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# The role of inflammatory processes in the etiopathogenesis of schizophrenia

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**Abstract**

**In** recent years, there has been a growing number of studies trying to explain the role of inflammatory processes in the pathogenesis of mental disorders, including schizophrenia. Epidemiological evidence supports the hypothesis of maternal immune activation during pregnancy, which increases the risk of schizophrenia in the offspring. Studies searching for potential biomarkers for schizophrenia suggest its links with pro-inflammatory cytokines. The process is also linked with complement cascade proteins and microglia cells, although the precise biological underpinnings still remain unclear. Importantly, several clinical trials provide evidence that certain anti-inflammatory substances have a beneficial effect on the treatment of schizophrenia. A better understanding of the role of inflammatory processes in the pathogenesis of schizophrenia will enable new solutions in preventive and therapeutic interventions. This paper aims to summarize current evidence on the potential biological mechanisms linking inflammatory processes to the ethiopathogenesis of schizophrenia.

**schizophrenia; psychosis; inflammation**

## INTRODUCTION

Schizophrenia is a complex mental illness, affecting perception, cognition, emotions and motivation of about 1% of the world's population [1]. In view of the expected increase in life expectancy, it can be assumed that the number of patients with schizophrenia is likely to double by 2030 and even triple by 2050 [2]. Delusions, hallucinations, disorganized thinking and cognitive dysfunction are listed as major components of its clinical presentation. The condition itself involves significant functional impairment as well as high socioeconomic burden. Suicide rates among affected patient populations reach 10-15% [3]. Significant discoveries related to early recognition, early intervention and pharmacological stabilization of the mental state of patients have substantially improved not only the prognosis, but also the conduct of further, more extensive research in this area.

Schizophrenia is likely the most frequently and widely investigated neuropsychiatric disease. Available evidence provides a comprehensive understanding of the underlying genetic, environmental, molecular and physiological factors. However, there is still a relative paucity of evidence concerning its etiology and course. This is mainly due to its complexity and the logistical challenges involved in investigating psychotic symptoms experienced by patients. Historically, the pathophysiology of schizophrenia was associated with abnormal neurological development and abnormal activity of the dopa-

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minergic pathways [4]. While the dopamine hypothesis has been accepted as one of the most likely theories explaining the causes of schizophrenia for years, many recent studies tend to shift their focus towards the relationship between the central nervous system function and processes occurring in other regions of the organism. More and more researchers notice the links between the mental state and the immune system, emphasizing the role of inflammatory processes in the etiopathogenesis of psychotic symptoms [5, 6]. As early as in the 1980s, the immune hypothesis was formulated, which assumes that disorders of the immune system and subsequent inflammation within the nervous system lead to progressive brain changes in patients with schizophrenia [7,8]. The aim of this paper is to review available evidence suggesting the involvement of inflammatory processes in the pathogenesis of schizophrenia and to discuss its potential underlying mechanisms.

## THE ROLE OF INFLAMMATION IN THE COURSE OF SCHIZOPHRENIA

Inflammation is a complex biological process activated by various innocuous stimuli. The presence of a noxious agent stimulates the response of the immune system to protect the body from such threats, minimize the risk of tissue damage and prevent systemic destabilization. In the case of an acute phase of inflammation, i.e. a physical injury or infection, typical symptoms of heat, pain, redness, or swelling appear [9]. When the harmful stimulus is neutralized, the acute inflammatory process tends to subside. There is, however, evidence of chronic inflammatory processes and continuous stimulation of the immune system in people with schizophrenia. The activation of the immune system can be measured by determining the level of cytokines, which are proteins modulating and influencing the inflammation process. Many of them have been tested as potential biomarkers of schizophrenia. For example, the levels of classical pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) are visibly elevated in patients with acute psychoses [10]. Interestingly, interleukin-12 (IL-12), gamma interferon (INF-$\gamma$) and TNF – $\alpha$ are raised not only during acute psychotic relapses but also in chronic presentations of schizophrenia [11]. Similar observations have been made in previously untreated patients with first-episode psychosis (FEP) [6] and those at a clinically high risk of developing psychosis [12], which may suggest that the generalized inflammation precedes the onset and development of overt psychotic symptoms. Unfortunately, most studies on inflammatory biomarkers in psychosis are cross-sectional, which makes it impossible to establish the cause and effect relationship between exposure (inflammation) and outcome (psychosis). Longitudinal studies are helpful in this case. Khandaker et al. demonstrated that elevated serum IL-6 levels in children aged 9 were associated with an increased risk of psychotic disorders at the age of 18 [13]. In addition, Metcalf et al. [14] observed that elevated levels of C-reactive protein (CRP) at the age of 15 were associated with an increased risk of developing schizophrenia at the age of 27. Without doubt, any definitive conclusions concerning this matter require further research. However, available findings seem to support the notion that inflammation does indeed increase the risk of psychosis.

