Review

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Psychoneuroimmunological Processes in Mood and Anxiety Disorders and Their Relation with Psychotherapy

Duygudurum ve Anksiyete Bozukluklarında Psikonöroimmünolojik Süreçler ve Psikoterapi ile İlişkisi

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ABSTRACT

Given high prevalence of mood and anxiety disorders and associated dysfunctions, better understanding, preventing, and treating these disorders are crucial. Along with psychological and other biological causal factors and mechanisms, inflammatory biomarkers, especially cytokines, have also been implicated in etiology and maintenance of mood and anxiety disorders. In the literature, it is generally acknowledged that there is a generalized inflammatory state in these disorders. Thus, several studies have focused on the impact of psychotherapy interventions on neuroimmunological parameters including cytokine levels. This review aims to discuss psychoneuroimmunological factors, especially changes in cytokine levels associated with mood and anxiety disorders and psychotherapy approaches which are commonly used for their treatment. Especially levels of pro-inflammatory cytokines have been shown in majority of those studies to be decreased while levels of anti-inflammatory cytokines have been reported to be elevated in individuals having psychotherapy for these disorders. Nevertheless, variability in study designs and cross-sectional designs in most studies create challenges for comparing results between studies and understanding cause-effect relationships between psychiatric symptomatology and immunological parameters. It is important to carefully determine sample groups and measurement methods in future studies in the field of psychoneuroimmunology. In addition, more studies are needed to figure out if findings showing that certain psychotherapeutic approaches can have anti-inflammatory effects are specific to those approaches or not.

Keywords: Anxiety disorders, mood disorders, cytokines, inflammation, psychotherapy

ÖZ

Duygudurum ve anksiyete bozukluklarının yaygınlık oranlarının yüksekliği ve bu bozukluklarla ilişkili işlev bozuklukları nedeniyle, bu bozuklukların daha iyi anlaşılması, önlenmesi ve tedavi edilmesi oldukça önemlidir. Psikolojik ve diğer biyolojik nedensel faktörlerin ve mekanizmaların yanı sıra, inflamatuar biyobelirteçlerin, özellikle de sitokinlerin, duygudurum ve anksiyete bozukluklarının kökeninde ve sürdürülmesinde rolü olduğu kabul edilmektedir. Buradan hareketle, birtakım çalışmalar psikoterapi müdahalelerinin sitokin düzeylerinin de dahil olduğu nöroimmünolojik parametreler üzerindeki etkisine odaklanmıştır. Bu derleme, duygudurum ve anksiyete bozuklukları ve bunların sağaltımında yaygın olarak kullanılan psikoterapi yaklaşımları ile ilişkili psikonöroimmünolojik faktörlerden, özellikle sitokin düzeylerindeki değişimleri tartışmayı hedeflemektedir. Alanyazındaki çalışmaların çoğunda ilgili bozukluklar için psikoterapi alan bireylerde özellikle pro-inflamatuar sitokinlerin düzeylerinin azaldığı gösterilirken, anti-inflamatuar sitokinlerin düzeylerinin ise yükseldiği bildirilmiştir. Yine de çalışma desenlerinin çeşitliliği çalışmalar arasında bulguların kıyaslanmasında ve çalışmaların çoğunun kesitsel desene sahip olması psikiyatrik semptomatoloji ve immünolojik parametreler arasındaki neden-sonuç ilişkilerinin anlaşılmasında zorluk yaratmaktadır. Psikonöroimmünoloji alanında yapılacak gelecek çalışmalarda örneklem gruplarının ve ölçüm yöntemlerinin dikkatle belirlenmesi önemlidir. Ayrıca belirli psikoterapi yaklaşımlarının anti-inflamatuar etkileri olabileceğini gösteren bulguların bu yaklaşımlara özgü olup olmadığının anlaşılması için daha fazla sayıda psikoterapi sonuç çalışmasına ihtiyaç duyulmaktadır.

Anahtar Sözcükler: Duygudurum bozuklukları, inflamasyon, anksiyete bozuklukları, psikoterapi, sitokinler

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Mood and anxiety disorders are among the common psychiatric disorders in the world. According to the data from the Global Burden of Disease Collaborative Network (2021) research conducted in 204 countries and regions including Turkey, anxiety disorders (3779.5 per 100 thousand) and mood disorders which include depressive disorders (3440.1 per 100 thousand) and bipolar disorder (489.9 per 100 thousand) appear to be disorders with a quite high prevalence rate compared to other psychiatric disorders subject to the research. It is reported that depression alone affects more than 300 million people in the world and causes more than 800 thousand people to die as a result of suicide while nearly 300 million people have an anxiety disorder (World Health Organization 2017). According to the findings of the National Burden of Disease Study 2013 conducted in our country (Çavlin 2017), depressive disorders were found as one of the three diseases with the highest burden. Since it is known that anxiety disorders are comorbid with especially major depressive disorder and that up to 60% of individuals with major depressive disorder meet the diagnostic criteria for one or more anxiety disorders in their lifetime (Kaufman and Charney 2000), these disorders seem to be frequently discussed together in the literature (e.g., Castle et al. 2006, Hofmann et al. 2012, Ressler and Mayberg 2007). In fact, it has been proposed to reduce the two disorder categories to a single mood disorder category (Watson 2005). Disability caused by disorders in the category of mood and anxiety disorders ranks first among disorders and diseases that cause disability globally (World Health Organization 2017). Considering the prevalence of these disorders and the extent of disability they cause, it is understood that efforts towards better understanding, preventing, or treating them are quite important.

