Publisher homepage: www.universepg.com, ISSN: 2663-7529 (Online) & 2663-7510 (Print)

https://doi.org/10.34104/ejmhs.023.01280144

European Journal of Medical and Health Sciences

Journal homepage: www.universepg.com/journal/ejmhs

Toxoplasmosis-related Psychological, Behavioral, Neurological, and Hormonal Changes: A Literature Review

Zuhair Dardona[1], Mounia Amane[1], and Samia BOUSSAA[1,2]*

[1]Microbial Biotechnologies, Agrosciences and Environment Laboratory (BioMAgE), Research Unit Labelled CNRST N°4, Faculty of Sciences Semlalia, Cadi Ayyad University, Marrakech, Morocco; [2]ISPITS-Higher Institute of Nursing and Technical Health Occupations, Ministry of Health and Social Protection, Rabat, Morocco.

*Correspondence: samiaboussaa@gmail.com (Prof. Samia BOUSSAA PhD, Microbial Biotechnologies, Agrosciences and Environment Laboratory (BioMAgE), Research Unit Labelled CNRST N°4, Faculty of Sciences Semlalia, Cadi Ayyad University, Marrakech, Morocco and ISPITS-Higher Institute of Nursing and Technical Health Occupations, Ministry of Health and Social Protection, Rabat, Morocco).

ABSTRACT

Toxoplasma gondii is an intracellular parasite responsible for causing toxoplasmosis, a disease that infects approximately one-third of the global population. It is crucial to note that this parasite can infect both mammals and birds. Furthermore, it can be transmitted to humans through different transmission routes. Vertical transmission from an infected pregnant woman to her fetus and horizontal transmission via contaminated or infected raw food or drinks are the most prevalent modes of transmission. While most cases of the disease area symptomatic or develop flu-like symptoms, it can lead to severe manifestations in fetuses, infants, and individuals with compromised immune systems. During the latent phase of the disease, numerous cysts form throughout the patient's body, with the brain being the most significant site for cyst development. The occurrence of these cysts in the brain and their long-term existence have sparked extensive investigation, leading to various hypotheses and recent experiments exploring their impact on behavioral, psychological, and neurological alterations such as schizophrenia, depression, bipolar disorder, Alzheimer's disease, and autism. Furthermore, emerging studies and research have revealed the parasite's ability to trigger hormone and neurotransmitters secretion in the host, including dopamine and sex hormones, with testosterone being particularly noteworthy. This study aimed to shed additional insight into the significance of this parasite in these alterations. It also aimed to shed insight into the mechanisms this parasite employs in creating these changes. This study clearly indicates, as numerous other studies and research have, that this parasite plays a major role in several behavioral, neurological, psychological, hormonal and neurotransmitters abnormalities in infected individuals.

Keywords: *Toxoplasma gondii*, Psychopathology, Behavioral, Hormonal, Neurological, and Disorders.

INTRODUCTION:

Toxoplasma gondii is a parasite that infects warm-blooded animals. It is interesting to note that the term "toxon" in Greek means "crescent-shaped," which accurately describes one of the parasite's three infectious stages known as the tachyzoite. Additionally, "plasma" is a Greek word for "creature." Consequently, the parasite's name is derived from its tachyzoite

form (Gunn and Pitt, 2012; Bogitsh *et al.,* 2018). Briefly: *T. gondii*'s life cycle is complex and involves both sexual and asexual reproduction. Asexual reproduction occurs in various tissues of mammals and birds, which serve as secondary or intermediate hosts. However, sexual reproduction exclusively takes place in felines' digestive epithelium, which serves as the primary or definitive host. Numerous studies have demonstrated that several feline species can function as definitive hosts for *T. gondii*. This leads to the formation of oocysts excreted in feces (Dubey *et al.,* 2009; Dubey, 2009a; Skariah *et al.,* 2010).

Furthermore, oocysts become infectious once they sporulate in the environment and can be transmitted through wind and water. Oocysts resist harsh environmental, physical, and chemical circumstances. This allows them to remain infectious as long as they remain in appropriate environments (Tenter *et al.,* 2000). This parasite belongs to the Apicomplexa phylum, which is commonly referred to as the sporozoa. It is a versatile unicellular protist that thrives in a variety of environments. Besides, it is assumed to be an obligate intracellular parasite, which means it can only live within living cells. The apical complex, an evolutionarily distinct organelle beneath the oral cavity, distinguishes this parasite. All apicomplexan parasite groups are pathogenic to humans and animals (Gould *et al.,* 2008; Yoon *et al.,* 2008). *T. gondii*'s life cycle includes three infectious stages: sporulated oocysts with sporozoites, tachyzoites, and tissue cysts containing bradyzoites. All three stages can infect both definitive and intermediate hosts. While, cats become infected by ingesting sporulated oocysts found in the feces of an infected cat through contaminated food or water. They can also become infected by consuming an intermediate host containing bradyzoites. On top of that, vertical transmission from a pregnant mother to her fetus is another significant route of infection (Gunn and Pitt, 2012). *T. gondii* can infect humans in a variety of ways, the most frequent being the ingestion of oocysts or tissue cysts. Oocysts are common in the environment and may be found in both domestic and stray cats, making them a source of infection. Another way is vertical transmission from mother to fetus. This occurs via the transplacental route (Frenkel *et al.,* 1970; Dubey and Beattie, 1988).