Tests of inflammatory biomarkers do not only offer a diagnostic value, but they can also be useful for prognostic purposes, to assess the effectiveness of treatment. There are reports that treatment-resistant patients have elevated levels of sTNFR1[15], IL-2 [16], IL-6[17], IL-8 and IL-10 [18]. In patients with first episode psychosis who did not respond to conventional antipsychotic treatment, elevated levels of IL-6 and INF-$\gamma$ were observed both at baseline and after 12 weeks of observation, while in treatment responders, they returned to normal [19]. These findings seem particularly relevant for those patients who do not respond optimally to traditional treatments, but may benefit from therapies targeting other biological pathways, such as anti-inflammatory or immunomodulatory agents.

## OXIDISING AND ANTIOXIDISING AGENTS

The concept of oxidative stress (OxS) is closely linked to the inflammatory theory of schizophrenia. Oxidative/nitrosative stress (O&NS) was first described as an imbalance between ox-

idants and antioxidants in favor of oxidants, potentially leading to damage at an oxidant/antioxidant ratio >1 [20]. Thus, O&NS is the result of a "lost battle" between the components necessary to combat pathogens and the mechanisms for their detoxification. Some by-products of mitochondrial function used to kill pathogens or foreign cells are free radicals (compounds with unpaired electrons, making them highly reactive). Most of them react immediately with other particles. These are mainly reactive oxygen species (ROS) or reactive nitrogen species (RNS). In moderate concentrations, free radicals play an important role as regulatory mediators in signaling processes such as regulation of vascular tension, platelet adhesion, oxidative phosphorylation and erythropoietin production and signal transduction from membrane receptors [21]. ROS can be released from damaged tissue, serving as inflammatory and immunological activators [22]. In addition, immune cells such as macrophages and microglia produce and use ROS to kill pathogens [23,24]. Thus, oxidative stress can be both an inductor and a product of inflammation.

The antioxidant system, responsible for carrying out free oxygen radicals into their inactive forms, is composed of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (Gpx) and glutathione reductase (GR). Non-enzymatic antioxidants include glutathione, albumin and vitamins A, E and C. Abnormal antioxidant levels and signs of oxidative stress in both peripheral [25-27] and nervous tissue [28, 29] of patients with schizophrenia have been identified in many studies. A recent meta-analysis of 44 studies showed decreased blood serum levels of antioxidant markers in patients with first episode psychosis and acute relapses of schizophrenia, which increased during antipsychotic treatment [26]. In another study, however, a decrease in superoxide dismutase activity (SOD) in blood serum and cerebrospinal fluid was described in patients experiencing the first episode of schizophrenia [30]. A recent meta-analysis of FEP studies showed similar findings of reduced total antioxidant status in patients with the first episode of psychosis compared to the control group [31]. Thus, psychotic disorders are characterized by an oxidative-antioxidative imbalance due to the exhaustion of antioxidant compensation mechanisms. Pro-oxidant factors contribute to protein, lipid or DNA damage and may become potential biomarkers of schizophrenia [32]. However, the question whether oxidative stress is the cause or rather the effect of inflammatory processes in the course of schizophrenia remains unresolved. Despite the lack of a clear answer, findings to date lay the grounds for new treatments with antioxidant substances and agents such as N-acetylcysteine [33] or polyunsaturated fatty acids [34].

## POTENTIAL SOURCES OF INFLAMMATION

Although there seems to be a consensus that factors associated with the inflammatory process coexist with the diagnosis of schizophrenia, the question arises as to the origins of this relationship. While the answer to this question remains unclear, it is known that the process is multidimensional.

