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Neurobiological mechanisms underlying the influence of parasitic infections on mental disorders: a literature review

Authors:

Aleksandra Sosin [AS]- corresponding author

Jagiellonian University Collegium Medicum, Świętej Anny 12, 31-008 Kraków

ORCID: https://orcid.org/0009-0008-0440-5431

E-mail: a.sosin@student.uj.edu.pl

Wojciech Bednarz [WB]

Independent Public Healthcare Institution of the Ministry of the Interior and Administration in Kraków, Kronikarza Galla 25, 30-053 Kraków

ORCID: https://orcid.org/0009-0003-9522-6298

E-mail: wojciechbednarz2@gmail.com

Katarzyna Torbacka [KT]

5 Military Clinical Hospital with Polyclinic SPZOZ, Wrocławska 1/3, 30-901 Kraków

ORCID: https://orcid.org/0009-0002-7208-3725

E-mail: katorbacka@gmail.com

Katarzyna Rozkosz [KR]

Independent Public Health Care Center of the Ministry of the Interior and Administration in Katowice named after sergeant Grzegorz Załoga, Wita Stwosza 39-41, 40-042 Katowice

ORCID: https://orcid.org/0009-0000-3610-1901

E-mail: km.rozkosz@gmail.com

Joanna Kaczor [JK]

Independent Public Healthcare Institution in Myślenice, Szpitalna 2, 32-400 Myślenice

ORCID: https://orcid.org/0009-0002-1714-2630

E-mail: joanna.kaczor97@gmail.com

Zuzanna Wróbel [ZW]

The West Hospital in Grodzisk Mazowiecki, Daleka 11, 05-825 Grodzisk Mazowiecki

ORCID: https://orcid.org/0009-0005-7529-0641

E-mail: zuzannaw76@gmail.com

Olga Jakubik [OJ]

Praski Hospital, Sp. z o.o., al. "Solidarności" 67, 03-401 Warszawa

ORCID: https://orcid.org/0009-0006-4378-7087

E-mail: o.jakubik.99@gmail.com

Natalia Wróbel [NW]

5 Military Clinical Hospital with Polyclinic SPZOZ, Wrocławska 1/3, 30-901 Kraków

ORCID: https://orcid.org/0009-0005-9236-9802

E-mail: natalia.wrobel2323@gmail.com

Patrycja Podlejska [PP]

Independent Public Health Care Center of the Ministry of the Interior and Administration in Katowice named after sergeant Grzegorz Załoga, Wita Stwosza 39-41, 40-042 Katowice

ORCID: https://orcid.org/0009-0002-0074-9778

E-mail: patrycja.podlejska@gmail.com

Maja Torbacka [MT]

Jagiellonian University Collegium Medicum, Świętej Anny 12, 31-008 Kraków

ORCID: https://orcid.org/0009-0000-7139-2134

E-mail: majka.torbacka@op.pl

Abstract

Parasitic infections pose a serious health threat worldwide, especially in developing countries, where they affect millions of people. Traditionally, they are seen mainly as something that impacts on the immune system and physiological functions but now more often potential mental health influence is also pointed out. In particular neurotropic parasites, like *Toxoplasma gondii*, *Plasmodium falciparum*, *Taenia solium* i *Trypanosoma brucei* are capable of modifying brain function which can lead to development of various mental disorders like schizophrenia, depression, epilepsy and sleep disorders. The purpose of this literature review is to analyze the available research on neurobiological mechanisms that show how parasites influence brain function and behaviour. Attention was given to main mechanisms such as changes in neurotransmission, microglial activation, inflammatory responses and structural changes in the brain. In the research results of brain imaging studies (MRI PET) were discussed. They can help understand these mechanisms in detail. Based on literature review, the role of environmental factors and comorbid conditions are also presented. Conclusions indicate the necessity of further research, that will allow understanding of the neurobiological mechanisms of parasitic infections and their influence on mental health.

Materials and methods:

The research reviews the literature on influence of parasitic infections on mental health and neurobiological mechanisms of it. Researches were analyzed focusing on parasites like *Toxoplasma gondii*, *Plasmodium falciparum*, *Taenia solium* i *Trypanosoma brucei* and their relation with disorders like schizophrenia, depression, epilepsy and sleep disorders.

The search was carried out in databases such as PubMed, Scopus and Google Scholar by using keywords related to the topic of parasites and mental disorders. Experimental, clinical, neuroimaging and review studies were selected that analyzed the impact of parasites on neurotransmitters, brain inflammation and structural changes in the brain.

