphoid tissues. However, lymphoid tissues associated with the respiratory and enteric nervous systems are possible exceptions [8].

Despite the scarcity of innervation by the parasympathetic nervous system, immune cells also have cholinergic receptors. The activation of these receptors leads to anti-inflammatory effects by controlling cytokine release and macrophage downregulation. Anti-inflammatory reflexes are composed of afferent cytokine production and efferent cholinergic innervation, which lack anatomical characterization. Acetylcholine can be synthesized by lymphocytes themselves and works in an autocrine and paracrine fashion [9]. Interestingly, although the vagus nerve does not supply the spleen, vagotomy extinguishes the anti-inflammatory response, whereas vagal simulation augments it, despite the missing cholinergic link [10]. The anti-inflammatory effect of the parasympathetic nervous system without apparent innervation can be explained through three main mechanisms [11].

The first hypothesis assumes that vagal innervation to the spleen is indirect through splenic nerves or post-ganglionic sympathetic nerve fibers, but this hypothesis is rejected because the vagus is not connected to any of them [12]. Second, vagal stimulation causes the recruitment of acetylcholine-synthesizing T-cells from the gastrointestinal system to the spleen, which in turn exerts a local anti-inflammatory action [11] [13].

Taking into consideration the recent growth and advancements. The cardinal role of parasympathetic innervation has come to light mainly through the vagus nerve. Acetylcholine from the vagus exhibits anti-inflammatory role mediated through interaction with $\alpha 7$ nicotinic receptors. Stimulation of efferent vagal fibers in dorsal motor nucleus through optogenetics revealed significant suppression on IL-6 and TNF-α in peripheral tissues like the pancreas. Thus, preventing excessive inflammation, which paves the road of future breakthroughs in therapeutic intervention.

Optogenetic stimulation of the vagal circuits in the gastrointestinal tract demonstrated promising therapeutic effects in metabolic disorders, for instance, enhancement of glucose metabolism through proliferation of pancreatic beta cells. Along with this, the mere principle of vagal circuits manipulation can lay the groundwork for novel approaches towards treating inflammatory bowel pathologies, rheumatoid arthritis, arrhythmias, obesity, aging, and it might play a role in whole body homeostasis [14].

Finally, catecholaminergic-cholinergic sympathetic neurons switch to healthy tissues neighboring inflamed ones. This occurs under the influence of specific immunological signals. This case was investigated using an animal model of rheumatoid

arthritis [15]. Innervation of lymphoid organs might regulate immune functions, such as immune cell trafficking and homing, by modulating blood flow, especially in lymphoid organs that lack lymphatic vessels, such as the spleen [16] [17]. However, this assumption requires further exploration and investigation (see **Figure 1**).

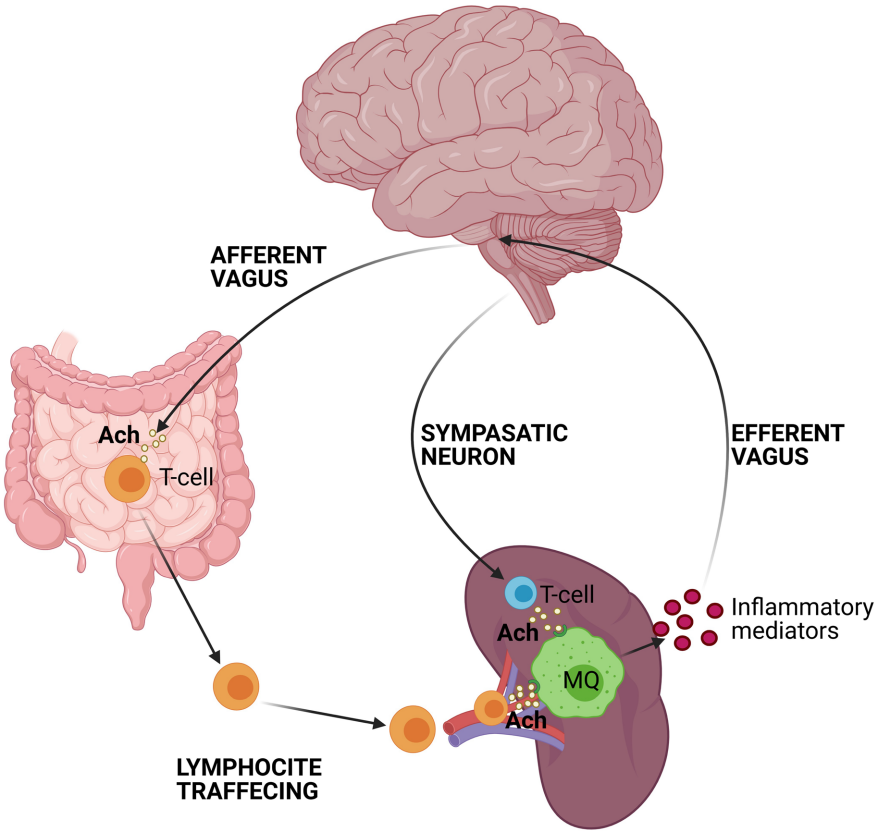

Figure 1. Inflammatory reflex arc.