There are currently several leading hypotheses about the mechanisms of occurrence of mood and anxiety disorders (see Craighead 2017) while immunological pathways also draw attention among the new approaches. In particular, studies on immune variables that may affect the emergence and course of these disorders have been increasing in recent years (e.g., Leonard 2010, Myint 2013). In the literature, it is stated that increased cytokine levels during neuroinflammation, which may start due to various reasons such as autoimmunity, smoking, air pollution and trauma, may be associated with psychiatric symptomatology by various mechanisms (e.g., Najjar et al. 2013). Possible mechanisms include the direct effect of inflammatory cytokines on monoamine levels, hypothalamo-pituitary-adrenal axis dysregulation, pathological microglial cell activation, damaged neuroplasticity, and certain structural changes in the brain (Rosenblat et al. 2014). In addition, it was previously shown that bipolar disorder and panic disorder, which are included in the mood and anxiety disorders categories, may be associated with inherited defects in the immune system (Foldager et al. 2014). Studies have even suggested that the effect size of inflammation is high enough and that psychiatric disorders can be differentiated from each other using inflammatory biomarkers (Yuan et al. 2019). The main purpose of this review is to discuss the psychoneuroimmunological factors, especially the changes in cytokine levels, associated with mood and anxiety disorders and the psychotherapy approaches commonly used in their treatment. In other words, the article aims to summarize the neuroinflammatory mechanisms associated with mood disorders and anxiety disorders, and to discuss the effects of psychotherapeutic interventions on these mechanisms. In addition, this article aims to review the findings and opinions that the therapeutic effect of psychotherapies frequently used in these disorders may occur because of anti-inflammatory effects on the immune system in addition to fostering psychological well-being. Although the relationship of pharmacological treatments for mood disorders and anxiety disorders with neuroimmunological processes has been studied previously (e.g., Boorman et al. 2005, Hannestad et al. 2011, Vojvodic et al. 2019), the relationship between psychotherapies and inflammation has not previously been adequately addressed in any source, to the best of the authors' knowledge.

Psychiatric Disorders and Immune System

How behaviors and emotions can affect immune function is an important research topic in animal and human research. Although Solomon first coined the term psychoimmunology in 1964, it is noteworthy that until the 1980s there was very little human research in this area (Kiecolt-Glaser et al. 2002). Psychoneuroimmunology, as an important interdisciplinary field with significant focus in researches in the past 40 years, generally examines the interaction of the nervous system with the immune system and how mental processes modulate the function of the immune system (Daruna 2012). It is thought that the origins of psychoneuroimmunology, which has an ever-expanding field with the contributions of disciplines such as psychiatry, neuroscience, immunology, physiology, genetics, pharmacology, molecular biology, endocrinology, and psychology, are based on the study of psychologist Robert Ader and immunologist Nicholas Cohen (1975). Ader and Cohen used sugar water as a conditioned stimulant together with the application of cyclophosphamide, an immunosuppressive drug, in their classical conditioning experiment conducted on mice. Finding a significant immunosuppression compared to the control group with presenting sugar water alone in conditioned mice was considered as one of the first evidences that the central nervous system is related to the immune system. In the following years, a case example that presented the success of treatment obtained as a result of conditioning a young person with systemic lupus erythematosus who received cyclophosphamide treatment with a similar protocol was found to be important in terms of showing that similar processes can also be applicable in humans (Olness and Ader 1992).

The immune system is a large and complex system that works with natural or acquired cellular response and antibody cycles (Klimov 2019). Main diseases that concern this system are autoimmune diseases, allergies, immunodeficiencies and cancers. Pathologies concerning the immune system are not limited to this, in fact, an immune response occurs in many events that occur in the body. This immune response, which can occur with physical, biological, chemical or psychological effects, is called inflammation

(Punchard et al. 2004). Chemical mediators, cytokines, which are responsible for the immune response are soluble bioactive mediators that ensure communication between cells, between main immune system cells in the body. Especially since it is known that cytokine activity is closely related to behavioral changes such as psychomotor retardation, eating and sleep disorders, and also to changes in the metabolism of monoamines such as serotonin, dopamine and norepinephrine, which are thought to have a role in the etiology of psychopathologies (Dantzer et al. 1999a, 1999b), it is thought that examining the relationship between cytokines and common psychiatric disorders would be beneficial in terms of enhancing the knowledge about these disorders.

Cytokines, which are mostly mediators of immune activation or cell differentiation/death, are generally categorized as pro-inflammatory and anti-inflammatory (Klimov 2019). Main pro-inflammatory cytokines that play the role of initiator of inflammation are interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-12 (IL-12), tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ). The main anti-inflammatory cytokines that have a balancing function to suppress the inflammatory response are interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-13 (IL-13) and alpha and beta interferons (IFN-α and IFN-β) (Klimov 2019). While the brain and other central nervous system organs are mostly not affected by the peripheral immune response thanks to the blood-brain barrier, the occurrence of inflammation in the central nervous system is called neuroinflammation (Najjar et al 2013). Neuroinflammatory processes are known to play a role in the etiology of many neurological diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and AIDS-related dementia (e.g., Anthony et al. 2005, Heneka et al. 2015, Hirsch et al. 2012, Rosenberg 2002). It has been previously emphasized that inflammation-related diseases play an important role in deaths all over the world (GBD 2017 Causes of Death Collaborators 2018). For this reason, examination of diseases and disorders that may be related to the immune system is important in terms of reducing the morbidity and mortality that may arise due to these.