In countries where raw or undercooked meat consumption is common, the estimated prevalence of *T. gondii* is greater than 50%. For instance, in France, where this dietary practice is prevalent, the prevalence rate was 54%. Analogously, tropical regions in Latin America and Africa, characterized by high cat populations and favorable climate conditions for oocyst survival, exhibit a high seroprevalence of the parasite (Jones *et al.,* 2001; Di Carlo *et al.,* 2008; Dubey *et al.,* 2009). Shockingly, an estimated 15% of women of childbearing age, between 25 and 44 years old, in the United States are infected with *T. gondii*. Moreover, congenital toxoplasmosis is estimated to occur annually from 400 to 4,000 cases (Jones *et al.,* 2001). On the other hand, *T. gondii* infects 25% to 30% of the world's population, although infection rates vary among ethnic groups. In North America, Asia, and Northern Europe, infection rates range from 10% to 30%. Central and Southern Europe report moderate rates of 30% to 50%, while Latin America and the tropical regions of Africa exhibit a high incidence of infection (Robert-Gangneux and Dardé, 2012).

Although *T. gondii* infection usually remains asymptomatic or causes mild flu-like symptoms in healthy individuals, it can have serious consequences for those with compromised immune systems. Toxoplasmosis may cause central nervous system abnormalities, myocarditis, or pneumonitis in immunocompromised persons. Notably, among immunocompromised persons with toxoplasmosis, Toxoplasmic encephalitis is the most prevalent cause of intracerebral mass lesions. This is related to the reactivation of their chronic infection (Schmidt-Hieber *et al.,* 2009; Siberry *et al.,* 2013; Hadiloo, 2023).

Psychopathology definition and statistics

Typically, an individual's psychological state is categorized as balanced or imbalanced based on their level of participation in social activities within society. This is also accompanied by the existence of functional impairments or weaknesses. Psychopathology encompasses various elements, such as functional limitations, distress, irrationality, and lack of control. It is significant to note that there may be additional problematic psychological traits that should not be disregarded (Bergner, 1997; Maddux and Winstead, 2015; Cicc-

hetti, 2016). Despite the extensive criteria and numerous research papers available, there remains a significant amount of uncertainty and lack of awareness regarding psychopathology's development. These uncertainties result from the complex interconnections between an individual's genotype and various social environments. In addition, they stem from the fundamental and intense experiences they endured during their early growth stages. However, they also stem from persistent stress and hormonal imbalances they may have faced. Moreover, recent studies have highlighted the potential involvement of diverse parasites and microbes in contributing to these psychological consequences (Giudice and Ellis, 2016; Manning, 2019; Rantala *et al.,* 2019). According to recent statistics, more than 10% of the world's population suffers from psychological, mental, and behaveoral disorders. These disorders exert a substantial influence on public health and are associated with numerous factors such as personal distress, disability, and premature mortality. Additionally, these disorders have a substantial economic impact, contributing to 12% of the worldwide disease burden. They also lead to diminished productivity and strain on healthcare resources due to excessive utilization (W.H.O., 2001; Demyttenaere *et al.,* 2004; Wang *et al.,* 2007).

Toxoplasma gondii as a potential cause of behavioral disorders

Previously, it was widely accepted and acknowledged that toxoplasmosis infection in healthy individuals remained dormant and asymptomatic. However, this perspective has evolved over time. Ongoing investigations have revealed a connection between latent toxoplasmosis infection and cognitive function changes in both children and older individuals. Moreover, numerous studies have associated *T. gondii* infection with various psychiatric conditions, including schizophrenia, bipolar disorder, and obsessive-compulsive disorder. Additionally, this infection has been linked to elevated mortality risk in schizophrenia patients (Dickerson *et al.,* 2007; Campos-Carli *et al.,* 2017). The prevailing consensus among scholars and experts is that behavioral disorders have varied and a variety of causes, including genetic and environmental factors. Nevertheless, it is noteworthy to highlight that numerous theories propose the involvement of infectious agents, such as *T. gondii*, viruses like herpes simplex, CMV, and influenza. This is associated with the occurrence of certain mental and behavioral disorders. *T. gondii* serves as a significant model for examining the influence of microorganisms on human behavior and mental disorders, as it are frequently related with neuropsychiatric disorders (Fekadu *et al.,* 2010; Flegr, 2013). Schizophrenia factors have been extensively studied and can be categorized into two main groups: genetic and environmental variables. Environmental factors implicate numerous infectious pathogens in schizophrenia development. Particularly, *T. gondii* has received significant attention and is consistently associated with schizophrenia in various research studies (Sutterland *et al.,* 2015; Owen *et al.,* 2016).