3. Neuronal and Hormonal Influences on Immune System

3.1. Catecholamine

Catecholamines reach the immune system through sympathetic nerve terminals that innervate the immune tissues [8]. It is important to note that immune cells also have the machinery to synthesize and break down norepinephrine to function in an autocrine and paracrine fashion [9]. Immune cells express various types of catecholaminergic receptors, such as the $\beta 2$, $\alpha 1$, and $\alpha 2$ subtypes. Cells in the innate immune response have all three types of receptors [18] [19]. In contrast, cells of the adaptive immune response commonly have $\beta 2$ adrenoceptors. The effect of adrenergic stimulation on innate immune cells, such as macrophages and monocytes, is very complex because these cells express the three subtypes of receptors. For instance, stimulation of $\alpha 1$ and $\alpha 2$ receptors leads to enhanced production of proinflammatory cytokines, whereas stimulation of β receptors inhibits cytokine production [8] [20].

In addition, activation of $\beta 2$ receptors eases monocyte egression from the bone marrow and brain ingress to guide resident microglial activation, which causes anxiety-like behaviors [21]. Animal models of inflammatory lung injury have demonstrated the above disassociation in the effect of adrenergic receptors. It has been observed that α-adrenoceptor blockage reduces innate immune cell trafficking and consequently lung inflammation, in contrast to α stimulation, which exacerbates such conditions [22].

With regard to cells of the adaptive immune response, it has been proven that Th1 helper cells lack $\beta 2$ adrenoceptors at the minimum in the murine system; on the other hand, Th2 helper cells and B cells both express it. Activation of this receptor by terbutaline, a selective $\beta 2$ agonist, has an inhibitory effect on the T-cell response [23]. Although beta agonists render Th2 helper cells less active, they promote the differentiation of naïve T-cells into Th1 helper cells, which secrete more interferon γ [24]. For this reason, exposure to sympathetic antagonists or sympathetic denervation has a negative effect on type 4 hypersensitivity reactions that depend on Th1 cells. $\beta 2$ receptor activation in B cells causes magnification of the immunoglobulin response [25].

3.2. Glucocorticoids

In 1950, the Nobel Prize in medicine was given to three scientists who demonstrated the anti-inflammatory effect of glucocorticoids [26]. They exert anti-inflammatory effects by downregulating genes encoding inflammatory mediators and adhesion molecules. They also managed to elevate macrophage migration inhibitory factor [27]. In contrast, glucocorticoids can prime pro-inflammatory effects under specific circumstances. This is clearly observed, for instance, when a stress response occurs before an inflammatory stimulus [28].

Furthermore, it has been observed that the proinflammatory response takes place solely at a physiological level, unlike the pharmacological dose that always causes anti-inflammatory effects. The pro-inflammatory effect of steroids explains the flare of autoimmune diseases during periods of stress [29]. If they had exclusive anti-inflammatory effects, autoimmune disease would wane during stress [30]. Steroid administration to patients with autoimmune diseases causes lymphopenia and increases the number of neutrophils because they cannot leave the blood to the bone marrow or tissues because of a lack of adhesion molecules. Extra-adrenal steroidogenesis can occur in many epithelial cells, such as keratinocytes, in the skin and the intestinal epithelium. Local synthesis of steroids promotes wound healing and inhibits inflammation [31].

3.3. Growth Hormone and Prolactin

Growth hormones and prolactin have regulatory effects on immune cells. As with previously mentioned neuroendocrine influencers, immune cells can produce local auto- and para-effects in addition to circulating hormones that originate from the anterior pituitary gland [32]. Rat models lacking the production of these

hormones present a reduced antibody response to sheep red blood cells and type four hypersensitivity reaction [31]. This can be reversed by the administration of growth hormone and prolactin. B- and T-lymphocytes possess specific binding sites for these hormones. The calcineurin inhibitor cyclosporin raises the level of circulating prolactin due to competition at the binding site with lymphocytes [33].