Psychoneuroimmunological Factors Associated with Mood Disorders

Although various psychological factors such as stressful life events, predispositional factors, interpersonal relationships, helplessness, and hopelessness to explain the etiology of mood disorders (Hooley et al. 2017) exist in the literature, biological mechanisms have also been extensively studied. While candidate gene scans, neurotransmitter levels, neuroendocrinological axes, and morphological changes in the cerebral cortex were the subjects of biological models, etiological studies referring to systemic inflammation led by psychoneuroimmunology have also begun (Craighead 2017).

The inflammatory etiology discussed for major depression is mainly about serotonergic destruction, endocrinological pathway, microglial processes and morphological changes in the brain. It is thought that a low-level inflammation occurs with the increase in the level of pro-inflammatory cytokines and acute-phase proteins in depression (Euteneuer et al. 2017). In the meta-analysis conducted by Valkanova et al. (2013), it has been found that the increase in inflammatory biomarkers were observed prior to depressive episodes. Increase in cytokines and inflammation can lead to various symptoms and psychiatric disorders (Sözeri Varma, 2014). Various biomechanisms with etiological importance are discussed in the literature. In this context, an important pathway that has been extensively studied is the tryptophan/kynurenine pathway and indolamine 2,3-dioxygenase (IDO) enzyme activity. Tryptophan amino acid is the precursor of serotonin; and it turns into metabolites of kynurenine, which plays an important regulatory role on the immune system with an alternative pathway to serotonin (Comai et al. 2016). IFN-α and some cytokines that work synergistically with IFN-α increase the activity of the IDO enzyme, which mediates the conversion of tryptophan to kynurenine. In this way, more of the tryptophan in the brain is spent on the kynurenine pathway while more limited substrate (tryptophan) remains for serotonin synthesis. It is acknowledged that the decreased serotonin level with this mechanism induced by cytokine mediates depression (Mándi and Vécsei 2012).

Except for the effects on neurotransmission, it is known that cytokines such as IL-1, IL-6, TNF-α and IFN-α activate the hypothalamic-pituitary-adrenal axis, corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol levels increase and thus play a role in inflammation (Beishuizen and Thijs 2003). While this axis is kept under control with negative feedback with the anti-inflammatory effect of cortisol, continuous cortisol stimulation caused by chronic inflammation results in decreased sensitivity and bioavailability of the hormone (Raison and Miller 2003). Another critical mechanism is the activation of microglia, which can be called immune cells of the nervous system. Microglia activated by TNF-α and IL-1β lead to increased synaptic pruning and apoptosis of neurons. This situation mediates the emergence of non-adaptive behaviors and suboptimal brain functions (e.g., impairment in attention, executive functions, and verbal memory) in bipolar disorder and major depressive disorder (Ekdahl 2012, Paradise et al. 2012, Park and Bowers 2010, Stertz et al. 2013). Another proposed mechanism is the anatomical and functional changes that occur in the brain structure. In the process of chronic neuroinflammation, enlargement of the lateral ventricles in the brain, changes in the subgenual cingulate cortex, and decrease in mesolimbic connections are the changes thought to play a role in mood disorders (Harrison et al. 2009).

These propositions explaining possible immune mechanisms of mood disorders have been tested by various cross-sectional studies. According to the findings of Dowlati et al.'s (2010) meta-analysis covering 24 studies in the literature, the serum TNF-α and IL-6 levels of those diagnosed with major depressive disorder were significantly higher than the control group. Aslan (2018) also found that TNF-α and IL-6 levels were higher in patients with a diagnosis of major depression than compared to the

healthy control group and that these values were higher in those with recurrent depression compared to those with first episode depression. Recent studies also repeat the finding that IL-6 levels are higher in those with major depressive disorder (Choi et al. 2021). Choi et al. (2021) also indicated that TNF-α levels are a predictor of suicidal thoughts in patients with depression. Krogh et al. (2014) conducted a study with 112 participants, 57 of whom were in the control group, and found higher levels of IL-6 and CRP in those with major depressive disorder. In another study conducted in Norway, 50 individuals with a diagnosis of major depressive disorder were compared with 34 healthy controls, and serum IL-1β, IL-5, IL-6, IL-7, IL-8 and IL-10 levels of those with a diagnosis were found to be significantly higher (Dahl et al. 2014). There are also studies suggesting that inflammatory activity may vary according to the subtypes of major depression. In the samples taken from 105 individuals with major depression, 35 of whom had atypical depression, IL-2 levels were found to be increased, however, IL-4 levels were decreased in those with atypical depression. While no significant change was observed in IL-6 and TNF-α levels, this was explained by the difference in distribution in leukocyte subtypes (Yoon et al. 2012). Finally, another remarkable study suggested that cognitive or somatic symptomatology in depression is differently related to inflammation (Duivis et al. 2013). In this multicenter study with 2861 participants, it was found that the severity of the somatic symptoms of depression was associated with the increase in the levels of inflammation markers CRP, IL-6 and TNF-α, however, this relationship was not present for cognitive symptoms only.

