Neuroinflammation in the Pathogenesis of Psychiatric Disorder

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ABSTRACT: The mechanism of psychiatric disorders biologically has not been fully explained. The development of the pathogenesis of various diseases lately can be explained through the theory of inflammation. The theory of inflammation that may be related to the pathogenesis of psychiatric disorders is the kynurenine theory. From this kynurenine theory, the author tries to construct the mechanism of psychiatric disorders such as those that occur in cases of anxiety, depression, schizophrenia, insomnia to psychosomatic cases and epilepsy. From the various courses of psychiatric disorders, the author concludes that the mechanism of the occurrence of various psychiatric disorders is actually the same, but in the end, what distinguishes the occurrence of certain types of psychiatric disorders is the genetic factor of each individual who experiences it. It is essential to understand the mechanisms underlying psychiatric disorders from a biological perspective, as this knowledge serves as a foundation for managing such conditions, particularly through the use of psychopharmacological treatments and other adjunctive therapies.

INTRODUCTION

The concepts surrounding the development of psychiatric disorders have progressed over time. A significant concept that clarifies the emergence of psychiatric disorders is the inflammation theory. This theory is perpetually being adjusted to account for the biological processes that underlie psychiatric disorders. The evolution of the inflammation theory highlights the kynurenine pathway as a critical element in the initiation of psychiatric disorders (Marx et al., 2021).

Numerous reviews and studies have been carried out to clarify the pathophysiological mechanisms that underlie psychiatric disorders. Tami et al., in their review examined the inflammatory pathways implicated in the development of schizophrenia and depression (Tami et al., 2020). The kynurenine pathway itself has been thoroughly investigated in instances of major depressive disorder, bipolar disorder, schizophrenia, and Alzheimer's disease (Marx et al., 2021; Fernandes et al., 2023; Inam et al., 2023).

Despite the many reviews and studies, a thorough synthesis of inflammation theory with the varied range of psychiatric disorders and the often co-occurring psychosomatic issues is still absent. The author seeks to combine various elements of the inflammation and kynurenine theories to clarify the mechanistic pathways through which these psychiatric disorders emerge.

METHODS

This study is a literature review that discusses the pathogenesis of psychiatric disorders from the perspective of neuroinflammation. The method of tracing scientific literature in the form of journals, books, and articles were carried out by means of an evidence-based search through trusted databases, namely PubMEd, Cochrane, Medscape, Springer, Scholar in the last 25 years using The Boolean Operator method.

RESULTS AND DISCUSSION

Stressors Contributes to Inflammatory Process

Stressors are frequently experienced in human life, typically classified as either physical or psychological. Both physical and psychological stressors, whether they are acute or chronic, provoke inflammation within the body through different pathways. These stressors kickstart the release of pro-inflammatory cytokines, which in turn activates the inflammatory process (Maydych V, 2019).

Physical stressors that can trigger inflammation include thrombogenesis, immune system malfunctions, malignancy, infection, chemical exposure, and physical injury (Roe K, 2021). These physical stressors stimulate T cells (D'Alessio et al., 2019; Reina-Campos et al., 2021). The activation of T cells subsequently causes the activation of nuclear factor-kappaB (NFκB), which then encourages the production of pro-inflammatory cytokines and instigates inflammation (Smith-Garvin et al., 2009).

Psychological stressors also cause inflammation, but they do so through a pathway different from that of physical stressors, specifically via microglial activation (Li et al., 2022). Microglia are glial cells located throughout the brain, tasked with the immune defense of the central nervous system (Ginhoux et al., 2013). The activation of microglia leads to the activation of NFκB, which then triggers the production of pro-inflammatory cytokines, reflecting the process seen with physical stressors (Smith-Garvin et al., 2009; Anilkumar et al., 2024).

In situations of inflammation, increased cortisol levels are typically noted. This rise in cortisol results in a decrease in prostaglandin levels in the body (Lee at al., 2007). Importantly, the reduction of prostaglandin and T cell activation can separately activate NFκB, thereby continuing the production of pro-inflammatory cytokines and maintaining the inflammatory process (Smith-Garvin et al., 2009; Poligone & Baldwin, 2001).

Inflammation and Anxiety

Population-based research conducted globally shows that anxiety disorders represent the most common type of mental disorders. Simultaneously, our comprehension of the neurobiology associated with fear and anxiety is continuously progressing (Kaplan & Sadock, 2017). Anxiety serves as a typical emotional reaction to perceived threats, essential to the evolutionary "fight or flight" survival mechanism (Stahl, 2021). This adaptive reaction increases alertness, aids in the memory of potentially dangerous stimuli, and triggers quick physiological changes to ready the organism for imminent peril. Nevertheless, when fear learning extends too broadly to harmless stimuli, the "fight or flight" reaction becomes counterproductive, resulting in anxiety disorders. Various neurochemical pathways are involved in anxiety (Figure 1), including the noradrenergic system or sympathetic nervous system (SNS), the hypothalamic-pituitary-adrenal (HPA) axis, corticotropin-releasing hormone (CRH), among others (Kaplan & Sadock, 2017).