The synthesis of these hormones in the pituitary gland and immune cells is regulated by immune factors. These hormones have different immunomodulatory effects that are attributable to their numerous isoforms generated by post-transcriptional and post-translational modifications [34].

3.4. Opioid Peptides

Opioid peptides, their precursors, and binding sites have been found in the leukocytes of several species. Opioid-containing leukocytes migrate to the site of inflammation to secrete their contents on sensory neurons to act on opioid receptors [35]. This will lead to an increased pain threshold by reducing intracellular cyclic AMP and opening potassium channels, which makes the nerve fiber less excitable and abrogates the pain [36]. Opioid peptides released from immune cells are mediated by various molecules, such as norepinephrine corticotrophin, which releases hormones and IL-1B. This negative effect on pain receptors antagonizes the positive effect caused by the release of proinflammatory cytokines by the cells of the innate immune response [37].

Exogenous chronic opioid administration to patients with severe pain or illegal consumption by drug abusers leads to the inhibition of activated immune cells [38]. Nonetheless, opioids can also promote the activation of inactive immunocytes. Therefore, they calibrated and refined the immune response.

3.5. Adrenocorticotrophic Hormone (ACTH)

ACTH is synthesized from the precursor, proopiomelanocortin, in the anterior pituitary. Immune cells have the ability to produce ACTH in the same manner as in the anterior pituitary. When exposed to viral infection, laboratory mice develop a surge in cortisol production by splenic lymphocytes. Earlier, it was suggested that this was due to INFα because this cytokine has an ACTH-like moiety [39].

3.6. Thyroid Stimulating Hormone (TSH)

TSH is secreted by anterior pituitary cells and is part of the hypothalamus-pituitary thyroid axis. It is secreted in response to thyrotrophin-releasing hormones released from the hypothalamus. It is a major regulator of thyroid function and its subsequent metabolic effects [40]. TSH, T4, and T3 affect the cells involved in innate and adaptive immune responses (see **Figure 2**). TSH and thyroid hormones crosstalk with immune cells through various cellular and molecular pathways [41].

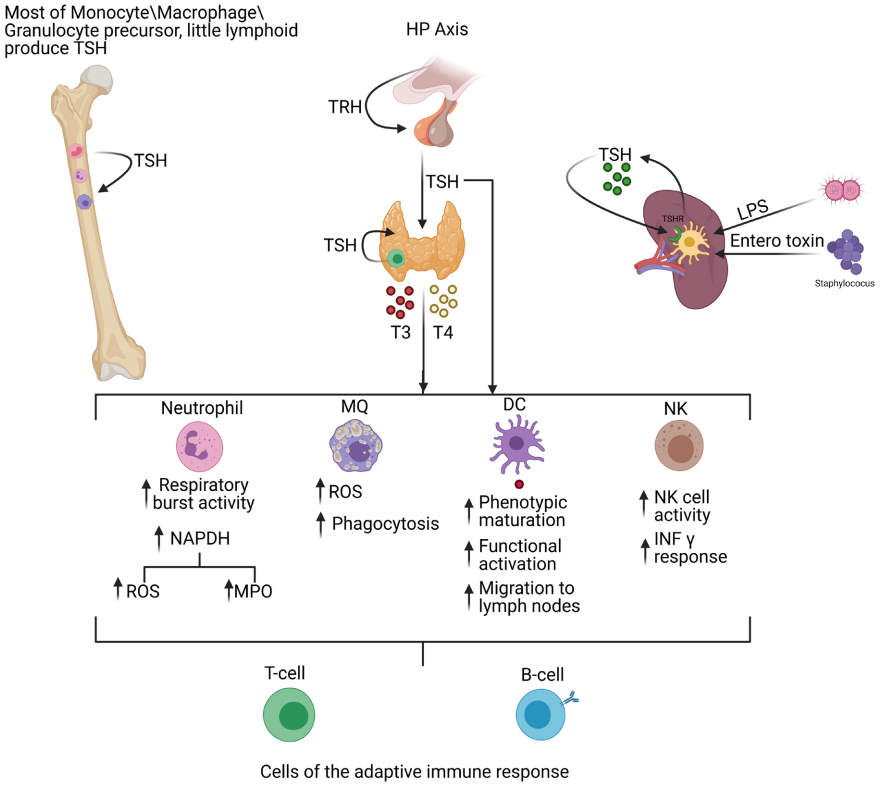

Figure 2. Effect of TSH, T3, and T4 on innate immune cells.