Bipolar disorder, on the other hand, is another mood disorder whose mechanism of formation has not yet been fully explained, but it is seen that the disorder associated neuroprogression with immune dysfunction, increased oxidative stress, and decreased neurotropic support, and increased the incidence of certain autoimmune diseases (e.g., SLE, autoimmune hepatitis, autoimmune thyroiditis, MS) in individuals with the disorder (Barbosa et al. 2014). In their review, Kalelioğlu et al. (2017) stated that although studies in the literature generally indicate an increase in cytokine levels during episodes, each cytokine may behave differently. Studies in the literature also reveal that cytokine levels differ in different episodes or stages of the disorder. Altamura et al. (2014) in their review of the findings in the literature stated that pro-inflammatory cytokines such as IL-8, CRP and TNF-α increase during depressive episodes, and IL-6, IL-8 and TNF-α levels increase during manic episodes, and there are inconsistent results for IL-4. When these studies are reviewed, for instance, in a study conducted by Brietzke et al. (2009), patients with bipolar disorder were divided into different groups on the basis of whether they met the diagnostic criteria for euthymic, manic and depressive episodes during data collection, and compared with the control group. According to the findings, only IL-4 levels were increased in euthymic patients while IL-2, IL-4 and IL-6 levels were increased in manic episode and only IL-6 levels in depressive episode. In this respect, it has been stated that although the depressive episode of bipolar disorder has common pathophysiological mechanisms with major depressive disorder, manic episodes are different from them. In a study in which 60 individuals diagnosed with bipolar I disorder were divided into two groups as early and late stage and compared with a healthy control group consisting of 60 participants, IL-6, IL-10 and TNF-α in individuals with early stage bipolar disorder were found to be significantly higher, and IL-10 and TNF-α levels were found to be significantly higher in patients with late stage disorders compared to the control group (Kauer-Sant'Anna et al. 2009). Similarly, in another study in which patients with bipolar disorder were divided into two groups as chronic or early stage, it was observed that those with chronic disorders had higher TNF-α and IL-6 levels compared to the early stage and healthy control groups (Karabulut et al. 2019). On the other hand, in a study conducted in patients with bipolar disorder, no significant difference was found in terms of peripheral inflammatory markers (IL-2, IL-4, IL-8, IL-10, and TNFα) compared to controls, and also among individuals with subtypes of the disorder (Özen et al. 2019).

When these findings are considered together, it is seen that the levels of cytokines, which are a marker of systemic inflammation, are significantly higher in individuals diagnosed with mood disorders compared to healthy controls. It is thought that increased cytokine levels may contribute to the formation and course of psychopathology through different biological mechanisms.

Psychoneuroimmunological Factors Associated with Anxiety Disorders

Although the high rate of comorbidity between anxiety disorders and mood disorders (Kaufman and Charney 2000) causes difficulties in differentiating the etiology of their disorders, it is known that the factors that cause susceptibility to these disorders vary in a wide range from genetic basis and antenatal development characteristics to temperament, negative childhood experiences and modeling (Manassis and Bradley 1994). Recent studies also highlight the importance of oxidative stress in understanding anxiety disorders (Fedoce et al. 2018). Increasing levels of pro-inflammatory cytokines activate inflammation-related transcription factors that control enzymes that regulate free oxygen radicals in the body. Thus, increased oxidative stress inhibits neurogenesis by creating mitochondrial dysfunction and accelerating telomere shortening in cells. Another effect of the increase in pro-inflammatory cytokines is that it creates neuronal toxicity by increasing glutamate by disrupting neuronal signals and has an anxiogenic effect by reducing GABA activity (Hovatta et al. 2010). Decreased GABA activity is an important etiological factor for anxiety disorders in general (Craighead, 2017). In conclusion, it is thought that changes in oxidative mechanisms may be responsible for the pathophysiology of psychiatric disorders (Vismara et al. 2020). Vismara et al. (2020) state that the HPA axis and the stress response mechanisms mediated by the autonomic nervous system and the relationship between inflammation are significant for anxiety disorders. Particularly, epinephrine and norepinephrine hormones are directly related to cytokine release. In this respect, it is clear that efforts to

understand the psychoneuroimmunological factors associated with anxiety disorders are significant. However, although anxiety disorders are the most common category among all disorder categories in the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association [APA] 2013) (Bandelow and Michaelis 2015), there are limited studies investigating the change in immunological parameters in it. One reason for the limited number of studies included in this review is that posttraumatic stress disorder and obsessive-compulsive disorder, which have relatively large numbers of studies, were excluded from the anxiety disorders category in DSM-5 (APA 2013). Another reason is that some of the studies (e.g., Duivis et al. 2013, Lee 2020, Liukkonen et al. 2011) were conducted not on individuals with anxiety disorders, but by using anxiety measures in the general population and examining the relation between anxiety scores and immunological parameters.