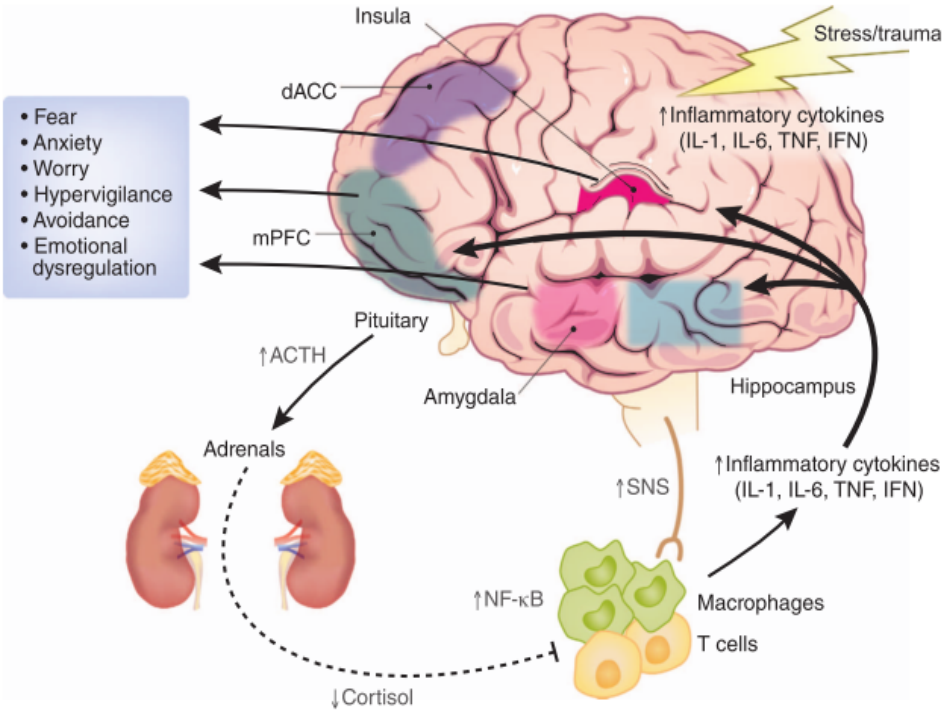

Figure 1. Stress, Inflammation, and Anxiety (Michopoulos et al., 2016)

Prolonged exposure to stressors that induce fear, and anxiety activates both central and peripheral immune cells, triggering the NLRP3 (Nucleotide-binding Oligomerization Domain-like Receptor Protein 3) inflammasome response, which is a multiprotein complex that facilitates the activation of inflammatory cytokines, resulting in the release of interleukin-1β (IL-1β). In glial cells, IL-1β promotes NFκB transcriptional activity, leading to increased levels of circulating interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (Michopoulos et al., 2016; Gomez et al., 2017; Miller & Raison, 2016). Pro-inflammatory cytokines, especially IL-6, stimulate the production of acute-phase proteins (a significant inflammatory biomarker) C-reactive protein (CRP), and both further enhance the function and expression of SERT and serotonin reuptake (Felger & Lotrich, 2013). Additionally, pro-inflammatory cytokines induce the enzyme indoleamine 2,3-dioxygenase (IDO), which transforms the essential amino acid tryptophan into kynurenine (a precursor of the bioactive metabolites quinolinic acid and kynurenic acid), thereby diminishing serotonin levels (Miller & Raison, 2016). Kynurenine and quinolinic acid are anxiogenic as a result of their inhibition of γ-aminobutyric acid (GABA) and stimulation of glutamate secretion (Webster et al., 2017). The inhibition of GABA and the excessive release of glutamate lead to heightened activity of the cortico-striato-thalamo-cortical (CSTC) brain circuit, resulting in anxiety and obsessive-compulsive disorder (OCD) (Stahl, 2021).

Functional magnetic resonance imaging (fMRI) studies have shown that heightened inflammation is also linked to increased activation of neural pathways associated with threat and anxiety, which include the insula and amygdala. Importantly, the dACC and amygdala are regions that display increased activity in individuals with high anxiety and neuroticism traits (Miller & Raison, 2016). Reduced serotonin and elevated norepinephrine in the amygdala stimulate activation of the amygdala and have been noted to provoke anxiety-like behaviors (Forster et al., 2012). The activated amygdala then stimulates various structures, including the HPA axis, locus coeruleus, hippocampus, periaqueductal gray, parabrachial nucleus, dorsal anterior cingulate cortex (dACC), and orbitofrontal cortex (OFC) (Stahl, 2021).