Patients with schizophrenia may have a genetic predisposition to increased inflammatory activity. Genome-wide association studies allow identification of genetic polymorphisms that may cause genetic susceptibility to infection [35]. Such studies indicate that the main tissue compatibility system on chromosome 6p, known for its key role in the mechanisms of immune response, is an important polymorphic region (single nucleotide polymorphism, SNP) in patients with schizophrenia [36, 37]. The most important investigated associations concern the HLA system genes that modulate inflammatory response [38], peptide genes involved in antimicrobial defense against pathogens [39] and genes potentially involved in DNA repair and methylation [40, 41]. It appears that the risk of schizophrenia is particularly associated with a mutation of the 4A complement coding gene (C4A) [41]. What is more, several SNPs have been identified to play an important role in inflammatory and immunological processes in schizophrenia patients [42]. For years, schizophrenia had been considered a heterogeneous disease. In 1988 Carpenter et al. [43] developed the concept of deficit schizophrenia describing patients with primary and permanent negative symptoms. Despite a relatively small number of studies in this subgroup of patients, there are indications that polymorphisms of immune response genes may also af-

fect the onset and presentation of the deficit syndrome. Findings suggest that polymorphism of CD28 protein may affect the risk of deficit schizophrenia [44].

According to epidemiological studies, there is a link between prenatal exposure to pathogens and the onset of schizophrenia. Pregnancy is a period in which the mother is more susceptible to infections and increased pro-inflammatory cytokine levels. The increased incidence of influenza and exposure to infection from winter to spring increases the risk of having offspring that will develop schizophrenia in the future [45]. Respiratory [46, 47] and reproductive [46, 48] infections during pregnancy are also associated with an increased incidence of schizophrenia in the offspring. Other pathogens potentially associated with schizophrenia include maternal infection with T. gondii [49], rubella [50], measles [51], polio [52] and type 2 herpes [52]. Activation of the maternal immune system, probably in combination with other factors, may affect the process by which prenatal exposure to infections leads to an increased risk of neuropsychiatric disorders in the child [53]. Evidence to support this hypothesis also comes from numerous animal studies [54, 55]. For example, in mice, exposure of the mother to lipopolysaccharide, which induces an immune response, increased anxiety and reduced social interaction in her offspring [56].

There is a confirmed link between childhood trauma and increased risk of psychosis [57-59]. Incidentally, it is also significantly linked with the severity of positive symptoms in people with psychotic disorders [60]. There is evidence of increased baseline inflammation in adults with a history of childhood trauma. A recent meta-analysis found significantly higher levels of CRP, TNF-$\alpha$ and IL-6 in adults who were abused as children [61]. Interestingly, another study found that TNF-$\alpha$ levels are related to the severity of childhood trauma. Chronic inflammation seems to be a common biological mechanism underlying both trauma and psychosis. Early childhood trauma leads to dysregulation of the immune system, resulting in the development of a specific hypersensitivity, which leads to the development of a pro-inflammatory phenotype [62].

Another evidence of the relationship between the immune system and the stress response was a study on mice where prenatal immune activation was followed by exposure to stress during puberty. In mice exposed to both, elevated levels of neuroinflammatory markers were observed, including increased activation of the microglia during adolescence. It may therefore suggest that prenatal immune activation results in increased susceptibility to harmful effects of stress [55].

Numerous studies on the effect of gastrointestinal and microbial functioning on the pathogenesis of schizophrenia are currently underway [63]. For example, coeliac disease, an autoimmune disease affecting gastrointestinal function, is associated with an increased risk of schizophrenia [64]. The intestines, together with their bacterial flora and the central nervous system, are closely connected through the brain-gut microbiota axis. This is a two-way communication pathway, involving both neural and immune mechanisms [65]. Gut microbiota has been shown to play an important role in brain development, specifically in the formation and maturation of nerve synapses [66]. Hypotheses that schizophrenia has its source in the gastrointestinal tract appeared in the mid-20th century. The Buscaino post-mortem study on patients with schizophrenia [67] revealed numerous inflammatory changes within the gastrointestinal tract – in half of them it was gastritis, while in the majority of patients it was inflammation of the small or large intestine. It is now believed that increased intestinal permeability in patients without visible symptoms of gastrointestinal diseases, caused by factors such as stress or infection, allows the antigens to enter the portal circulation, triggering an inflammatory reaction – a process which is called bacterial translocation [68]. Elevated markers of bacterial translocation in plasma of patients with schizophrenia suggest the presence of microbial disturbances [69].