Studies were subjected to inclusion criteria based on their association with the impact of parasites on mental health and nervous system. Researches that were not associated with this topic were excluded.

Keywords:

parasites, *Toxoplasma gondii*, *Plasmodium falciparum*, *Taenia solium*, *Trypanosoma brucei*, neurobiology, mental disorders, schizophrenia, depression, epilepsy, sleep disorders, neurotransmitters, microglia, neuroinflammatory responses, neurocysticercosis, malaria, African sleeping sickness, neuroimaging, MRI, PET, structural changes in the brain

Introduction:

Complex relationships between parasites and their hosts have been of interest to researchers from various fields of since for years- from evolutionary biology and ecology to medicine and neurobiology. Influence of parasitic infections on functioning of the human nervous system and its implications for mental health are particularly interesting. In recent decades, research has indicated significant correlations between infections caused by specific parasitic pathogens and

the occurrence of mental disorders such as schizophrenia, affective, anxiety or neurocognitive disorders.

The neurobiology of infections deals with the study of the mechanisms by which various pathogens, including parasites, directly or indirectly affect the functioning of the nervous system. Infections can lead to direct damage of neural structures, cause inflammatory brain reactions and modify the activity of the immune system. All these processes have potential impact on neurochemical processes and neuroplasticity, which can result in the development of certain psychopathological symptoms.

Parasites are organisms which use other organisms (hosts) as a source of nutritional ingredients and as a living environment. They can be divided into internal (endoparasites) and external (ectoparasites). In case of the impact on mental disorders parasites that have crucial meaning are the one that are capable of invading the nervous system, such as protozoa (e.g. Toxoplasma gondii), tapeworms (e.g. Taenia solium causing neurocysticercosis0 and some species of tropical parasites (e.g. Trypanosoma brucei, Plasmodium falciparum).

Mental disorders, according to classification of World Health Organisation (WHO) and American Psychiatric Association (APA), pose a diverse group of diseases that are characterised by changes in thinking, emotions, perception and behaviour. These include psychotic disorders (e.g. schizophrenia), mood disorders (e.g. depression, bipolar disorder), anxiety disorders and cognitive and neurodegenerative disorders. Understanding the way parasitic infections can contribute to these disorders is an important scientific and clinical challenge.

The main point of this work is to review current knowledge regarding neurobiological mechanisms linking parasitic infections with the risk of developing mental disorders. The most important parasites that are crucial in this context were discussed, their effects on the nervous system, as well as clinical and therapeutic implication resulting from the presented analyses.

3. General characteristics of parasitic infections

Parasites, which have the ability to infect humans, can cause a variety of diseases, including those that affect the nervous system. In the context of mental disorders special attention is paid to neurotropic parasites that can infect the brain, causing functional changes there. Among parasites, which show the ability to infect the human nervous system, *Toxoplasma gondii, Plasmodium, Trypanosoma* and *Taenia solium* are most common. Every of these parasites have a different biology, mode of transmission and infection mechanisms but all can affect brain function and nervous system which can lead to mental disorders development.

3.1. *Toxoplasma gondii*

Toxoplasma gondii is one of the most common parasites in the world, which infect both people and animals. Infection occurs mainly through the consumption of parasite cyst, which are present in the meat of farm animals, as well as by contact with contaminated soil or water. This parasite can survive in host organisms for life in the form of cysts in nerve tissue, most often in the brain and eyes. *T. gondii* can change the function of neurotransmitters and cause inflammation of the brain which affects the psyche of the host. There are plenty of studies that show the potential connection between infection of *T.gondii* and occurring schizophrenia, depression or anxiety disorders [1,2].

3.2. *Plasmodium spp.*

Parasites of the genus *Plasmodium* are responsible for causing malaria, one of the most dangerous infectious disease in the world. *Plasmodium* is transmitted by the bites of infected mosquitoes and the parasite reaches the liver and then to the blood where it attacks red blood cells. Even though the main target of this parasite is circulatory system, as a result of an intense inflammatory reaction there may be damage to the nervous system. In extreme cases, malaria can lead to so-called cerebral malaria, which is associated with brain damage and development of cognitive and mental problems. Chronic Plasmodium infection can also lead to mood disorders, depression and anxiety [3].

3.3. *Trypanosoma brucei*

Trypanosoma brucei is a parasite which causes african coma, the disease that spreads by the bite of the tse-tse flies. This parasite attacks the nervous system which can lead to progressive brain damage. Clinical signs include changes in behaviour, mental disorders, decreased ability to concentrate and in the advanced stages of the disease, coma and death may occur. *T. brucei* infection is one of the most dramatic parasite infections affecting the functioning of the nervous system causing neurological and psychiatric symptoms [4].