Activity of the hypothalamic-pituitary-adrenal (HPA) axis is marked by the release of glucocorticoids (cortisol) into the bloodstream. The HPA axis is activated when the paraventricular nucleus of the hypothalamus produces corticotropin-releasing hormone (CRH) and vasopressin, which in turn stimulate the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH then initiates the synthesis and secretion of cortisol into the blood (Kusnecov & Anisman, 2014; Melmed & Jameson, 2015). Cortisol activates the "fight or flight" response of the sympathetic nervous system. It contributes to enhancing alertness, attention, memory formation, and suppressing growth and reproductive systems, along with immune responses. Cortisol also plays a crucial role in regulating the functions of the hippocampus, amygdala, and prefrontal cortex, ultimately affecting behavioral reactions to acute stress (Kaplan & Sadock, 2017). Moreover, cortisol supplies the metabolic energy required for responding to threats (Slavich & Irwin, 2014). Conversely, cortisol's capacity to inhibit pro-inflammatory activity through NFκB suppression influences neurotransmitter systems and neural circuits, thereby alleviating anxiety and regulating stress-related behaviors (Michopoulos et al., 2016). Pro-inflammatory cytokines (IL-1β and TNF-α) can elicit glucocorticoid receptor resistance through multiple pathways, including the activation of mitogen-activated protein kinase (MAPK) p38, and induce changes in glucocorticoid receptor expression, resulting in cortisol's inability to halt the inflammatory process and triggering anxiety (Miller & Raison, 2017; Feltes et al., 2017).

In addition to the amygdala, the paraventricular nucleus of the hypothalamus, which contains CRH neurons, also sends projections to noradrenergic centers located in the brainstem and spinal cord. The locus coeruleus found in the brainstem provides direct projections to sympathetic preganglionic neurons in the spinal cord as well as to parasympathetic preganglionic neurons in both the brainstem and spinal cord, leading to increased sympathetic activity through α-1 adrenoceptor activation in sympathetic preganglionic neurons and reduced parasympathetic activity via α-2 adrenoceptor activation in parasympathetic preganglionic neurons (Stahl, 2021; Won & Kim, 2016). Individuals with various anxiety disorders display symptoms indicative of excessive output from the noradrenergic system (SNS), such as intense worry, avoidance behaviors, heightened vigilance, and exaggerated startle reflexes, along with increased autonomic and sympathetic activity (Kaplan & Sadock, 2017). The sympathetic nervous system (SNS) contributes to stress responses by releasing catecholamines, specifically epinephrine and norepinephrine, within lymphoid tissues. The presence of stressors and the rise in norepinephrine production following exposure to stressors trigger nuclear factor kappa B (NFκB) activity, which in turn activates the immune system and amplifies cytokine production. Importantly, research indicates that the activation of the parasympathetic nervous system can also influence T cell immune system activity by changing vagal acetylcholine release. Together, these findings suggest that any chronic conditions resulting in heightened sympathetic and reduced parasympathetic activity are correlated with increased inflammation (Smith-Garvin et al., 2009; Li et al., 2022; Anilkumar & Wright-Jin, 2024; Michopoulos et al., 2016). In contrast, the activation of parasympathetic nerves leads to a decrease in the release of pro-inflammatory cytokines (Wohleb, 2019).

The hippocampus and amygdala mutually influence one another in relation to stressors, anxiety, and memory. The hippocampus is crucial for the process of memory formation. The basolateral amygdala (BLA) is also involved in the formation of memories. The BLA impacts hippocampal functioning through efferent projections from the amygdala to the hippocampus. Furthermore, manipulating the amygdala alters neurochemical and molecular changes related to learning in the hippocampus, suggesting that BLA activity is essential for the hippocampal modulation involved in memory consolidation (Roesler et al., 2021). On the other hand, memories (especially traumatic ones) retained in the hippocampus can stimulate the amygdala, prompting it to activate other brain regions and initiate fear responses, such as re-experiencing in post-traumatic stress disorder (PTSD). The activation of the amygdala also influences the periaqueductal gray,

producing other PTSD symptoms, including avoidance behaviors (flight) or various motor responses such as freezing or fighting (Stahl, 2021).

Activation of the amygdala initiates a response in the parabrachial nucleus, which impacts respiration. When the parabrachial nucleus is activated, individuals facing anxiety may report an elevated respiratory rate, feelings of shortness of breath, worsened asthma, or sensations of choking, which are commonly experienced during panic attacks (Stahl, 2021). Research by Smith et al. involving rats has also highlighted a connection between the activation of this nucleus and chronic pain, encompassing both neuropathic and inflammatory pain (Smith et al., 2023).