However, current studies reveal that there are significant immunological changes in individuals with anxiety disorders. For example, in a cohort study conducted with 2288 participants, 556 of whom were in the control group, with continuing or previous common anxiety disorder, social anxiety disorder, panic disorder or agoraphobia (Vogelzangs et al. 2013), CRP, IL-6 and TNF-α levels were examined. While CRP levels were found to be significantly higher in men with anxiety disorders compared to controls, CRP levels were found to be similarly higher in late-onset (50 years and later) anxiety disorders. Wagner et al. (2015) indicated an increase in CRP and TNF-α levels in patients with agoraphobia. In their systematic review and meta-analysis, Costello et al. (2019) found that CRP, IFN-γ and TNF-α levels increased in common anxiety disorder compared to healthy controls. Zou et al. (2020) also revealed that IFN-γ levels are positively related to the severity of anxiety in generalized anxiety disorder. In the same study, IL-6 levels were observed to be similarly high in those with generalized anxiety disorder. However, although IL-6 levels increase with anxiety, it has been shown that increased levels of this biomarker do not predict anxiety symptoms after six years (Lee 2020).

The number of studies on panic disorder in the category of anxiety disorders is relatively high. For example, in a study conducted with individuals with panic disorder, IFN-γ and IL-12 levels were found to decrease (Tükel et al. 2012). Petrowski et al. (2018) also indicated that anti-inflammatory activity increases in patients with panic disorder during baseline and psychosocial stress conditions. Hoge et al. (2009) previously showed that IL-1β and TNF-α levels were increased in addition to IL-6. Similarly, in a recent study, IL-6 levels were found to be higher in patients with panic disorder compared to healthy controls (Choi et al. 2021). In a systematic review of the role of cytokines in panic disorder, it was reported that IL-6, IL-1β and IL-5 levels were consistently high in patients with panic disorder, however, there were inconsistent findings regarding IL-2, IL-12 and INF-γ (Quagliato and Nardi 2018).

To summarize, when the literature is examined, it can be seen that inflammatory biomarkers in anxiety disorders are examined in the context of panic disorder, generalized anxiety disorder, and social anxiety disorder. No studies on other anxiety disorders (e.g., specific phobia, separation anxiety disorder) were found in the DSM-5 (APA 2013). It has been suggested that conflicting findings in the literature on panic disorder are related to the measurement of biomarkers and differences in samples (Quagliato and Nardi 2018). In addition, it is recommended to investigate how the cytokine level increases mentioned in this article play a role in the etiology of anxiety disorders (Costello et al. 2019). In particular, it has been suggested previously that certain biomarkers (e.g., Type-I [IFN-alpha, IFN-beta] and Type-II [IFN-γ] interferons) may act as antagonists to each other (see Deczkowska et al. 2016). In order to better understand the conflicting findings, it is important to focus more on such possible mechanisms in studies and to create study designs in a way that allows the findings to be compared.

Relationship of Psychotherapies with Immunological Factors in Mood and Anxiety Disorders

It is known that psychotherapies, which are a way of helping individuals with various psychiatric disorders and emotional difficulties, contribute to improvement in symptoms and increase in level of functioning (Parekh and Givon 2019). Although psychotherapy is a frequently used treatment method for various psychopathologies, studies on related biological mechanisms are limited when compared to pharmacological treatments (Etkin et al. 2005). It is also acknowledged that the biological changes caused by psychotherapies are different from the changes associated with pharmacotherapies (Fuchs 2004). This highlights the importance of addressing changes that may be associated with psychotherapy approaches used in common disorders.

In the literature, there is evidence for neural and/or epigenetic changes that occur after successful psychotherapy interventions for psychiatric disorders. For instance, it has been previously reported that changes were observed in certain areas of dorsomedial prefrontal cortex, posterior cingulate gyrus/precuneus and temporal lobe (Messina et al. 2013) and left paracingulate gyrus (Kalsi et al. 2017) between neural changes related to mood regulation in psychotherapies towards depression and anxiety disorders. In addition, it was found that there were changes in neural activity in the left amygdala, left hippocampus, and subgenual anterior cingulate cortex in those undergoing psychotherapy for major depressive disorder (Straub et al. 2015). In addition to these, it has been stated that epigenetic changes such as DNA or histone changes observed after successful psychotherapy interventions can be transferred to future generations and this may contribute to the prevention of certain disorders (Schiele et al. 2020).

In addition to the changes mentioned above, the literature on the relationship of psychotherapies with changes in various immunological parameters is limited. However, intervention

studies in the field of psychoneuroimmunology focused on different strategies including hypnosis, relaxation, exercise, classical conditioning, self-disclosure, exposure techniques, and cognitive behavioral therapy (CBT) in various samples (Kiecolt-Glaser and Glaser 1992). Many of the abovementioned psychotherapy techniques are frequently used in mood and anxiety disorders. It can be seen that the American Psychological Association (2021) recommends various evidence-based therapies such as cognitive therapy, CBT, acceptance and commitment therapy, emotion-focused therapy, short-term psychodynamic therapy for major depression, and cognitive therapy, family-focused therapy, interpersonal and social rhythm therapy, psychoeducation, and systematic care for bipolar disorder. In the same source, it is seen that various psychotherapy approaches such as progressive relaxation, CBT, psychoanalytic therapy, exposure therapies are offered among the evidence-based psychological treatments for anxiety disorders. A recent meta-analysis study provided evidence that cognitive therapy, behavioral therapy, or CBT and similar interventions are associated with overall improvement in immune system function over time in those with diseases or disorders such as autoimmune disorders, cancer, HIV, insomnia, stress, and depression (Shields et al. 2020). However, Lopresti (2017) emphasized that the relationship between CBT and inflammation should not be discussed from one side only. Accordingly, as well as the anti-inflammatory effects of therapy, inflammation affects the treatment response in client groups with high levels of inflammation.