What are the mechanisms and reasons behind *Toxoplasma gondii* infection leading to behavioral, psychological, and neurological disorders in the host?

Characteristically, when a woman is infected with parasites during pregnancy, it can influence the development of specific brain neurons. These neurons include mesolimbic dopaminergic or prefrontal cortical neurons. This impact might involve issues like abnormal migration, altered location, or reduced connections, leading to neurodevelopmental problems. Interestingly, these initial flaws may not immediately manifest as disease symptoms, but instead, they may emerge after a latency period of one to three decades. During childhood, glial progenitor cells continue to undergo proliferation, migration, differentiation, and maturation. In addition, the amount of grey matter in the brain reaches its peak during puberty before gradually declining. Furthermore, significant changes occur in the brain's wiring and connections during this period, potentially contributing to symptoms later in life. Understanding these developmental pathways is crucial for identifying early biomarkers and developing effective therapies for neurodegenerative diseases (Paus, 2005; Stiles and Jernigan, 2010). Furthermore, like other pathogens, parasites can modify their own behavior and influence the behavior of their hosts to enhance their survival and reproductive success. Consequently, parasite genes can interact and generate traits that extend beyond the physical boundaries of the

parasite's own body (Tong *et al.,* 2021). *T. gondii*, one of the most extensively studied infectious agents, is frequently associated with neuropsychiatric and behavioral disorders. However, some explain this phenolmenon through manipulation theories. This theory proposes that parasites, in general, can significantly alter the characteristics of their hosts, a feature that facilitates their transmission to new hosts. In this context, scientists, particularly biologists, psychologists, and evolutionary scientists, cite *T. gondii* as a compelling example. The parasite's global existence and remarkable dissemination success, coupled with the severe diseases it causes in humans, contribute to its recognition. Besides, all forms of toxoplasmosis impose substantial economic and social burdens worldwide (Pappas *et al.,* 2009; Torgerson and Macpherson, 2011).

Nonetheless, it has been suggested that chronic infection with *T. gondii* leads to numerous alterations in the neurotransmitters involved in the communication between nerve cells within the body. For instance, the parasite controls the secretion rate of specific hormones in the infected individual. The genome of *T. gondii* contains two regions that closely resemble mammalian genes responsible for encoding the enzyme crucial for dopamine production, called amino acid hydroxylase. This similarity explains the increased availability of dopamine in the host's brain following chronic localization of *T. gondii* (Gaskell *et al.,* 2009). *T. gondii* infection manifests asymptomatic and can lead to mild symptoms. However, it usually begins during childhood and persists in a chronic state, causing the parasite to reside inactively within the organism infected with it. Subsequently, it takes advantage of weakened immunity in certain patients, such as those with AIDS, organ transplant recipients, individuals with various immune disorders, and cancer patients. Exploiting the compromised immune system, the parasite can reactivate the infection, leading to a range of symptoms and potentially fatal outcomes. Reactivation symptoms usually include neurological manifestations like meningitis and encephalitis, as well as cysts and abscesses in the brain. These observations provide additional insights into the potential impact of latent and chronic *T. gondii* infection on the psychological, behavioral, and neurological conditions of some toxoplasmosis patients (Roberts *et al.,* 2001; Montoya and Liesenfeld, 2004). Due to its direct impact on nerves, *T. gondii*, the parasite responsible for toxoplasmosis, has been linked to numerous sensory and congenital neurological disorders (Torrey *et al.,* 2007; Torrey and Yolken, 2019). Moreover, numerous research studies have shown that *T. gondii* possesses an intricate mechanism to penetrate and invade various cells in the brain, particularly those of the central nervous system. Furthermore, the parasite can form cysts within these cells, enabling it to influence the host's behavior and consequently induce a range of neurological and psychological symptoms in certain patients (Holliman, 1997; Webster *et al.,* 2006; Carruthers and Suzuki, 2007). It is also intriguing to note that both sexually transmitted parasites and the genes of the host share a common interest and objective, which is to alter the host's programming to enhance reproductive viability. Therefore, the host's survival is crucial to the parasite's survival. On the other hand, parasites transmitted through food, such as *T. gondii*, have different interests and goals. For instance, the parasite aims for the definitive host, such as a feline, to prey upon and consume the intermediate host, such as a mouse. The mouse strives to survive and reproduce to ensure its offspring's continuation. Among the various behaviors associated with toxoplasmosis, one notable example is the elongation of response times in infected hosts. This arises from the parasite's manipulative activities rather than being mere side effects of the infection (Poulin, 1995; Hrdá *et al.,* 2000). To guarantee their survival and propagation, certain parasites implement strategies to modify their hosts' physical characteristics and behaviors. This manipulation increases the likelihood of transmission from an infected host to an uninfected one. *T. gondii* can exploit these manipulative activities, both in terms of behavior and morphology, to achieve this goal (Flegr and Hrdy, 1994; Webster, 1994). Numerous mechanisms and pathways have been suggested to explain how the *T. gondii* parasite influences its host's behavioral state. One such mechanism involves cytokines, associated with *T. gondii* infection. These cytokines activate microglia and facilitate neurodegeneration, leading to activation and apoptosis. These proposed mechanisms may contribute to the impact of *T. gondii* infection on mental disorders in the