As a concluding element of amygdala activation, the dorsal anterior cingulate cortex (dACC) and orbitofrontal cortex (OFC) are likewise involved. Fear regulation is facilitated by reciprocal interactions between the amygdala and dACC, in addition to the amygdala and OFC. In particular, heightened activation of these pathways may produce the fear that is typically seen in phobic disorders (Stahl, 2021). The dACC is engaged during experiences of social rejection or unfavorable evaluation, often seen in social phobia (Dedovic et al., 2016). In obsessive-compulsive disorder (OCD), hyperactivity of the dACC is also noted, leading to an increased significance of particular stimuli. This causes a misjudgment of the danger presented by these stimuli, appearing as obsessive thoughts, escalated anxiety, and insufficient cognitive responses, which hinder the initiation of actions and lead to ongoing disruption of goal-directed behavior (Stahl, 2021; Van der Veerdonk et al., 2023). The OFC also has a significant function in the failure to suppress current actions, which underpins compulsivity in OCD, addiction, and overeating (Stahl, 2021).

Inflammation and Schizophrenia

Schizophrenia is a serious, intricate, and multifactorial disorder that affects around 0.7% of the worldwide population (Garcia-Alvarez et al., 2017). A central pathophysiological mechanism of schizophrenia is the dysregulation of the dopaminergic system, and the antipsychotic drugs currently available focus on dopaminergic transmission. Nonetheless, the exact pathogenic mechanisms of schizophrenia are still not fully understood. Psychoneuroimmunology research is a developing field that emphasizes the possible influence of immune or inflammatory processes on the dopamine dysfunction seen in schizophrenia (Muller, 2018).

Just like anxiety and depression, schizophrenia is marked by an elevated production of pro-inflammatory cytokines. IL-1β, IL-6, TNF-α, CRP, and transforming growth factor-β (TGF-β) have been observed to be increased both in the acute and chronic stages of schizophrenia, while brain-derived neurotrophic factor (BDNF) is present in lower levels (Upthegrove & Kandakher, 2018). However, during exacerbations, TNF-α levels might remain unchanged (Goldsmith & Rapaport, 2020). These cytokines, similar to those in anxiety and depression, also promote the enzyme indoleamine 2,3-dioxygenase (IDO), which transforms the essential amino acid tryptophan into kynurenine, a precursor of the bioactive metabolites quinolinic acid and kynurenic acid (Miller & Raison, 2016).

In contrast to anxiety and depression, kynurenic acid significantly influences the pathogenesis of schizophrenia, even though its association is not always consistent. Kynurenic acid functions as an antagonist of NMDA receptors in the human central nervous system (Muller, 2018). This NMDA receptor antagonism by kynurenic acid impacts the cortico-brainstem glutamate pathway, resulting in excessive glutamate release from the cortex to the brainstem neurotransmitter center known as the ventral tegmental area (VTA). This region regulates both mesolimbic and mesocortical dopamine pathways, where the mesolimbic pathway links the VTA to the nucleus accumbens, and the mesocortical pathway connects the VTA to the prefrontal cortex (Stahl, 2021).

Within the mesolimbic dopamine pathway, the cortico-brainstem glutamate neurons seem to innervate the dopamine neurons projecting from the VTA to the nucleus accumbens directly. Hence, the over-release of glutamate from the cortico-brainstem glutamate neurons promotes dopamine

production in the nucleus accumbens by the mesolimbic dopamine neurons. Besides the cortico-brainstem glutamate pathway, the ventral hippocampal glutamate pathway to the nucleus accumbens is also impaired by NMDA receptor antagonism, causing excessive glutamate release in the nucleus accumbens. This results in excessive stimulation of GABAergic neurons to the globus pallidus, which inhibits GABA release from the globus pallidus to the VTA, thereby further increasing dopamine production in the nucleus accumbens. The hyperactivity of the mesolimbic dopamine neurons is the basis for the positive symptoms of schizophrenia (Stahl, 2021).

In the mesocortical dopamine pathway, in contrast to the mesolimbic dopamine pathway, the cortico-brainstem glutamate neurons do not innervate the mesocortical dopamine neurons directly. Rather, they innervate GABA interneurons, which in turn innervate the mesocortical dopamine pathway. When NMDA receptor antagonism results in excessive glutamate release onto GABA interneurons, it activates these interneurons and ultimately acts to inhibit the mesocortical dopamine neurons. A reduced activity of dopamine in the mesocortical dopamine neurons is linked to the negative and cognitive symptoms of schizophrenia (Stahl, 2021). Pro-inflammatory cytokines like IL-6, IL-1β, and TNF-α, as well as CRP, additionally play a role in the negative symptoms experienced by patients with schizophrenia. Elevated levels of CRP (CRP > 0. 5 mg/dL), IL-6, and TNF-α are associated with more severe negative symptoms. In contrast, anti-inflammatory cytokines such as IL-10 demonstrate an inverse relationship with negative symptoms (Goldsmith & Rapaport, 2020).