When the studies in the literature are examined in more detail, it is seen that there are positive changes in immunological parameters in some individuals who receive psychotherapy for these disorders. For example, in a study including 97 individuals with major depressive disorder, it was indicated that CBT provided a significant decrease in serum IL-6 and TNF-α levels, and this decrease was greater than the decrease after narrative cognitive therapy (Moreira et al. 2015). Walsh et al. (2016) found a significant decrease in salivary IL-6 and TNF-α levels in the treatment group compared to the control group after a four-week mindfulness-based intervention in their study conducted with 64 women with depressive symptoms. Similarly, Del Grande da Silva et al. (2016) found that there was a significant decrease in serum IL-6 and TNF-α levels after an 18-session supportive-expressive dynamic psychotherapy provided to 46 participants with a diagnosis of major depressive disorder. In another study (Eisendrath et al. 2016), a significant decrease was observed in CRP levels after an eight-week mindfulness-based cognitive therapy provided to a group of 11 people diagnosed with major depressive disorder. In a longitudinal study conducted with 50 participants diagnosed with major depressive disorder, the cytokine levels of 29 individuals who received 12-week relational psychodynamic therapy combined with only CBT applications without drug treatment in the usual treatment scheme were controlled. It has been reported that IL-6, IL-10, IFN-γ and TNF-α levels in this group decreased significantly after psychotherapy and reached the same level as those in the control group (Dahl et al. 2016). In the study conducted by Euteneuer et al. (2017), it was found that the level of IL-10, an anti-inflammatory cytokine, was increased in participants with a diagnosis of depression who received a behavioral activation treatment with emphasis on physical exercise, compared to active and passive control groups. Studies with participants diagnosed with first episode major depressive disorder have revealed inconsistent findings. In one of these studies (Gazal et al. 2013), IL-6 levels decreased after seven weeks of CBT, however, in another study (Keri et al. 2014) there was no change in IL-6 and CRP levels after 16 weeks of CBT.

In the field of psychoneuroimmunology, there are much fewer studies on bipolar disorder and anxiety disorders compared to major depressive disorder. In a study which provided a 20-week interpersonal relations and social rhythm therapy to 27 individuals diagnosed with bipolar II disorder with quetiapine (n = 10) or placebo (n = 17), IL-6 and TNF-α levels increased in the group undergoing drug treatment with psychotherapy while IL-6 and TNF-α levels decreased in the group receiving psychotherapy only (Fiedorowicz 2019). The only study indicating that psychotherapy approaches used in anxiety disorders are effective on cytokines was conducted by Hoge et al. (2018). In this study, IL-6 and TNF-α levels of those diagnosed with common anxiety disorder were significantly reduced compared to baseline after a mindfulness-based intervention.

When these findings are discussed together, it appears that the findings of the studies in the literature indicate that, in general, CBT, relational psychodynamic therapy, behavioral activation, mindfulness-based interventions, interpersonal relations and social rhythm therapy, supportive dynamic psychotherapy approaches can improve immunological parameters in these disorders when used in mood and certain anxiety disorders, and possible changes can be reversed. However, it is clear that there are not sufficient studies on bipolar disorders and anxiety disorders in particular.

Despite the studies showing that psychotherapies are associated with changes in immunological parameters, there are also various studies in the literature that show that psychotherapies are not associated with such a change. For example, Memon et al. (2017) did not observe any difference in the levels of IL-6, IL-8 and CRP tested before and after treatment in two separate groups to which they applied mindfulness-based group therapy and CBT in their study on individuals with depression and anxiety symptoms. They explained that the increase in inflammatory cytokine levels may be a result of depression-related changes in brain function rather than a result of depression, and therefore may not be associated with response to treatment. It has also been stated that CRP levels may be associated with certain features such as late-onset depression or female sex (Memon et al. 2017). Since it is known that high CRP level predicts negative results in psychotherapy for depressive symptoms (Harley et al. 2010), it is recommended to focus on certain subgroups in studies on the change in CRP levels. Koh and Lee (2004) also indicated in their study conducted with panic disorder patients that there was no difference in IL-2 level when CBT was provided together with an anxiolytic drug. It was seen that there was no change in cytokine

levels after music-assisted psychotherapy applied for depressive and anxiety symptoms in groups receiving cancer treatment (Zeppegno et al. 2021), and it was stated that it is important to understand the role of immunotherapy in psychopathologies in explaining these findings. In this context, it seems important to create study samples, considering that the methods used in the treatment of physical diseases related to the immune system may be a confounding variable in psychotherapy outcome studies in the field of psychoneuroimmunology.