4. Immune Modulation of Neuroendocrine and Behavioral Function

4.1. Immune Influence on Nervous System

Immune effects on the nervous system represent a relatively new field of science. Kroemer *et al.*, fascinating physiological studies, revealed that the hypothalamic-pituitary axis and sympathetic nervous system are switched on during peak antibody response in mice exposed to antigens [42]. Molecules that link the immune system to the nervous system have not been identified or confirmed [43].

The discovery of interleukin1 (IL-1) in the 1980s brought about a magnificent thrive in the field of neuroimmunology with the contributions of cell biologists, neuroendocrinologists, and immunologists [6]. Before cytokine discovery, the immune system was thought to have intrinsic regulatory mechanisms only. Teamwork between Dinarello, who cloned IL-1 and Besdovsky, demonstrated that IL-1 has the same action as a glucocorticoid-increasing factor [44] [45]. This increase in glucocorticoids was found to be due to IL-1 action on the hypothalamus rather than the anterior pituitary or adrenal cortex [46].

The immune system influences the nervous system through immune factors, which were previously seen as long-range interactions; however, recently, immune factors that are locally produced have gained more interest and are defined as short-range interactions. Research on cytokine action in the brain began with the exploration of fever physiology and subsequently broadened to include all

aspects of immune physiology [47].

Febrile Effect of Cytokines

Fever can be defined as an elevated body temperature due to the resetting of the hypothalamic thermostat to a higher temperature. This change in the thermoregulatory center is induced by pyrogens released into the circulation by activated mononuclear cells [47] [48]. Microbial agents do not directly affect the hypothalamic thermostat. However, in 1984, the first endogenous pyrogen, IL-1, was cloned and characterized. IL-1 is an important cytokine that comes from two different genes: IL1-A and IL-1B. IL-1 is not the only cytokine with pyrogenic effect [44] [45].

Other cytokines that can cause fever include IFN-γ, TNF-α, and IL-6. Innate immune cells produce pyrogenic cytokines in response to bacterial infections. Pyrogens cannot be admitted to the nervous system because of their large molecular size and polar nature [48].

It has been well documented by fever physiologists that cytokines exert their action by inducing prostaglandin E biosynthesis in the organum vasculum laminae terminals, a brain area that lacks blood-brain barrier. Prostaglandin E then perfuses through brain parenchymal tissues to reach the thalamus to reset it to a higher body temperature. However, recent studies have revealed that the fever response to lipopolysaccharides has two phases.

The first phase occurs when Kupffer cells in the liver release prostaglandins in response to complement activation. The released prostaglandins stimulate prostaglandin receptors in the efferent vagus nerve fibers, which end in the nucleus of the solitarius tract in the medulla [49]. The message for thermostat resetting reaches the hypothalamus through adrenergic nerve fibers, which project from the dorsomedial medulla.

The second phase occurs because of the induction of central cytokine synthesis by astrocytes, which mainly produce IL-6 in response to peripheral cytokine production. Central cytokine production causes prostaglandin formation in the cerebral endothelial cells. The febrile response wanes owing to heat stress on macrophages and increases the production of peripheral and central anti-inflammatory cytokines [48].

4.2. Immune modulation of Hypothalamic-Pituitary-Adrenal Axis (HPA) and Hypothalamic-Pituitary-Thyroid Axis (HPT)

4.2.1. Activation of Hypothalamic-Pituitary-Adrenal Axis (HPA) by Cytokines

It has been proved that systemic administration of cytokines activates the hypothalamic-pituitary axis to release corticosteroids from the adrenal cortex [46]. Although there is strong evidence that interleukins have a direct effect on the anterior pituitary to release adrenocorticotrophic hormones, corticosteroid release is mainly mediated via the activation of hypothalamic parvocellular neurons to increase the release of corticotrophin-releasing hormones [50]. This is supported by the abolished

corticosteroid effects that occur in response to stressors in the case of immunoneutralization of CRH [51].

The direct effect of lipopolysaccharides on adrenocortical cells has been reported. However, this concept was refuted by mouse models that lacked specific adrenocortical cells but still showed HPA activation [52]. These positive effects of cytokines on the HPA axis are restricted by corticosteroid resistance in cases of persistent inflammation. Resistance occurs because of receptor alterations and disruptions [53].

4.2.2. Effect of the Immune System on the Hypothalamic-Pituitary-Thyroid Axis

Immune cells can synthesize and secrete TSH, which works in an autocrine and paracrine manner [54]. TSH production by immune cells occurs as a consequence of bacterial infections or exposure to TRH. Interestingly, TSH secreted by bone marrow-derived thymocytes may regulate thyroid hormone synthesis in the thyroid gland under disease and stress conditions [55].