host, as neurotransmitters and immune dysregulation also play significant roles in the pathophysiology of psychosis and schizophrenia (Flegr, 2013; Fabiani *et al.,* 2013). While postnatal toxoplasmosis contributes to various psychological and neurological impairments, it targets specific neurotrophic regions in the brain. These regions include the cerebral hemisphere, cerebellum, basal ganglia, and brain stem. The formation of tissue cysts within neurons and glial cells further explains the emergence of these psychological and behavioral disabilities in individuals who acquire postnatal toxoplasmosis. Congenital toxoplasmosis, on the other hand, presents a range of clinical manifestations. Some newborns show no symptoms while others experience severe symptoms due to possible neurological abnormalities that may arise years after birth or even during puberty (Avelino *et al.,* 2014; Elzeky *et al.,* 2022). An additional justification for the impact of *T. gondii* on infected individuals' behavior is based on the parasite's inclination towards specific regions of the brain. This selective affinity can account for behavioral changes observed in the host, due to localized signal modifications. Furthermore, *T. gondii* induces specialized enlargement in the brain, eyes, and testes. These are immune-privileged sites that immune cells cannot access. Experimental evidence suggests *T. gondii* can enter these areas through brain endothelial cells and dendritic immune cells. Consequently, the occurrence of cysts in these regions disrupts their normal functioning, leading to impairments in fear processing and decision-making abilities (Gonzalez *et al.,* 2007; Lachenmaier *et al.,* 2011; Vyas, 2015). Unquestionably, *T. gondii* is among the most conspicuous infectious agents linked to mental and neurological disorders. Given its relationship to a range of psychological, behavioral, and neurological issues in infected patients, this parasite serves as an excellent model for studying the impact of micro-organisms on human behavior and mental disorders (Flegr, 2013).

Behavioral, neurological, and psychopathological disorders associated with *Toxoplasma gondii* infection

While the host itself influences some behavioral changes following infection, the pathogen causes others to facilitate its own transmission. This provides a plausible explanation for certain parasites' ability to interact with their hosts' central nervous systems (CNS). Although some infection-related behavioral changes, such as feelings of sadness or overall malaise, may appear broad, they target specific physiological traits of the host to enhance the parasite's chances of survival and propagation (Webster *et al.,* 2013). One of the remarkable behavioral changes associated with *T. gondii* is the phenomenon called "fatal attraction," where infected mice display an unusual attraction to cats' scent instead of their natural aversion to it. This alteration in behavior is accompanied by increased activity levels and reduced fear. This is believed to be influenced by the learning and memory impairments caused by the parasite, distinguishing infected mice from their uninfected counterparts (Berdoy et al., 1995; Berdoy *et al.,* 2000; Webster, 2001). It is also intriguing and noteworthy that *T. gondii* infection is associated with behavioral and cognitive changes in intermediate hosts. For instance, infected chimpanzees are attracted to tiger urine, a member of the feline family. This behavior is interpreted as a developmental adaptation to facilitate the completion of the *T. gondii* life cycle within the definitive host, which exclusively belongs to the feline family (Webster, 2001; Poirotte *et al.,* 2016; Brüne, 2019). Additionally, the formation of persistent cysts by *T. gondii* in brain tissue may directly impact specific regions of the brain, such as the amygdala or hippocampus, potentially explaining the occurrence of behavioral and psychological changes observed in individuals infected with *T. gondii* (Mortensen *et al.,* 2007; Carruthers and Suzuki, 2007; Hari Dass and Vyas, 2014).