4. Neurotransmitters disorders: dopamine, GABA, glutamate

Parasite infections, especially those which influence on a nervous system have the ability to modify neurotransmitters, which can lead to brain function disorder and development of psychopathology. The most commonly studied neurotransmitters that are modulated by parasites are dopamine, GABA (gamma-aminobutyric acid) and glutamate. All these neurotransmitters play a crucial role in regulating cognitive, emotional and motivational functions, and their disorders ar strictly connected with development of mental disorders such as schizophrenia, depression or anxiety disorders.

4.1. Dopamine

Dopamine is one of the main neurotransmitters related with mood, motivation and cognitive processes regulation. Dopamine hyperactivity is closely related to psychotic symptoms such as hallucinations or delusions, which are characteristic for schizophrenia. *Toxoplasma gondii* infection has the ability to influence dopamine metabolism in the brain, which can explain the connection of this parasite with the development of mental disorders. The work of Prandovszky et al. (2011) encodes that *T. gondii* encodes an enzyme similar to tyrosine hydroxylase which increases dopamine synthesis in infected neurons. This action can lead to dopaminergic hyperactivity, which is particularly important in the context of the development of schizophrenia [6].

4.2. GABA

GABA is the main inhibitory neurotransmitter in the brain and has an important role in regulating the activity of neurons and maintaining the balance between stimulation and blocking in the central nervous system. A deficiency in GABA activity is associated with various neurological oraz psychiatric disorders, such as anxiety, depression and epilepsy. Studies have shown that parasites such as *Toxoplasma gondii* can influence the action of GABA through the changes in the actvity of microglia and the production of inflammatory cytokines.

T. gondii infection causes less GABA activity in areas of the brain that may lead to problems with emotions and cognition [7]. Also, changes in GABA activity may be one of the ways that parasites impact on the development of anxiety and depression.

4.3. Glutamate

Glutamate is the main excitatory neurotransmitter and plays a crucial role in processes related to memory, learning and neuroplasticity. Excessive glutamate activity, especially in regions such as the frontal cortex and hippocampus, can lead to neurotoxicity and neuronal damage. *Toxoplasma gondii* infection can influence the glutaminergic system by increasing the secretion of glutamate and this can cause neuroinflammatory response in the brain and damage to nerve cells. As with dopamine, changes in glutamate metabolism can contribute to the development of cognitive and mental disorders, including schizophrenia and anxiety disorders [8].

Parasites, such as *Plasmodium* and *Trypanosoma brucei* also can impact on activity of the glutaminergic system. *Plasmodium* infection leads to an increase in the level of oxidative stress, which can disrupt the balance of neurotransmitters, including glutamate. Changes in the glutaminergic system after *Plasmodium* infection can cause cognitive and mental disorders, such as depression and difficulty concentrating, which are commonly observed in people with chronic malaria [3].

5. Inflammatory and immune responses of the body: cytokines and microglia

Parasitic infections can trigger immune and inflammatory responses, which have crucial influence on brain function and may lead to psychiatric disorders development. Parasites, such as *Toxoplasma gondii, Plasmodium, Trypanosoma brucei* and *Taenia solium* create changes in activity of immune system, including in response to cytokines, microglia and other immune cells within the central nervous system (CSN). Changes in these mechanisms can lead to chronic inflammation, which has a significant impact on mental health.

5.1. The role of microglia in the immune response

Microglia are immune cells in the brain, which have defensive functions, including monitoring the microenvironment and eliminating pathogens and damaged cells. In response to parasitic infection, microglia activates, causing inflammation, that can both be beneficial (pathogens removing) and harmful (chronic inflammation). *Toxoplasma gondii* is one of the parasites that can significantly impact microglia function. Infection by this parasite leads to the activation of the microglia and the secretion of inflammatory cytokines, such as TNF-α, IL-6 i IL-1β, that has a role in neuron functioning and may cause damage to the nervous tissue. Increase of microglial activity in response to *T.gondii* infection is connected with cognitive and mood disorders and also with higher risk of developing mental disorders such as schizophrenia and depression.

5.2. Proinflammatory cytokines and their role in the pathogenesis of mental disorders

Proinflammatory cytokines, such as TNF-α, IL-6 i IL-1β, as well as gamma interferon (IFN-γ), play a crucial role in immune response of the body for parasitic infections. Parasitic infections, especially chronic ones, lead to excessive production of these cytokines, which can cause chronic illness within the central nervous system. Increasing of proinflammatory cytokines level affects the synthesis of neurotransmitters, changes the functioning of neurotransmitters

such as dopamine, GABA, glutamate and also causes disorders in neuroplasticity and neurogenesis.