Sick euthyroid syndrome is an example of the interaction between the immune and neuroendocrine systems. This condition occurs during inflammation, sepsis, trauma, myocardial infarction, fasting, and infection, where thyroid function is altered in the absence of overt thyroidal dysfunction [56]-[58]. The mechanism of sick euthyroid syndrome is not well understood, but it may help conserve energy and reduce metabolism during the critical stages of illness [59]. The rise of inflammatory cytokines caused by infections or inflammatory conditions may directly lead to inhibition of the synthesis of thyroid hormones or thyroid-stimulating hormone (TSH). Lipopolysaccharide infusion in laboratory animals enhances the formation of T3 in the ventricular area, which causes a negative feedback inhibition of the HPT axis [60].

4.3. Behavioral Effects of Cytokines

Immune cytokine or lipopolysaccharide administration in laboratory animals produces a range of symptoms that recapitulate sickness behaviors in human beings [61]. These include, but not limited to, fatigue, pain, sleepiness, anorexia, and social withdrawal. These changes in behavior also appeared in volunteers injected with the typhoid vaccine and a minute dose of LPS. They show disorders of affect, anhedonia, and malaise [62]-[64]. In other words, sickness behaviors in response to immune stimuli represent an adaptation to increased metabolism and fever.

Despite the fact that the pyrogenic effect and sickness behavior of cytokines are connected, there is substantial evidence proving that they are mediated in different manners. For example, IL-6 is a strong febrile cytokine but lacks behavioral effects [65]. Likewise, vagotomy subsides social withdrawal behavior in response to cytokines, but it does not affect the febrile response.

Concisely, the peripheral production of cytokines by the innate immune system results in fever, stimulation of the HPA, and sickness behavior. Peripheral immune signals are conveyed to the brain via different mechanisms such as vagal efferent

neurons [66]. When these signals are conveyed to the brain, they increase the synthesis of local prostaglandins in the cerebral vascular endothelium. Furthermore, they can enhance de novo brain cytokine production by resident microglia and astrocytes [6] [67].

4.4. Role of Brain Cytokines in Synaptic Plasticity

Microglial cells are a part of the tissue macrophages that arise from the yolk sac. Beyond their role in brain immune vigilance, they can produce cytokines [68] [69]. Microglia are also important for normal synaptic functions because they can eliminate inactive synapses [70]. The pruning process of inactive synapses by macroglia is mediated by several pathways, including the complement system. The classical complement cascade is part of the innate immune response. C1q down to C3 complement proteins opsonizes immature synapses to be engulfed by microglial cells that express C3 receptors.

In addition to complement pathways, fractalkine chemokines are involved in the demolition of inactive synapses. This chemokine allures microglia to the sites of immature synapses [71]. Knockout mice with this chemokine showed reduced clearance of immature synapses in the second and third postnatal weeks.

Presumably, this effect is due to the diminished migration of microglial cells to the brain, which utilizes the fractalkine pathway rather than tagging immature synapses. The lipopolysaccharide-binding protein pathway (LBP) is also involved in tagging the immature synapse, preparing it to be cleared by microglia. Exposure to stressors in the early postnatal period causes a reduction in brain LBP but not plasma LBP. Abnormality in this pathway reduces the termination of inactive synapses in the hippocampus, which are connected to anxiety-like behaviors in adulthood [71].

Cytokine production by microglia occurs because of peripheral immune stimulation. Furthermore, microglia exhibit constitutive production that is unrelated to peripheral cytokines. Tumor necrosis factor (TNF) is an example of a constitutive cytokine that has the ability to control several synaptic and neuronal circuits. TNF also affects astrocyte function by controlling their ability to release glutamate. Experimental animal models with knocked out TNF or TNF receptors lack the ability to release glutamate. Glutamate shortage impairs neuronal neurotransmitter release and synaptic strength at the glutamatergic synapse level. This happens because of insufficient stimulation of presynaptic NMDA receptors [72].

5. Conclusions

Neuroimmune interactions have made a huge step from being opaque to a critical area in the study of medicine. This crosstalk plays an insensible role in the harmony between neuronal function and immune response, which catalyzes grand revolution in future therapeutic approaches. Aberration in said harmony is now recognized as a factor in the progression and development of various autoimmune, neurodegenerative and psychiatric disorders.

Gaps in current understanding are advised to be addressed in future studies. Understanding chronological patterns of pathologies and the role of immune cells and cytokines in each stage serves the goal of minimizing the error in newer treatments. Tackling these unresolved questions will open the door towards the development of individualized therapies that foster the full potential of neuroimmune modulation.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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