Inflammation and Mood Disorder (Depression and Mania)

Major depressive disorder ranks among the most common mental disorders. The World Health Organization (WHO) estimates that approximately 5% of adults suffer from depression (WHO, 2023). This condition is linked to considerable disability and adversely affects quality of life, yet its causes and underlying mechanisms are not fully understood. To clarify these matters, researchers have started to explore the psychobiological components of major depressive disorder. Several theories have been formulated to account for the roots of depression (Zunszain et al, 2012; Singh, 2015; Noto et al., 2015; WHO, 2023).

A widely recognized theory is the Monoamine/Serotonin Theory, which asserts that depression results from the dysfunction of monoamine neurotransmitters (Stahl, 2021). Historically, decreases in monoamines like serotonin and norepinephrine have been suggested as mediators of major depressive disorder. Nevertheless, a direct causal relationship between changes in monoaminergic neurotransmission and depression has not been conclusively determined. Additional research stemming from this theory has generated alternative hypotheses, particularly the inflammation hypothesis. The more recent Macrophage Theory of Depression (1991) proposed by Smith et al. argues that heightened pro-inflammatory cytokines are causative elements in depression (Figure 2), as their research indicated that administering cytokines to healthy subjects triggered depressive symptoms and brain effects, including HPA axis activation. The Kynurenine Theory of Depression connects the immune system with variations in tryptophan metabolism (Feltes et al., 2017; McCusker et al., 2014, Haapakoski et al., 2015).

In initial studies, individuals with depression displayed dysfunction in the peripheral immune system and had a higher risk of developing cancer and infectious diseases. As research advanced, it became clear that people with depression present increased levels of pro-inflammatory cytokines in their blood plasma, such as IL-1β, IL-6, and TNF-α, alongside the acute-phase protein CRP (Zunszain et al., 2012; Haapakoski et al., 2015; Dungey et al., 2013). The link between depression and raised pro-inflammatory cytokines is further substantiated by the capacity of these cytokines to cause depression-like symptoms in both animals and humans (Järventausta et al., 2017). Within the central nervous system (CNS), these pro-inflammatory cytokines seem to arise from microglial activation in response to external stress. The idea of microglial activation has been acknowledged

since microglia were identified as a source of inflammatory mediators typically absent from the CNS under normal circumstances. During immune responses, these cytokines influence the regulation of monoamine neurotransmitters (Yrondi et al., 2017).

The pro-inflammatory cytokines IL-1β, IL-6, and TNF-α collaboratively coordinate the functions of various cells that trigger and amplify inflammation (Slavich & Irwin., 2014). Elevated levels of IL-1β and TNF-α are observed in major depressive disorder and are diminished in bipolar depression, while IL-6 is higher in bipolar depression and reduced in major depressive disorder (Brunoni et al., 2019). In line with findings in anxiety, pro-inflammatory cytokines, especially IL-6, promote the production of the acute-phase protein CRP, while both enhance the function and expression of SERT and serotonin reuptake (20). IL-1β and TNF-α activate the MAPK p38 pathway, which raises the expression and activation of the serotonin transporter (SERT), dopamine transporter (DAT), and norepinephrine transporter (NET), as well as diminishing monoamine synthesis by reducing enzymatic cofactors like tetrahydrobiopterin (BH4). This contributes to various sickness behaviors, including lethargy, depression, anxiety, reduced appetite, anorexia, hypersomnia, fatigue, cognitive impairment, psychomotor retardation, and diminished social behavior and activity (Miller & Raison, 2016; Haapakoski et al., 2016; Hughes et al., 2016; Ma et al., 2016).

Tetrahydrobiopterin (BH4) is a cofactor that phenylalanine hydroxylase requires to transform phenylalanine into tyrosine, and tyrosine hydroxylase requires to change tyrosine into dopamine and dopamine into norepinephrine. It also serves as a cofactor for tryptophan hydroxylase in the process of converting tryptophan into serotonin. A decrease in BH4 will lower the production of monoamines including dopamine, norepinephrine, and serotonin. A decline in dopamine, especially in the mesolimbic region, will suppress elements of reward and motivation. Reduced dopamine function in the anterior insula and orbitofrontal cortex results in diminished cognitive regulation of emotional responses (blunted reactions) to rewarding stimuli. The interaction of these dopamine activity disruptions provokes anhedonia in individuals suffering from depression. A reduction in dopamine function within the basal ganglia is significant to psychomotor retardation and fatigue or energy loss (anergia) (Swardfager et al., 2016). It is believed that declines in serotonin and norepinephrine are connected to sleep disturbances experienced by depressed individuals, such as decreased rapid eye movement (REM) sleep latency, increased REM sleep duration, and diminished non-REM (NREM) sleep duration (Wang et al., 2015).