Toxoplasma gondii infection causes the production of large amounts of cytokines that can induce changes in brain function, leading to behavioral and psychiatric disorders. Studies have shown that people infected with *T.gondii* have increased levels of IL-6 and TNF-α, which are associated with psychotic symptoms, such as hallucinations and delusions as well as cognitive impairment [2]. Similar mechanisms are observed in case of *Plasmodium* infection, which causes brain inflammation and can lead to mood disorders and reduced ability to concentrate [3].

5.3. Immune responses of parasites and their impact on the functioning of the central nervous system

Parasitic infections can also affect the functioning of the immune system in the context of regulating inflammatory mechanisms. Parasites such as *Plasmodium falciparum* and *Trypanosoma brucei* cause intense immune reactions, that lead to increased permeability of the blood-brain barrier.Chronic inflammation may cause damage to nerve cells and reduce neuroplasticity, which in turn affects the functioning of the nervous system. *T.brucei* infection leads to the development of „African coma", where chronic inflammation is closely linked to neurological disorders such as behavioral changes and concentration problems [4].

6. Structural and functional changes in the brain: MRI, PET

Parasitic infections, that impact on the nervous system, may cause visible changes in both the structure and function of the brain. Imaging with methods such as magnetic resonance imaging (MRI) and positron emission tomography (PET) provides valuable information about these changes, allowing a better understanding of the mechanisms by which parasites affect the brain and can contribute to the development of mental disorders. These techniques allow not only to evaluate anatomical changes in the brain, but also to track metabolic and functional activity in different regions of the brain, which is crucial in the context of parasitic infections.

6.1. Magnetic resonance imaging (MRI)

MRI is one of the most commonly used imaging techniques that assess structural changes in the brain. Being infected by parasites such as *Toxoplasma gondii, Taenia solium* or *Plasmodium* may lead to structural damage to the brain that can be observed in MRI imaging. In case of *Toxoplasma gondii* infection, MRI studies show changes within the gray matte, especially in regions such as the amygdala and hippocampus, which are connected with emotions, memory and cognitive functions. These changes may include areas of atrophy that are often associated with psychiatric symptoms such as anxiety disorders or depression [1].

In case of neurocysticercosis, caused by *Taenia solium*, MRI examinations show the presence of cysts in the brain, which can lead to the formation of inflammatory foci and swelling, which can result in damage to nervous tissue. Structural changes in the brain associated with neurocysticercosis can lead to symptoms such as epilepsy, headaches, behavioral changes and problems with consciousness [5].

6.2. Positron emission tomography (PET)

Positron emission tomography (PET) is an imaging technique, which enables evaluating functional changes in the brain, such as glucose metabolism, neurotransmitter activity or blood flow. In case of parasitic infections, PET is used to evaluate changes in brain function, especially in the context of metabolic activity in different areas of the brain. *Toxoplasma gondii* infection can lead to decrease in metabolic activity in the brain regions responsible for emotions and cognition, such as the prefrontal cortex, which can affect the development of mental disorders such as schizophrenia or depression [6].

In turn, in people with malaria caused by *Plasmodium falciparum*, PET shows changes in blood flow to the brain, which can lead to neuronal damage and cognitive disorders. All these changes can explain problems with concentration, reduced learning ability and mood disorders that are commonly seen in patients with chronic malaria [3].

6.3. Structural and functional changes associated with *Trypanosoma brucei* infection

Trypanosoma brucei infection that causes African coma, also leads to crucial changes in the brain structure and function. All these can be evaluated using MRI and PET. In case of African coma, MRI shows changes in the brain structure, such as swelling and reduced brain volume, especially in areas responsible for controlling behavior and emotion, such as prefrontal cortex and basal nuclei. In turn PET presents metabolic activity decreasing in the same brain areas, that leads to motivational and cognitive disorders that are characteristic of this disease.

7. *Toxoplasma gondii* and schizophrenia

Toxoplasma gondii is a common parasite that has the ability to infect humans and also a wide circle of animals. This infection is usually asymptomatic but may have serious consequences for people with weakened immune systems. Moreover, a lot of studies indicate a possible link between *T.gondii* infection and the development of mental disorders, especially schizophrenia. In this context, *Toxoplasma gondii* becomes an interesting model for studying neuroinfections and their impact on the development of mental illness.