Schizophrenia

Toxoplasmosis transitions from a mild and acute infection to a chronic and latent stage. Over the past two decades, numerous studies and research have continuously shown that this latent stage is strongly associated with an increased risk of psychological, neurological, and behavioral disorders in patients. This association has been well-documented, with a notable relationship between toxoplasmosis and schizophrenia patients. Research focusing on these patients has revealed a high prevalence of *T. gondii* infection, particularly among those experiencing persistent symptoms of schizophrenia and other mental disorders (Torrey *et al.,* 2007; Torrey *et al.,* 2012; Flegr *et al.,*

2014; Sutterland *et al.,* 2015). In addition to what has been mentioned, studies have demonstrated that *T. gondii* could influence schizophrenia clinical characteristics (Flegr, 2013; Fabiani *et al.,* 2013). Numerous clues have indicated a relationship between toxoplasmosis and schizophrenia, as changes in brain structure, such as reduced grey matter in the frontal cortex, temporal cortex, cingulate cortex, and thalamus, are commonly observed in individuals with schizophrenia. These same alterations have been found in patients with schizophrenia with toxoplasmosis (Niebuhr *et al.,* 2007; Horacek *et al.,* 2012; McConkey *et al.,* 2013).

Furthermore, it extends beyond mere alterations in brain morphology. Studies have revealed that schizophrenia patients infected with *T. gondii* exhibit 15 times more positive symptoms than non-infected schizophrenic patients. Moreover, there is a higher likelihood of developing a persistent course of the disease in individuals with both schizophrenia and toxoplasmosis (Wang *et al.,* 2006; Holub *et al.,* 2013; Çelik *et al.,* 2015). Further research and hypotheses have expanded our understanding of this area. It has been proposed that certain characteristics and symptoms observed in schizophrenia patients could be attributed to toxoplasmosis infection. Additionally, schizophrenia and toxoplasmosis may share psychological symptoms. For instance, both schizophrenia patients and individuals with latent or chronic toxoplasmosis exhibit increased startle reflex latency. In addition, they show a diminished effect of prepulse on latency in the acoustic startle reflex inhibition test (Horacek *et al.,* 2012; Pearce *et al.,* 2013; Příplatová *et al.,* 2014). The association between schizophrenia and toxoplasmosis extends beyond behavioral and psychological disorders and includes an interconnection with distinctive changes in certain senses, like smell. Moreover, toxoplasmosis' impact on smell differs based on gender. For instance, research revealed that males perceive diluted cat urine as more pleasant (Flegr *et al.,* 2011). In contrast, infected females find cat urine's diluted smell less pleasant (Berdoy *et al.,* 2000). However, several studies have indicated a significant negative impact of schizophrenia on patients' performance in odor identification tests, characterization, and smell recognition memory (Flegr *et al.,* 2017).

Self-directed violence, suicide attempts and others

While the majority of studies on *T. gondii* have mainly concentrated on its associations with schizophrenia, increased rates of toxoplasmosis exposure have been detected in the various other mental diseases, which include psychotic disorder-like symptoms, bipolar disorder, self-directed violence, the suicide attempts, generalized anxiety disorder, the mixed anxiety and depressive disorder, obsessive-compulsive disorder, autism, and pregnancy depression (Xiao *et al.,* 2018).

Fascinatingly, several animal studies have revealed a strong correlation between toxoplasmosis infection and heightened risk-taking behaviors, including attraction to cat urine, increased adventurousness, exploratory behavior, reduced fear response, and a lack of aversion to open spaces. Surprisingly, toxoplasmosis infection has also been associated with a higher occurrence of motor vehicle accidents, mental and neurological disorders, and substance abuse in humans. Additionally, suicide attempts have increased (Johnson *et al.,* 2018).

Parkinson's disease

Furthermore, several findings regarding *T. gondii* infection have established its association with various neurological disorders in humans, including Parkinson's disease. Parkinson's disease is a neurological condition characterized by the degeneration of specific neurons in the substantia nigra. This is a region in the brain stem responsible for dopamine production. Dopamine serves as a crucial neurotransmitter involved in coordinating normal movement (Golbe *et al.,* 2010; Miman *et al.,* 2010). It is worth mentioning that, in a study conducted by Miman *et al.* (2010), the potential association between *Toxoplasma gondii* infection and Parkinson's disease was investigated. The researchers analyzed data from a large study involving individuals in Turkey. They observed a higher likelihood of Parkinson's disease development in those infected with Toxoplasma gondii. The authors proposed that this connection could be attributed to the parasite's ability to damage brain neurons. However, further research is required to validate this correlation and gain a deeper understanding of the underlying mechanism through which Toxoplasma gondii might contribute to Parkinson's disease (Miman *et al.,* 2010).