Under normal physiological circumstances, merely 1% of the circulating tryptophan is transformed into serotonin, with most of it occurring in the gut and only 10–20% in the brain. The remaining 99% of tryptophan is converted into kynurenine by the enzyme tryptophan 2,3-dioxygenase (TDO) in the liver. During inflammatory responses, pro-inflammatory cytokines prompt the enzyme indoleamine 2,3-dioxygenase (IDO), which converts the essential amino acid tryptophan into kynurenine. Kynurenine serves as a precursor to the bioactive metabolites quinolinic acid and kynurenic acid. Quinolinic acid activates the N-methyl-D-aspartate (NMDA) receptor, which, in conjunction with cytokine induction, reactive oxygen species (ROS), and reactive nitrogen species (RNS), decreases glutamate reuptake and encourages glutamate release from astrocytes, resulting in an excess of glutamate. When this surplus glutamate binds to extrasynaptic NMDA receptors, it lowers brain-derived neurotrophic factor (BDNF) and is neurotoxic due to excessive calcium influx into nerve cells (Miller & Raison, 2016; Swardfager et al., 2016; Javed & Fountoulakis, 2005). As a consequence of IDO activity, the availability of peripheral tryptophan is diminished, resulting in serotonin insufficiency in the brain. Pro-inflammatory cytokines also influence neurogenesis and neuronal cell mortality; IL-1β decreases neurogenesis, while TNF-α blocks proliferation and induces neuronal cell death (apoptosis), particularly impacting the amygdala and hippocampus, thus disrupting learning and decision-making processes. The confluence of these factors ultimately instigates depression (Zunszain et al., 2012; Swardfager et al., 2016; Javed & Fountoulakis, 2005).

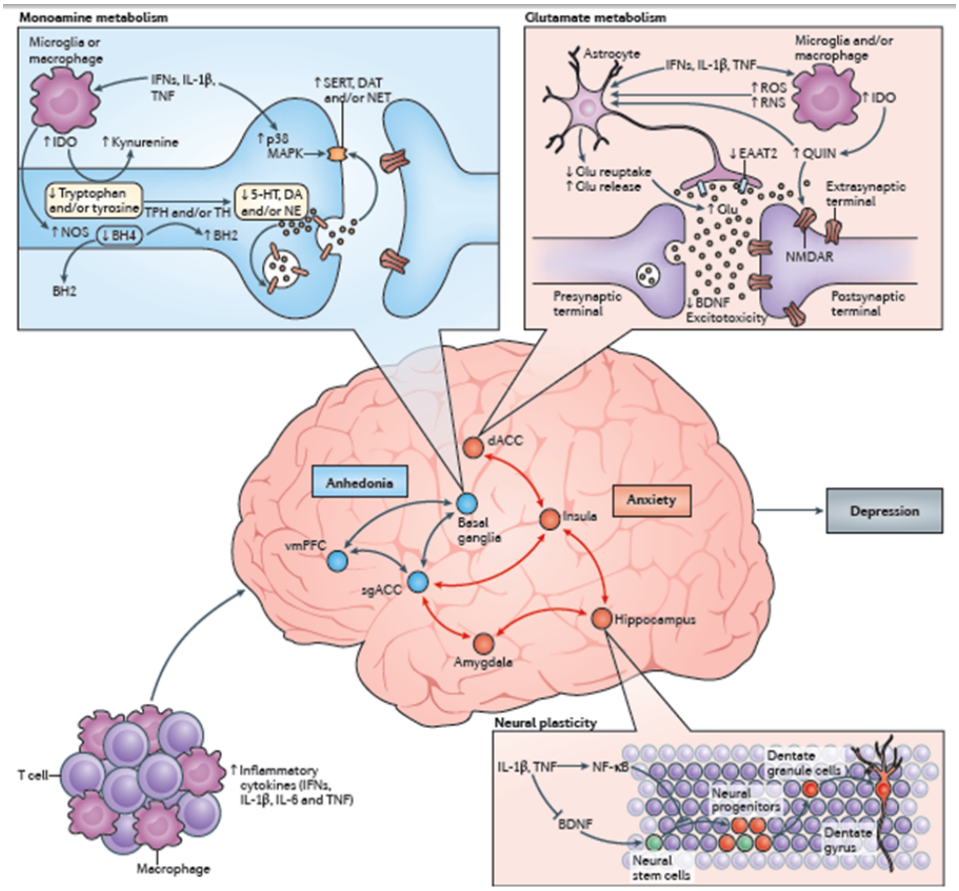

Figure 2. Cytokine target in the brain: neurotransmitter and neurocircuit (Michopoulos et al., 2016)