7.1. Epidemiology and connection with schizophrenia

Schizophrenia is a chronic mental disorder characterized by symptoms such as hallucinations, delusions, thinking and emotional disorders. Although the exact etiology of schizophrenia is not fully understood, several risk factors are distinguished in the literature, including genetic, environmental and infectious factors. Among the latter, *T.gondii* drew attention of scientists as a potential factor increasing the risk of developing schizophrenia.

Epidemiological studies have shown a higher seroprevalence of antibodies against T.gondii among people diagnosed with schizophrenia compared to healthy people. These studies suggest that people infected with *T.gondii* are more likely to develop psychotic symptoms, especially those linked with delusions and hallucinations [1]. This connection can be related to how the parasite affects the host's nervous system.

7.2. Neurobiological mechanisms: dopamine, microglia and neuroinflammatory responses

One of the main mechanisms by which *Toxoplasma gondii* can influence schizophrenia development is neurotransmission modification, especially the dopaminergic system. *T.gondii* has the ability to produce a tyrosinase-like enzyme hydroxylase, which can increase dopamine synthesis in the host brain. Increased level of dopamine is one of the crucial pathophysiological mechanisms of schizophrenia and dopaminergic hyperactivity in the brain has been linked to psychotic symptoms such as delusions and hallucinations [6].

Another mechanism by which *T.gondii* can influence the nervous system is the microglia activation and inflammatory reaction in the brain. Infection with this parasite leads to the secretion of pro-inflammatory cytokines such as IL-6 and TNF-α, which can disrupt the balance of neurotransmitters and lead to nerve cell damage [2]. Chronic activation of microglia can also lead to structural changes in the brain, particularly in regions responsible for emotion, memory and decision-making, such as the amygdala and hippocampus [9].

7.3. Evidence from neuroimaging

Neuroimaging tests such as magnetic resonance imaging (MRI) and positron emission tomography (PET) show changes in structure and brain function in *T.gondii* infected people. In such patients, a decrease in brain volume is often observed in areas associated with emotional control and cognitive functions. In studies, where PET was used, a decrease in metabolic activity in these areas was also observed, which can explain mood disorders and cognitive problems in people infected with this parasite [10].

7.4. Controversies and directions of future research

Despite the crucial evidence that shows a connection between *T.gondii* and schizophrenia, not all research not all studies confirm this hypothesis. This is still a topic of controversy and needs more detailed studies, which may allow better understanding of the mechanisms that can connect parasite infections and development of mental illness. Longitudinal studies are also needed to determine whether T.gondii infection may actually be a causal of schizophrenia or is only correlated with other risk factors.

8. *Plasmodium falciparum* and cognitive disorders

Plasmodium falciparum is the most dangerous parasitic species that causes malaria. Although malaria is mainly associated with febrile symptoms, chills and hematological disorders, an increasing number of studies indicate the long-term impact of *P.falciparum* infection on cognitive functions. These conditions may be the consequence of acute illness or chronic, subclinical infection. *P. falciparum* infection most especially has been linked with decreased ability to concentrate, memory loss and problem-solving capacity as well as a general decline in intellectual function.

8.1 Neurobiological mechanisms of cognitive disorders connected with malaria

Plasmodium falciparum infection leads to intensive immune response, which has a direct influence on the nervous system. The parasite penetrates the erythrocytes and then causes changes in microcirculation, especially in the blood vessels of the brain. The result of these

changes is that the blood-brain barrier is damaged, which allows pro-inflammatory cytokines and other inflammatory factors to enter the brain tissue [11]. This chronic immune response leads to damage to neurons and changes in brain structures such as the hippocampus and frontal cortex, that are responsible for memory, concentration and decision-making processes [12].

In addition, *Plasmodium* infection leads to oxidative stress, which can damage nervous cells and disrupt their functions. This damage can occur as cognitive disorders at the time of acute infection and also as chronic cognitive deficits after being cured of malaria, especially in children and adults in endemic countries.

8.2. Brain malaria and its impact on cognitive functions

Brain malaria, which is the one of the most severe complications of *Plasmodium falciparum* infection, leads to the development of coma, neurological damage and permanent cognitive deficits. These symptoms are the result of the blockage of small blood vessels in the brain by infected erythrocytes, which leads to local tissue damage. As a result of this process, brain hypoxia, swelling and decline of cognitive functions occur [13].

In studies that have taken place in African countries, children who survived brain malaria often showed lower grades in memory tests, learning difficulties, and problems with concentration. In patients that suffered severe brain malaria episodes, a decrease of brain volume has also been observed, especially in areas responsible for cognitive processes such as the hippocampus and frontal cortex [14].