Other postulated sources of inflammatory processes in schizophrenia include obstetric complications [70], prenatal [71] and postnatal malnutrition [72] and use of psychoactive substances [73]. Inflammation in the course of schizophrenia does not have to be a response to infection. It may also be caused by disturbances in cell homeostasis control processes. The immune response and inflammatory processes are not only

stimulated by pathogens, but are also used as signals to maintain cell homeostasis in the nerve tissue. Therefore, blocking of NMDA receptors may cause oxidative stress in interneurons expressing parvalbumin, which is mediated by IL-6 [74]. Findings from post-mortem studies on patients with schizophrenia suggest the presence of damage to these neurons [75]. In fact, there is probably a certain constellation of genetic and environmental factors which, acting together, increase the risk of psychotic disorders in susceptible individuals, and this process can be at least in part modulated through inflammatory mechanisms.

## MECHANISMS LINKING INFLAMMATORY PROCESSES AND PSYCHOSIS

Although there is evidence of a relationship between inflammatory processes and schizophrenia, the underlying mechanisms by which these processes can ultimately lead to the onset of psychotic symptoms are not fully understood. One of the proposed theories relates to the influence of cytokines on the kynurenine pathway. Proinflammatory cytokines such as IL-6 activate indolamine 2,3-dioxygenase (IDO), an enzyme that breaks down tryptophan into potentially neurotoxic kynurenine metabolites such as kynurenic acid (KYNA) or quinoline acid (QA). Changes in the metabolism of the kynurenine pathway were found in the prefrontal cortex and cerebrospinal fluid of patients with schizophrenia [76-79]. Kynurenic acid is also an endogenous NMDA receptor antagonist and is involved in the functioning of mesocorticolimbic neurons, thus combining the dopamine hypothesis of schizophrenia with the concept of glutaminergic transmission deficit [80].

The second proposed mechanism is related to the cascade of toll-like receptor proteins (TRLs), which are expressed in the cell membrane of cells of the congenital immune system, including macrophages [81]. Recognizing specific molecular structures that are components of pathogens, TLRs serve as the first-line defense against microbial invasion. Their activation leads to the activation of signal pathways and subsequent production of pro-inflammatory molecules, including cytokines [82]. It has been shown that excessive activity of TLR-containing pathways can be associated with psychosis [83]. The TLR-induced release of IL-1β, IL-6, IL-8 and TNF-α was significantly higher in schizophrenic patients to whose blood specific TLR agonists were added, compared to the control group [83]. In addition, post-mortem studies showed TLR4 over-expression in the brains of patients with schizophrenia [84], while in animal models TLR4 was associated with a neuroinflammatory process induced by bacterial translocation of intestinal flora (66]. It is now assumed that pathogenic molecules from maternal infections may be a source of activation of some TLRs [85].

Another mechanism linking inflammatory factors and psychosis is the concept of "sterile inflammation". There is evidence to suggest that chronic activation of complement cascade proteins directly triggers the inflammatory process within the brain, thus affecting its proper functioning [86]. This process is initiated by the presence of damage associated molecular patterns (DAMPs), which are recognized by the mannose binding lectin (MBL), activating the lectin pathway of the complement cascade [87].

## THE BRAIN AND INFLAMMATORY PROCESSES

The brain is considered to be an 'immunologically privileged' organ, thanks, among other, to the presence of the blood-brain barrier (BBB), which is designed to protect the structures of the central nervous system from systemic infection. Numerous studies have distinguished immune signals by dividing them into innate immunity, in which monocytes and macrophages predominate, and acquired immunity, including cytokines and chemokines secreted from these cells [6, 88]. Cytokines and their receptors seem to be essential for growth, migration and survival of fetal neurons [89, 90]. In adults, apart from their immune function, cytokines play a signaling role and are an important link in the communication of astrocytes and glial cells [88].