In sum, studies examining the relationship of psychotherapies with changes in the immune system have focused on biomarkers associated with a reduction in the severity of symptoms in individuals with various psychiatric disorders. The findings presented in the article are summarized in Table 1. Although biomarkers in these studies are generally IL-6, IL-8, IL-10, TNF-α and IFN-γ, it is seen that CRP levels are also measured in a few studies. In other words, in most of the psychotherapy outcome studies, there is a decrease in the levels of pro-inflammatory biomarkers included in the studies. In a small number of studies, no change was observed in immunological parameters, possibly due to sample characteristics. However, while evaluating the findings, it should be kept in mind that although there are similarities between studies in terms of diagnostic groups, sample characteristics and preferred psychotherapy approaches are different, and therefore it may be difficult to draw conclusions about the findings in general. Pre-treatment inflammation stands out as an important factor, especially in relation to sample characteristics. Studies in the literature indicate that the presence of inflammation before treatment adversely affects the outcome of psychotherapy (for a review, see Lopresti 2017). In these studies, it was reported that participants with high pretreatment CRP, TNF-α, and IL-6 levels in general benefited less from CBT, acceptance and commitment therapy, or relaxation interventions compared to participants with lower levels. In this respect, pre-treatment inflammation should also be taken into consideration in terms of how effective psychotherapies are on inflammation.

Table 1. List of studies examining cytokine levels following psychotherapy

Reference	Sample	Intervention	Impact
Studies showing significant changes in cytokine levels following psychotherapy			
Moreira et al. 2015	Major depressive disorder	CBT	IL-6 ↓ TNF-α ↓
Walsh et al. 2016	Depressive symptoms	Mindfulness-based intervention	IL-6 ↓ TNF-α ↓
Del Grande da Silva et al. 2016	Major depressive disorder	Supportive-expressive dynamic psychotherapy	IL-6 ↓ TNF-α ↓
Eisendrath et al. 2016	Major depressive disorder	Mindfulness-based CT	CRP ↓
Dahl et al. 2016	Major depressive disorder	Relational psychodynamic therapy combined with CBT	IL-5 ↓ IL-8 ↓ IL-6 ↓ IL-10 ↓ TNF-α ↓ IFN-γ ↓
Euteneuer et al. 2017	Major depressive disorder	Behavioral activation	IL-10 ↑
Gazal et al. 2013	Major depressive disorder	CBT	IL-6 ↓
Fiedorowicz 2019	Bipolar II disorder	Interpersonal and social rhythm therapy (+ quetiapine or placebo)	IL-6 ↓ TNF-α ↓
Hoge et al. 2018	Generalized anxiety disorder	Mindfulness-based intervention	IL-6 ↓ TNF-α ↓
Studies showing no significant changes in cytokine levels following psychotherapy			
Keri et al. 2014		CBT	IL-6 ↔ CRP ↔
Memon et al. 2017	Depressive/anxiety symptoms	Mindfulness-based group therapy or CBT	IL-8 ↔ CRP ↔ CRP ↔
Reference	Sample	Intervention	Impact
Koh and Lee 2004	Panic disorder	CBT (combined with pharmacotherapy)	IL-2 ↔
Zeppegno et al. 2021	Depressive/anxiety symptoms	Psychotherapy with music intervention	IL-6 ↔ TNF-α ↔ CRP ↔

Note: CBT = Cognitive behavioral therapy, CT = Cognitive therapy, IL = Interleukin, TNF-α = Tumor Necrosis Factor alpha, CRP = C-Reactive Protein, IFN = Interferon gamma

Discussion

Today, with the increase in studies in the field of psychoneuroimmunology, it is seen that efforts to examine the relationship between psychiatric disorders and the immune system have begun to increase. This review article aims to provide an overview of the relationship between mood and anxiety disorders, which are the most common psychiatric disorder categories, and the relationship between individuals with these disorders and commonly used psychotherapy approaches with immune function. It is predicted that a better understanding of the relationship between psychotherapies and these biomarkers may contribute to interventions aimed at maintaining remission and preventing relapse in psychiatric disorders, particularly since the increase in pro-inflammatory biomarkers may affect neural plasticity and cause new episodes of disorder (Moreira et al. 2015).

In mood and anxiety disorders, it is known that cytokines such as IL-1, IL-2, IL-6, TNF-α and acute phase reactants such as CRP increase and an inflammatory process progresses in the body (e.g., Krogh et al. 2014, Wagner et al. 2015). However, it is noted in the literature that no single biomarker has sufficient specificity and sensitivity in understanding disorders (Lopresti et al. 2014). The presence of similar findings regarding cytokines in different psychiatric disorders also increases this challenge. For this reason, it is recommended to standardize the measurement and storage of inflammatory markers in studies (Hou and Baldwin 2012, Lopresti et al. 2014). As Van Duinen et al. (2004) highlighted, it is possible that the use of different measurement methods such as radioimmune testing or ELISA method in the literature may be related to the emergence of inconsistent findings between studies. Similarly, it can be seen that the diagnosis method is not the same in studies; some studies (e.g., Dahl et al. 2016, Moreira et al. 2015) used standard diagnosis interviews and measurement tools while some (e.g., Del Grande da Silva et al. 2016, Koh and Lee 2004) only conducted expert interviews. In this respect, it should be considered that the different diagnostic methods for psychiatric disorders may have an effect on the findings. In addition, while designing studies on this subject, careful creation of sample subgroups is among the suggestions. For example, since certain psychiatric disorders are more common in women in general (Castle et al. 2006), women make up the proportional majority in the study sample. The fact that they are more prone to disorders such as depression due to psychosocial risk factors such as hormonal differences between the sexes and lack of social support may cause gender differences in the inflammatory response (Duivis et al. 2013). Therefore, it should be taken into account that sex may be an important variable when creating research samples. In addition to this, it is observed that the sample groups in the studies were formed on the basis of the diagnosis of psychopathology. However, it is possible that the response to treatment may differ according to the initial level of inflammation (Morin-Alain et al. 2020). For this reason, it is thought that it will be important to control the baseline levels in treatment outcome studies. The relatively small sample size of the studies in the literature raises questions about the generalizability of the findings and the actual effect sizes. Therefore, it appears that it would be beneficial to target larger samples in future studies. In addition, it is suggested that unhealthy lifestyle indicators such as smoking and obesity may be mediator or confounding variables between mood and anxiety disorders and inflammation, and it may be important to control these indicators in multiple analyzes (Duivis et al. 2013, Himmerich et al. 2019). Therefore, it seems important to consider these indicators in studies. Finally, since genetic markers in these disorders have previously been associated with the immune system (Foldager et al. 2014), it would be significant to repeat studies on genotype-immune system interaction in our country.