Gender-related alterations associated with *Toxoplasma gondii* infection.

Even though the vast majority of infected individuals show no apparent health consequences from *T. gondii* infection, latent and chronic forms of the disease can lead to involuntary changes in behavior and personality. Interestingly, these behavioral alterations can vary depending on the infected person's sexuality. For instance, infected men may display higher levels of suspicion, jealousy, and dogmatism. On the other hand, infected women may exhibit increased moral values, conscientiousness, and persistence compared to others. These findings suggest a potential gender-specific impact of infection on the personality traits. However, further research is required to fully understand the extent and causality of these associations (Flegr, 2007; Del Giudice, 2019).

Impulsivity and aggression

Additionally, toxoplasmosis impacts the corticolimbic region, which regulates impulsivity and aggression in humans. Furthermore, recent studies have broadened the investigation into psychological and mental disorders, including schizophrenia, obsessive-compulsive disorder, and suicidal tendencies in individuals with latent and chronic toxoplasmosis. These findings suggest a potential connection between toxoplasmosis and various psychological conditions (Torrey and Yolken, 2019; Inceboz and Inceboz, 2021). Nevertheless, studies investigating the behavioral biology of the parasite *T. gondii* have revealed the fascinating neuroendocrinological discoveries, particularly in terms of the regulation & interaction between the brain and hormones (Tong *et al.,* 2021).

Furthermore, pursuant to a study conducted by Cook and colleagues, there was a correlation between *T. gondii* IgG seropositivity and increased impulsive sensation-seeking, specifically related to suicidal self-directed violence (SSDV) disinhibition, in young men aged 20 - 59 years (with a median age of 60). The study also observed that aggression and impulsivity, which are considered endophenotypes for SSDV, were associated with latent *T. gondii* infection in a manner specific to gender and age. This study suggests that *T. gondii* infection may influence behavior & mental health, particularly in terms of impulsivity & aggression (Cook *et al.,* 2015).

Cancers

Toxoplasmosis has been detected in various cancer types, including lymphoma, acute and chronic leukemia, and myeloma. Furthermore, recent research has identified the presence of anti- *T. gondii* antibodies in women with breast and ovarian cancers. However, the specific mechanism behind this association remains unknown, but it is evident that toxoplasmosis contributes to tumor advancement (Aabasian *et al.,* 2016). Yuan and colleagues conducted a study to examine the potential association between Toxoplasma infection and cancer by detecting anti- *T. gondii* antibodies in cancer patients. The study involved 267 cancer patients who underwent ELISA testing. It revealed higher rates of *T. gondii* IgG positivity than the control group. Specifically, the nasopharyngeal carcinoma and rectal cancer groups exhibited significantly higher rates of *T. gondii* IgG seropositivity than other cancer groups. However, IgM seropositivity rates fluctuated not significantly. These findings suggest a link between *T. gondii* infection and various cancers, including nasopharyngeal carcinoma and rectal cancer. Nevertheless, further research is required to determine whether *T. gondii* infection is a causal factor for cancer and whether it can be targeted for cancer prevention. This study underscores the importance of investigating infectious agents' involvement in cancer development and progression (Yuan *et al.,* 2017).

Psychological disorders in individuals co-infected with Toxoplasmosis and HIV/AIDS.

Toxoplasma gondii-related psychological disorders are prevalent in AIDS patients with compromised immune systems, where latent infection is reactivated. Pursuant to research on AIDS cases with toxoplasmosis, up to 60% of patients have abnormal mental states that appear as delusions, auditory hallucinations, and cognitive deficits (Israelski and Remington, 1988).

Bipolar disorder

Bipolar disorder (BD) is a chronic and recurring mental disorder that contributes to disability and mortality on a global scale. BD origins are complex, involving a combination of genetic inheritance and environmental risk factors. Among the various factors implicated, infectious agents have been enumerated. There is growing evidence pointing to the significance of immunological dysfunction in the development of

the disorder. Moreover, inflammation and oxidative stress have been suggested as potential contributors to the onset and progression of BD, highlighting the importance of a systematic treatment approach that addresses both the biological and psychological aspects of the disorder (Del Grande *et al.,* 2017). Highlighting the potential indirect contribution of *T. gondii* to bipolar disorder, also known as manic depression, is important. Numerous infectious agents, including *T. gondii*, have been linked to psychosis, either through direct effects on brain cells or indirect influences on immune cells and neurotoxic compounds (Inceboz and Inceboz, 2021). Numerous investigations have been conducted to investigate the relationship between bipolar disorder (BD) and toxoplasmosis infection. One such study involved 110 BD patients and 106 healthy individuals residing in France, a country with a high toxoplasmosis seroprevalence rate. The study found significantly higher seropositivity and antibody levels to *T. gondii* in BD patients compared to the control group. These results indicate that toxoplasmosis infection could potentially play a role in the development of BD (Hamdani *et al.,* 2013).