It is difficult to unequivocally infer the presence of inflammatory processes in the CNS based only on increased levels of proinflammatory markers in peripheral blood. Nevertheless, there is a lot of evidence for the presence of CNS inflammatory processes in the course of schizo-

phrenia from cerebrospinal fluid (CSF) examinations. The results of a meta-analysis conducted in 2018 clearly indicate a significant increase in IL-6 and IL-8 levels in CSF of patients with schizophrenia relative to controls [91]. Although various inflammatory markers have been extensively analyzed, the most consistent data to date concern the increased CSF and IL-6 serum levels in patients with schizophrenia. Initially elevated levels of IL-6, IL-10 and TNF-$\alpha$ were recorded especially in medication-naive patients with first episode psychosis. Risperidone therapy resulted in reduced concentrations of all three cytokines to the levels appropriate for healthy individuals [92]. This seems particularly interesting because IL-6 is directly excreted from monocytes and constitutes the main component of the adaptive immune system [93].

The temporal and pathogenetic relationships between peripheral and central inflammatory processes in schizophrenia remain unclear. Cytokines are relatively large molecules that do not easily penetrate the undamaged BBB. Researchers highlight three pathways through which peripheral cytokines may affect the CNS. Firstly, pro-inflammatory cytokines can access the brain through the perivascular organs (ie. the humoral pathway). Secondly, peripheral cytokines can stimulate the vagus nerve, leading to activation of the nucleus of the solitary band (ie. the neural pathway). Finally, cytokines can stimulate the microglia to recruit monocytes (ie. the cellular pathway) [94]. Regardless, damages to the barrier itself seem to occur in the very course of psychosis. Indeed, ultrastructural abnormalities and increased BBB permeability were observed in patients with schizophrenia [95, 96]. In addition, the results of a meta-analysis of case-control studies [97] indicate 76% higher serum levels of S100 calcium-binding protein B (S100B), considered a marker of brain damage and BBB dysfunction, in patients with schizophrenia compared to the control group. Pollak et al. [98] analyzed evidence of BBB dysfunction from cerebrospinal fluid, post-mortem and neuroimaging studies, observing an increased permeability of BBB in psychosis, which is a credible mechanism by which pro-inflammatory cytokines from the peripheral regions can penetrate BBB and directly affect inflammation in the CNS.

Another important element of the mechanism explaining the formation of inflammatory processes in the central nervous system is the function of microglia cells. They are the cerebral equivalent of macrophages, and one of their main roles is to defend the CNS. The microglia cells are considered the most sensitive "sensors" in the brain. When a pathogen is detected, they undergo a complex, multi-stage process called microglia activation [99]. Activated microglia produces, among others, prostaglandins, chemokines, cytokines, complement proteins or proteinases, whose long-term activity, by increasing oxidative stress and activating cell death trails, can have harmful effects on sensitive cell populations [100]. There is evidence of increased activation of microglia in the course of schizophrenia. Neuroimaging with positron emission tomography has shown the activation of microglia in patients with diagnosed schizophrenia as well as in individuals at high risk of psychosis [101]. A meta-analysis of post-mortem studies [102] revealed a significant increase in the microglia density in the brains of patients with schizophrenia compared to healthy individuals. Interestingly, findings suggest that the activation of microglia can be inhibited by atypical neuroleptics such as olanzapine, risperidone or ziprasidone [103].

An important element as regards the effect of inflammatory processes on the functioning of the CNS is the complement system. This group of plasma proteins constituting the key element of innate immunity is activated in a cascade fashion by foreign or damaged cells in one of three ways (classical, alternative or lectin), ultimately leading to the formation of a complex attacking the membrane. The proteins of the complement system have several immune functions [104]. Abnormal activity of complement proteins is associated with numerous diseases such as systemic lupus erythematosus [105], epilepsy [106] and Alzheimer's disease [107]. Sekar et al. [41] demonstrated the relationship of allele genes encoding the 4A and 4B components of the complement system (C4A and C4B) with schizophrenia and increased expression of C4A mRNA in brain tissue of patients with schizophrenia. Another study showed differences in complement component levels in patients with first episode psychosis and chronic schizophre-

nia. In patients with a long history of treatment, elevated levels of the C4 component were reported with decreased levels of the C3 component, while in patients with FEP both components were elevated [108]. It has also been shown that the C3a component may be a risk predictor and potential marker of FEP [109]

Therefore, abnormal activity of the complement system, disturbing pruning processes during significant developmental periods, may be considered an important element of the pathogenesis of schizophrenia [110].