It is important to include parameters such as leukocyte activity, the distribution of their number and subtypes, cytokine receptors, gene expression of cytokines, apart from cytokines and acute phase reactants, while investigating changes in post-treatment immunological parameters in the future studies. It has been previously shown that especially hemogram-derived peripheral biomarkers may have an important role in mood disorders (e.g., Kirlioglu et al. 2019, Mazza et al. 2018, 2019). In this respect, it is thought that it will be significant to focus on different biomarkers in future studies. In addition, it seems necessary to establish new potential therapeutic targets by determining the direction of interaction between the nervous system and immune system with double-blind randomized controlled studies and longitudinal studies, which can help to better understand cause-effect relationships apart from cross-sectional studies. In addition, it was stated that neuroimaging studies can help determine whether cytokines are a causal or mediator variable (Valkanova et al. 2013).

In the literature, the idea that inflammation can be suppressed through the central nervous system, through psychological interventions, seems to have emerged relatively recently. Studies on this subject emphasize the mutual interaction between the central nervous system and the immune system. With a better understanding of the interaction between the systems, it will be possible to develop or regulate treatment approaches for these disorders. Ziemssen and Kern (2007) state that it may be possible to select specific psychological interventions on the basis of their ability to change the physiological parameters associated with the progression of certain disorders in the future. In this respect, it is anticipated that studies in the field of psychoneuroimmunology on the physiological processes associated with psychiatric disorders and psychotherapy interventions that have the capacity to change these processes will contribute significantly to the treatment of these disorders.

Conclusion

mood and anxiety disorders appear to be associated with certain immunological changes. It is thought that the therapeutic approaches applied in these disorders help to regress the high cytokine levels observed and thus suppress inflammation. As

stated earlier, it is thought that explaining the relationship between psychiatric symptomatology and immune system may pave the way for the reorganization of treatment modalities. Considering that most of the studies in the literature were conducted by comparing disorder and control groups and that symptoms were not the focus in these studies, studies that will examine the relationship between certain parameters and the type and severity of symptoms, e.g. the study of Duivis et al. (2013), will significantly help treatment planning. In addition, it is predicted that immunological parameters may be a new criterion candidate in the evaluation of the effectiveness of psychotherapy approaches, as well as the selection of pharmacotherapies according to their immunomodulation properties. Currently, the fact that central nervous system drugs suppress neuroinflammation in addition to their primary mechanism of action seems to be an important advantage for the success of pharmacotherapy, and the number of studies on the possible anti-inflammatory effects of antidepressants, mood stabilizers and anxiolytics increase more and more (e.g., Gałecki et al. 2018, Fruscella et al. 2001, Nassar and Azab 2014). It seems important to continue studies in this area in the future. However, since it is known that not all antidepressants effective on depressive symptoms are effective in reducing pro-inflammatory cytokine levels (Hannestad et al. 2011), there is a need for future studies in which the relationship of different pharmacotherapy with immunological parameters will be examined in detail. In addition, anti-inflammatory drugs can be used as primary or adjuvant treatment in mood and anxiety disorders (Berthold-Losleben et al. 2009, Sartori and Singewald 2019). It is suggested that simultaneous treatment of psychiatric disorders and inflammation in the presence of inflammation will accelerate recovery and reduce the risk of recurrence of the disorder (Kiecolt-Glaser et al. 2015). In this respect, it is observed that clinical drug studies for anti-inflammatory drugs to be indicated in mood and anxiety disorders and to determine the dose will be significant in terms of improving the treatment of psychiatric disorders. Today, studies on the development of monoclonal antibodies that bind directly to cytokine receptors and have fewer side effects are continuing (Himmerich et al. 2019), and this seems promising in this respect. In terms of psychotherapies, as Lopresti (2017) stated, although CBT has anti-inflammatory effects, it will be useful to examine whether changes are observed in immunological parameters when different psychotherapy approaches are used in order to understand whether these changes are specific to this therapy approach. In addition, considering that psychotherapies and the process of change are not independent of the cultural context (Wampold 2007), it is recommended that such outcome studies be repeated in our country.

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