Heightened libido

Toxoplasmosis is commonly known as a food-borne disease; however, it can also be transmitted sexually in rats. Infected rat males can carry *T. gondii* in their sperm, allowing the parasite to reach the female during mating. Interestingly, *T. gondii* -infected male rats become more attractive to females, while uninfected females tend to spend more time near infected males, providing them with increased reproductive opportunities. These findings indicate that the parasite manipulates the host's behavior to enhance its own sexual transmission routes. This demonstrates parasites' ability to influence their hosts' behavior for their own benefit. Such observations highlight the complex and intricate interactions between parasites and their hosts (Vyas, 2013; Vyas, 2015).

Autism

Autism, a neurodevelopmental disorder with diverse characteristics, affects approximately one in sixty-eight children and is typically diagnosed in their second year of life (Nayeri *et al.,* 2020). Numerous research studies have established a relationship between a positive maternal toxoplasmosis test and elevated autism risk. One hypothesis proposes that *T. gondii* tachyzoites may infiltrate specific types of brain cells in the cerebellum, influencing signaling pathways and transmission systems. The parasite participates in numerous tasks and functions, including cell apoptosis, immune cell maturation, and antimicrobial activities. Furthermore, studies have linked the parasite to the activation of apoptosis in neural stem cells through the stress pathway in the endoplasmic reticulum (Fond *et al.,* 2013; Wang *et al.,* 2014; Al Malki *et al.,* 2021).

Alzheimer's disease and insomnia

Nayeri *et al.* have determined that toxoplasmosis poses a risk factor for Alzheimer's disease. The findings of several studies linking toxoplasmosis infection and Alzheimer's disease reinforce this conclusion, highlighting the requirement for special attention from healthcare professionals and patients (Nayeri *et al.,* 2021). Furthermore, aside from the aforementioned association between *T. gondii* infection & Alzheimer's disease, another study revealed a relation-ship between toxoplasmosis prevalence and insomnia. Particularly, men over fifty with toxoplasmosis have shown a higher susceptibility to insomnia than others (Alvarado-Esquivel *et al.,* 2022).

Hormonal and neurotransmitter changes that can occur in people infected with *Toxoplasma gondii.*

Toxoplasma gondii infection promotes hormone and neurotransmitter changes. Patients infected with *T. gondii* have shown alterations in the levels and functioning of several hormones and neurotransmitters. For instance, the infection is related to fluctuations in dopamine, a neurotransmitter involved in motivation and reward. This results in elevated dopamine levels in certain areas of the brain. Likewise, *T. gondii* infection has been attributed to changes in serotonin, a neurotransmitter critical for mood control. The infection may also affect hormone levels such as cortisol, which regulates the stress response, and testosterone, which participates in reproductive and sexual processes. These findings illustrate the complicated link between *T. gondii* and the neuroendocrine system, revealing the parasite's potential influence across numerous physiological systems (Flegr *et al.,* 2014; Prandovszky *et al.,* 2020). Latent toxoplasmosis extends beyond psychological, behavioral, and neurological changes. Several studies have established a relationship between

latent toxoplasmosis and alterations in specific hormones and neurotransmitters in infected animals and humans. This influence is particularly notable on certain sex and steroid hormones (Henry and Beverley, 1976; Kittas and Henry, 1979). The part of the article that follows delves into some of the significant hormones and neurotransmitters influenced by toxoplasmosis infection.

Dopamine

Furthermore, *T. gondii's* contribution to the onset of psychological disorders in toxoplasmosis patients can be related to the brain's immunological response to the parasite as well as its biochemical activity (Silva *et al.,* 2002; Hunt *et al.,* 2017). In response to *T. gondii* infection, the body produces gamma interferon, which helps to maintain latent and chronic infection by stimulating astrocytes in the brain to produce indoleamine 2,3 dioxygenase (IDO), an enzyme involved in the degradation process via the Kynurenine metabolic pathway (Silva *et al.,* 2002; Hunt *et al.,* 2017).