As per the WHO, about 1 in 150 individuals (0. 53% of the worldwide population) are affected by bipolar disorder (WHO, 2024). Concerning mania, there are no available sources or research that clarify its psychobiological mechanisms at this time. However, an article points out the resemblances between schizophrenia and bipolar disorder regarding genetics, neurometabolites, unusual proteins, and brain structure. The key distinction between schizophrenia and mania mainly rests in the diminished negative symptoms and cognitive deficits seen in mania when compared to schizophrenia (Yamada et al., 2019).

Inflammation and Insomnia

Sleep disorders are a prevalent health issue, with insomnia being the most commonly noted. The incidence of insomnia fluctuates based on the definition applied, ranging from 5 to 50%, with the prevalence reaching 30 to 36% when at least one symptom of insomnia is reported. This number decreases to 10 to 15% when considering daily functional impairment. In general, around one-third of individual worldwide experience symptoms of insomnia, though only 5 to 10% fulfill the diagnostic criteria for insomnia (Klimt et al., 2023).

As previously mentioned, concerning inflammation and depression, the inflammatory process leads to a reduction in serotonin, causing sleep disturbances. The decline in serotonin results in a decrease in the melatonin hormone, as serotonin serves as a precursor for melatonin synthesis in the pineal gland and intestines (Ahmadi et al., 2023). The decrease in melatonin hormone leads to an increase in orexin, given that melatonin has been shown to inhibit orexin neurons in rats and promote sleep. Orexin neurons in the perifornical lateral-hypothalamus (PFH) are essential for fostering wakefulness due to their glutamatergic properties, releasing glutamate and inhibiting GABAergic neurons to induce neural excitation (Sharma et al, 2019; Bigalke et al., 2022; Jászberényi

et al., 2024). The interaction between orexin and GABA is reciprocal, since GABA neurons oppose orexin neurons. Thus, any circumstance that decreases GABA will activate orexin neurons (Konadhode et al., 2015).

Elevated histamine levels induce insomnia by enhancing motivation and cognitive function for wakefulness, and as we know, antihistamines possess sedative properties (Yu et al., 2018). Increased histamine can also be initiated by mast cell activation (Thangam et al., 2018). Mast cell activation results from T cell activation, even though mast cells also affect T cell activity, as their interaction is mutually influential (Mekori & Metkalfe, 1999). T cell activation might be triggered by heightened autonomic activity or elevated levels of epinephrine and norepinephrine, which occur as a consequence of locus coeruleus activation by the amygdala (Stahl, 2021; Dimitrov et al., 2009).

Inflammation And Psychosomatic

Psychosomatic disorder, also known as Somatic Symptom Disorder as per the American Psychiatric Association (APA), is identified when a person shows a significant preoccupation with physical symptoms, including pain, weakness, or shortness of breath, to the degree that it leads to substantial distress and/or issues in daily activities. The person experiences excessive thoughts, feelings, and actions concerning the physical symptoms they are undergoing. These physical symptoms might or might not be linked with a diagnosed medical condition, yet the person perceives the symptoms and believes they are unwell (i.e., not faking illness) (Muskin, 2024).

Building on the topic of insomnia, the inflammatory response triggered by stressors influences the rise in histamine levels. Increased histamine levels in the bloodstream are widely recognized to provoke allergic conditions such as asthma, rhinitis, urticaria, and others (Simons & Simons, 2011). Elevated histamine alongside reduced prostaglandin resulting from cortisol release can lead to dyspepsia and potentially gastric ulcers (Tolbert, 2021). Notably, these allergic and gastric conditions belong to the category of psychosomatic illnesses often encountered in everyday practice (Hange et al., 2007).

Pain ranks among the most commonly reported symptoms by patients pursuing medical attention. Histamine plays a role not only in causing itching (at lower concentrations) but also, at elevated concentrations, is believed to trigger pain. Research indicates that itching induced by histamine can evolve into pain linked to neuropathic hyperalgesia. Activation of histamine receptors within nociceptive pathways is also connected to heightened pain symptoms and is suspected to relate to several other chronic illnesses such as Diabetes, Parkinson’s disease, Alzheimer’s disease, and autoimmune disorders (Obara et al., 2020; Mehta et al., 2020).