8.3. Chronic malaria and subtle cognitive deficits

In case of chronic *P.falciparum* infection, which does not lead to full-symptomatic brain malaria, the infection can cause subtle but permanent changes in cognitive functioning. Studies suggest that chronic infections of this parasite leads to decrease in the ability to concentrate, learn, solve problems and make decisions. The decrease in cognitive performance is particularly evident in children who, as a result of infection, have lower results in IQ tests and tasks requiring concentration and operational memory [15].

Chronic malaria can also affect brain development in younger children, which can lead to delay in cognitive and educational development. Studies show that children with chronic malaria have concentration problems, which has a negative impact on their educational capacity and social development [16].

9. *Taenia solium* (neurocysticercosis) and epilepsy and depression

Taenia solium is a parasite whose eggs can cause infection of the brain resulting in neurocysticercosis, which is among the most frequent causes of brain infection in the entire globe. Neurocysticercosis is a serious public health problem caused by the migration of the larvae of the parasite into the brain and is most rampant in areas with low hygiene standards, e.g., Asia, Africa and Latin America. Neurocysticercosis is linked to various neurological symptoms such as epilepsy and mood disorders such as depression.

9.1. Neurocysticercosis: infection mechanism

Neurocysticercosis is the result of the consumption of *Taenia solium* eggs, which are found in contaminated water or raw meat. Once they are present in the digestive tract, the parasite's eggs turn into larvae that migrate to various organs, including the brain, where they develop into a cyst. These cyst can be found in various parts of the brain such as brain cortex, subcortical structures and brain stem [5]. These cysts cause brain inflammation, swelling and other damage to neurons, leading to neurological and psychiatric symptoms.

9.2. Epilepsy as a one of the main neurocysticercosis symptoms

One of the most frequent symptoms of neurocysticercosis is epilepsy. Its causes include local inflammation caused by the parasite's cysts in the affected area of the brain that may result in disruptions of the electrophysiological balance in the brain and give rise to epileptic seizures. Epidemiological studies demonstrate that individuals afflicted with neurocysticercosis are at a much higher risk of having epilepsy than uninfected individuals and that epileptic seizures most frequently occur in those with a large number of brain cysts (17). Epileptic seizures in neurocysticercosis can be resistant to treatment with antiepileptic medications and is a significant challenge to treating the disease.

Pathogenic mechanisms that lead to seizures include both direct brain damage by cysts and the body's inflammatory response to infection. The presence of cysts triggers an inflammatory reaction in the brain, which can lead to chronic irritation of nervous tissues and the generation of abnormal electrical impulses [18].

9.3. Depression and other mental disorders connected with neurocysticercosis

Neurocysticercosis is also associated with mood disorders, including depression, which is quite often symptoms among patients with this disease. There are plenty of mechanisms that can explain why people with neurocysticercosis are more likely to develop depression. First of all damage to the brain resulting from cysts, particularly in regions linked with mood regulation and emotions (such as the amygdala and prefrontal cortex), may result in the changed functioning of mood-regulating neurotransmitters serotonin and dopamine [19]. Secondly, chronic pain and limitations associated with seizures can lead to a decrease in the quality of life, which in consequence can trigger depression.

Studies conducted in endemic countries for *Taenia solium,* have shown that patients with neurocysticercosis often report depressive symptoms such as sadness, loss of interest, fatigue and sleep disorders. For this reason, the diagnosis and treatment of neurocysticercosis require a comprehensive approach, including both neurological and mental treatment, to improve the quality of life of patients [16].

9.4. Neurocysticercosis treatment and related disorders

Treatment of neurocysticercosis involves a combination of pharmacological therapies that aim to eliminate the parasite and control neurological and psychiatric symptoms. The drug of choice for the treatment of neurocysticercosis is albendazole or praziquantel, which help eliminate brain cysts [20]. For epileptic seizures, antiepileptic drugs are used, but their effectiveness can be limited, especially in cases where cysts are distributed in multiple parts of the brain.

Treatment for depression can include both pharmacotherapy (such as antidepressants) and psychotherapy to help patients cope with chronic symptoms.

10. *Trypanosoma brucei* and sleeping disorders (African coma)

Trypanosoma brucei is the causative parasite of African coma, a dangerous tropical illness that targets the nervous system. African coma, or trypanosomiasis, is a significant public health risk in sub-Saharan African areas where the transmission of the infection by the bite of the tse-tse fly is endemic. Progressive injury to the central nervous system gives rise to a variety of neurological manifestations of which sleep disturbance is one of the most early and typical symptoms of infection.