## SUPPORTIVE TREATMENTS

Given the above findings and the ever-growing evidence for understanding the role of inflammation in the course of psychosis, it can be concluded that some patients will benefit from therapies for inflammation. There are several classes of anti-inflammatory drugs with different mechanisms of action used in a number of inflammatory and immunological diseases. The most widely studied include non-steroidal anti-inflammatory drugs (NSAIDs), acetylcysteine (N-acetyl cysteine, NAC), omega-3 fatty acids and statins. The use of some of them shows promise in the therapy of schizophrenia, mainly as an add-on to standard forms of treatment.

Non-steroidal anti-inflammatory drugs are a group of agents that affect inflammation by inhibiting the enzyme cyclooxygenase (COX), responsible for the production of pro-inflammatory prostaglandins [111]. The first and most widely used drug in this group is acetylsalicylic acid (ASA). In a double-blind study involving 70 patients with diagnosed schizophrenia, participants received aspirin or placebo in addition to standard antipsychotic therapy. Treatment with aspirin was associated with a small but significant decrease in the general and positive symptom PANSS scores [112].

N-acetylcysteine (NAC) is a precursor of glutathione and has antioxidant and anti-inflammatory properties resulting from inhibition of TNF-$\alpha$, IL-1$\beta$ or IL-6 [113]. In a newly published study, patients who received additional NAC showed a significant improvement in the category of positive, negative symptoms and general psychopathology measured by the PANSS scale, compared to patients receiving placebo [114]. In another 12-month study, combined therapy with NAC resulted in an improvement in disorganized thinking and general score, as well as negative symptoms subscale, measured by the PANSS scale, compared to placebo [115].

A growing body of evidence in the field of neurophysiology underlines the role of polyunsaturated fatty acids (PUFA) in the protection of nerve cells against oxidative damage. They also influence the control of inflammation, regulation of neurogenesis and preservation of neuronal function [116]. According to a meta-analysis of 68 randomized studies, omega-3 fatty acid supplementation led to a significant decrease in TNF-$\alpha$, IL-6 and CRP levels in healthy individuals as well as in patients with chronic autoimmune and non-immune diseases [117]. In patients with chronic schizophrenia, the beneficial effect of omega-3 fatty acid supplementation on psychotic symptoms has not been demonstrated [118]. However, a beneficial effect compared to the placebo group was reported in FEP patients who received PUFA supplementation [119]. It seems, therefore, that the role of fatty acids is much more important in patients in the early stages of psychosis.

Statins are a group of drugs widely used in modern cardiology. Their action is based on inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA, hydroxy-methylglutaryl coenzyme A) – the enzyme responsible for the formation of endogenous cholesterol [120]. Apart from their hypolipidemic effect, they have a multidirectional role, inhibiting, among others, lipid oxidation or inflammatory reaction [121]. It has been shown that the administration of statins to patients with schizophrenia significantly improved their PANSS scores compared to the placebo group [122]. Given the increased risk of cardiovascular incidents in this patient population, statins may seem an attractive addition to standard therapy.

## CONCLUSION

The immune system seems to be an important element in the pathogenesis of schizophrenia on various neurobiological levels. Numerous epidemiological, biochemical or neuroimaging stud-

ies suggest the presence of elevated inflammatory markers in schizophrenia. This may occur in early stages of the disease, often preceding the onset of clinical symptoms. However, schizophrenia still remains one of the most mysterious diseases, and a great challenge to contemporary medicine. A translational approach, combining epidemiological, genetic, oxidative stress and clinical treatment concepts, has extended our understanding of the complex neuro-inflammatory processes associated with the onset and course of schizophrenia. Unfortunately, still little is known about the temporal relationship between inflammatory changes and its onset. Therefore, it seems that in order to thoroughly understand the role of the inflammatory process in the pathogenesis of schizophrenia, further research extending beyond the boundaries of classical psychiatry is necessary.

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