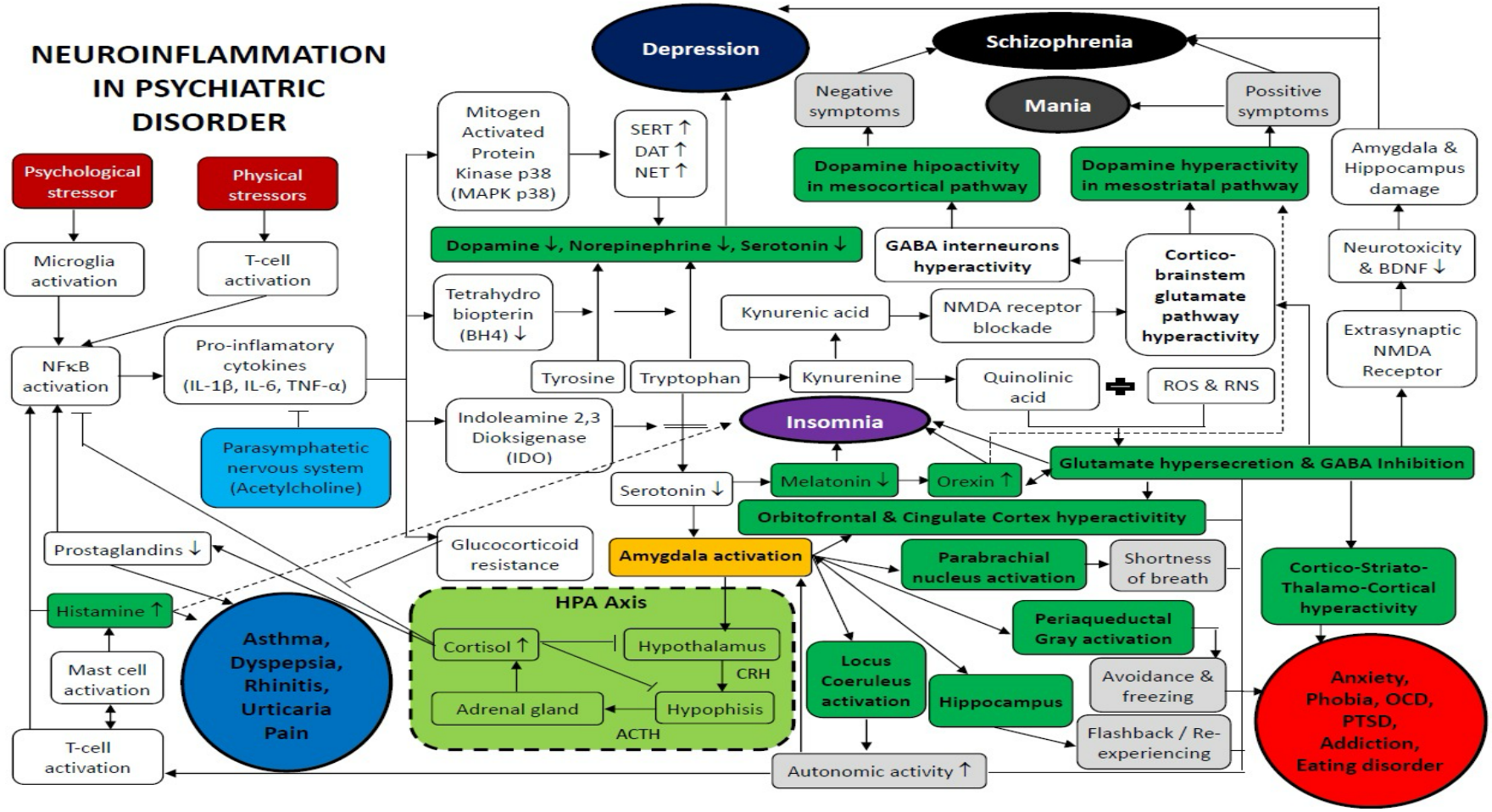

Figure 3. Neuroinflammation in the pathogenesis of psychiatric disorder

Limitations and Further Research

The limitation of this study is the limited availability of reference sources, resulting in most of the studies reviewed being more than 10 years old. This study is expected to serve as a basis for future psychobiological research considerations

CONCLUSION

Psychiatric disorders, which were historically often considered to have unclear mechanisms, are now, with the advancement of science and technology, increasingly being explained through the inflammation theory. All psychiatric disorders are, in fact, interconnected, but the factors that differentiate one psychiatric disorder from another in individuals may lie in their respective genetic aspects. It is essential to understand the mechanisms underlying psychiatric disorders from a biological perspective, as this knowledge serves as a foundation for managing such conditions, particularly through the use of psychopharmacological treatments and other adjunctive therapies.

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AUTHOR CONTRIBUTIONS STATEMENT

EHS and IDO agree to the final version of this article.

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