10.1. Pathogenesis of *Trypanosoma brucei* infection

Trypanosoma brucei is a parasite that attacks the nervous system of a host, leading to chronic brain and spinal cord inflammation. As the results in infected organisms, an intensive inflammatory process occurs, which includes microglia and immune cells such as T lymphocytes. This parasite has an ability to change expression of its own surface proteins, which allows it to avoid the host's immune response and maintain infection for a long time. When *T.brucei* attacks the brain, it affects the structures responsible for controlling sleep and wake rhythms, including the hypothalamus, which plays a key role in regulating sleep-wake cycles [4].

10.2. Sleeping disorders: pathophysiological mechanisms

One of the earliest symptoms of *Trypanosoma brucei* infection is a change in the sleep cycle, which leads to the development of serious sleep disorders, characteristic for the African coma. Patients start to experience periodic episodes of excessive sleepiness, which can lead to complete disorganization of sleep cycles. As the disease progresses, sleep disorders become more pronounced, including both excessive sleepiness and night time insomnia, which ultimately leads to a complete loss of the ability to sleep properly [21].

The parasite can disrupt the melatonin secretion cycle, leading to dysregulation of the body's biological clock, resulting in sleep disorders [22]. Neuroimaging research has revealed that pathological alterations in the hypothalamus and suprachiasmatic nucleus structures that control the diurnal cycle may be responsible for inducing these disorders. These pathological alterations result from chronic inflammation caused by *T. brucei*.

10.3. Progressive neurological disorders

As African coma develops, sleep disorders become more intense and patients begin to experience periods of loss of consciousness. In addition to sleep disorders, there are other neurological symptoms such as changes in behavior, dementia, motor disorders and at the end coma, which can lead to death. In the advanced stages of the disease, cognitive impairment, motor coordination disorders, a well as motor and sensory damage occur [23]. For that reason African coma is considered as one of the most dangerous parasitic infections, leading to a significant deterioration in the quality of life of patients and high mortality if untreated.

10.4. African coma treatment

African coma is treated largely with antiparasitic medications such as melarsoprol and suramin that are used to cure *Trypanosoma brucei* infection at the different stages of the illness. Melarsoprol is used to treat advanced stages of the infection where the parasite has invaded the nervous system [24]. This treatment does not, however, fully eradicate sleep disturbances and other neurological lesions and hence patients need clinical and rehabilitative assistance. While treatment of African coma is effective, it is costly and may be challenging to deliver in regions with limited levels of health resources. Therefore, prevention of infection by the effective management of populations of tse-tse flies and seeking treatment in the initial phases of the illness is a major part of health policy in affected regions.

11. Discussion

This review is a survey of the literature on the neurobiological mechanisms of how parasitic infection, including Toxoplasma gondii, Plasmodium falciparum, Taenia solium, and Trypanosoma brucei, impinges upon mental health and brain function. Numerous neurobiological mechanisms are described, such as disorders in neurotransmission, inflammatory responses to infection, structural brain reorganisation and dysregulation of diurnal rhythms. Drawing from the available evidence, in the following section we try to interpret the findings, to determine research directions in the future and to comment upon research controversies and limitations in this field.

11.1. Results interpretation

Available studies reveal that there is a likely association between parasitic infections and the etiology of psychiatric disorders like schizophrenia, depression, anxiety disorders and epilepsy. Specifically, infection with *Toxoplasma gondii* is the most researched parasite in psychopathology. Review of available literature reveals that *T. gondii* infection can influence dopamine metabolism to result in overactivity of the dopaminergic system and to be linked with symptoms of psychosis characteristic of schizophrenia. On the other hand, *Plasmodium falciparum* infection causing malaria affects cognition and mood of patients and predominantly in children in endemic areas

Taenia solium infection leads to neurocysticercosis that results in epilepsy and may accompany depression symptoms that point towards the neuroinflammatory mechanisms inducing the alteration of brain structures such as the prefrontal cortex and the hippocampus. *Trypanosoma brucei* that causes African coma induces sleep disorders associated with damage to brain structures that regulate diurnal rhythms.

All of these instances reflect a robust association between parasite infection and neurological and psychiatric pathology. Altered neurotransmission, microglial response, brain regions and desynchronisation of diurnal rhythms seem to be shared mechanisms by which parasites influence mental health.

11.2. Controversies and limitations of studies

Although there are various studies that suggest a hypothetical association between parasitic infections and psychiatric disorders, there are some significant controversies and limitations that should be mentioned:

1. Correlation vs. causality: Much of the research here is observational and correlations between psychiatric disorders and parasitic infection do not permit conclusions of causality. Parasitic infection is often associated with other risk factors, e.g., poverty, lack of access to health care or other infection, and these may be a more likely cause of mental disorder.

2. Social and environmental factors: In parasitic illnesses in general and in developing nations in particular, social and environmental factors may be of equally significant importance in the etiology of mental disorders. Inadequate health education, sanitation and epidemiological conditions, and high levels of poverty and social tension may be of similar significance to the parasitic illnesses themselves. These variables need to be considered in research to prevent incorrect conclusions concerning exclusive biological causes of disorder.

3. Comorbidities: people infected with parasites often also have other comorbidities (e.g., HIV, malaria, diabetes) that can further influence the development of mental disorders. Therefore, it is important to conduct studies that will control for these comorbidities to better understand how parasitic infections themselves affect mental health.

12. Conclusions

A review of the literature on the neurobiological mechanisms through which parasitic infection influences mental health identifies several key results:

1. Parasites influence mental health - Parasitic infection such as *Toxoplasma gondii*, *Plasmodium falciparum*, *Taenia solium* and *Trypanosoma brucei* has been implicated in the development of mental illnesses, with schizophrenia, depression, epilepsy and sleep disturbances being some examples. Parasites result in altered neurotransmission, inflammatory reaction, brain morphology and diurnal cycles and give rise to neurological and psychiatric symptoms.

2. Function of neurotransmitters - Parasites, especially *Toxoplasma gondii*, may have an impact on the metabolism of dopamine, GABA and glutamate, with particular importance in psychiatric illnesses such as schizophrenia. These include alterations in dopamine metabolism and modulation of the inflammatory response of the brain.

3. Sleep disorders - Parasitic infestation with Trypanosoma brucei (African coma) may result in serious sleep disorders that appear early in infection. Infection with the parasite causes interruption of the brain centers that regulate daily rhythms so that sleep disorders and lethargy may advance to total loss of the capacity to sleep normally.

4. Structural changes in the brain - Parasitic infections such as Taenia solium(neurocysticercosis) result in structural changes in the brain, such as cysts in nerve tissue, leading to epilepsy and mood disorders, including depression. Neurocysticercosis also affects cognitive function, leading to problems with concentration and memory.

12.2. Clinical and scientific importance

Parasites that cause mental disorders create a significant public health risk and in endemic areas where parasitic illnesses prevail. Knowledge of the mechanisms of action in which parasitic illnesses impact mental health is fundamental in treating and diagnosing neuropsychiatric illness in these areas successfully. Along with the removal of the parasite itself, treatment should focus on monitoring and treating concomitant psychiatric illness in the form of depression, epilepsy and sleep disorders.

Raising awareness of the role of parasites in mental health is also critical in prevention. Early detection of parasitic infection and its impact on mental health will lessen the long-term effects of cognitive and emotional disorders. Developing combination therapy that tackles both neurological and psychiatric factors is also required.

With regards to scientific research, the review's conclusions reflect a significant gap in what is known about the complete mechanisms through which parasitic infection influences the nervous system and mental health. Specifically, mechanistic research is needed to more comprehensively appreciate the effects of parasites such as *Toxoplasma gondii* and *Plasmodium falciparum* on neurotransmission, microglia function and brain morphology.

Furthermore, clarifying the interaction between causation and correlation with regard to parasitic infestation and psychiatric disorder development is also a significant challenge in science. Additional experimental research in animal models and also through long-term studies may offer significant insights into causal mechanisms. Utilization of novel brain-imaging technology such as fMRI and PET will be important in examining these relationships further.

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Author's contribution:

Conceptualization: Aleksandra Sosin, Maja Torbacka

Methodology: Katarzyna Torbacka, Zuzanna Wróbel

Visualization: Wojciech Bednarz, Olga Jakubik

Investigation: Joanna Kaczor, Natalia Wróbel

Writing - review and editing: Patrycja Podlejska, Katarzyna Rozkosz

Check: Joanna Kaczor, Natalia Wróbel, Katarzyna Rozkosz

Formal analysis: Olga Jakubik, Aleksandra Sosin

Resources: Olga Jakubik, Natalia Wróbel, Aleksandra Sosin

Data curation: Zuzanna Wróbel, Katarzyna Torbacka

Writing - rough preparation: Katarzyna Rozkosz, Patrycja Podlejska, Joanna Kaczor

Software: Zuzanna Wróbel, Katarzyna Rozkosz

Supervision: Aleksandra Sosin, Patrycja Podlejska

Project administration: Aleksandra Sosin

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