Consequently, due to the synthesis of indoleamine 2, 3 dioxygenase (IDO), there is a decrease in the level of tryptophan, an essential amino acid for *T. gondii* replication. This mechanism leads to the production of specific compounds with neurotoxic properties (Elsheikha *et al.,* 2016) and directly impacts the balance of neurotransmitters through the involve-ment of two genes. In a similar manner to the human gene, *T. gondii* directly enhances dopamine activity, which plays a crucial role in the development of schizophrenia, autism, and various other mental disorders (Torrey *et al.,* 2012; Krause and Müller, 2012; Sutterland *et al.,* 2015; Qayyum *et al.,* 2015). *T. gondii* may also affect the levels of the neurotransmitter in the intermediate hosts' brains and play a significant role in increasing the levels of dopamine secretion among neurons (Prandovszky *et al.,* 2011), possibly by influencing the ways of self-expression of the encoding genes for an enzyme that determines the rate of dopamine synthesis (Gaskell *et al.,* 2009). *T. gondii* also encodes two essential enzymes for the production of dopamine, a neurotransmitter whose concentration increases in the human brain of toxoplasmosis patients and plays a significant and crucial role in side effects (hallucinations and delusions) in schizophrenia patients (Willner, 1997; Flegr *et al.,* 2003; Gaskell *et al.,* 2009). Furthermore, elevated, or modified levels of dopamine have been observed in rodents and humans infected with *T. gondii*, as well as in individuals with schizophrenia and other affective disorders such as obsessive-compulsive disorder (OCD), bipolar disorder, and those with a history of suicide attempts. Additionally, recent research indicates that the parasite itself may be a potential source of this dopamine (Webster *et al.,* 2013). Studies on rats have revealed that the parasite has the potential to alter dopamine levels in the host, influencing glutamatergic brain circuits. Interestingly, these pathways closely match the recognized neurotransmitter patterns identified in people with schizophrenia, despite the fact that current treatment techniques for schizophrenia target antipsychotic medicines' anti-dopaminergic activity. Surprisingly, several antipsychotics have anti-parasitic characteristics (Brüne, 2020).

Sex hormones

An investigation suggested that the infection caused by *T. gondii* is influenced by sex hormones, which can impact the immune system and consequently affect susceptibility to diseases in general. This is particularly pertinent because *T. gondii* can lead to congenital disease if contracted during pregnancy (Roberts *et al.,* 2001). In addition to its association with psychiatric and behavioral disorders, toxoplasmosis has been linked to increased sex hormone secretion, particularly testosterone. Various studies have demonstrated that *T. gondii* enhances hormone production (Del Giudice, 2019; Tong *et al.,* 2019). Testosterone, known as the male sexual hormone, reduces anxiety and fear. It is believed to play a crucial role in *T. gondii*'s effects during its interaction with the brain. Furthermore, *T. gondii* infection also stimulates arginine vasopressin synthesis in a specific brain region called the medial amygdala. This area contains nerve cells involved in the perception of sexual hormones and is connected to brain regions responsible for arousal and stimulation (Hari Dass and Vyas, 2014; Tong *et al.,* 2019; Tong *et al.,* 2021b). In the male reproductive system, the testes serve as a barrier that restricts immune cells and pathogens' access. Nonetheless, pathogens, including *T. gondii*, surpass this barrier and invade rats' testes. This has been confirmed by the detection of *T. gondii* and other species in rat ejaculates. As a result, *T.*

gondii infection enhances the production of testosterone, and this hormone, in turn, interacts with the host's brain, further facilitating the effects of the parasite (Tong *et al.,* 2021). Furthermore, according to Oktenli *et al.* (2004), acute *T. gondii* infection can lead to temporary gonadal insufficiency unrelated to disease progression. Interestingly, *T. gondii* infection has been observed to increase testosterone levels in infected animals and promote the expression of luteinizing hormone receptor mRNA (LHR). On the other hand, women with hyperprolactinemia, a condition characterized by high levels of prolactin hormone, had a lower prevalence of toxoplasmosis than other women (Oktenli *et al.,* 2004; Galvan-Ramirez *et al.,* 2014). In more detailed terms, *T. gondii* infection leads to an elevation in the number of luteinizing hormone (LH) receptors and specific enzymes involved in testosterone conversion from its precursor within Leydig cells. *T. gondii* influences testosterone levels by this mechanism, subsequently; the increased testosterone circulates in the bloodstream and crosses the blood-brain barrier, resulting in an upregulation of arginine vasopressin (AVP) transcription in the medial amygdala. While these neurons are part of the extra-hypothalamic vasopressin system and influence male rodent sociosexual behavior. It is proposed that elevated levels of vasopressin in the central amygdala system reduce fear by enhancing approach behavior (Singh *et al.,* 2020). Furthermore, numerous studies have validated a notable rise in the levels of hormones 17β-estradiol and progesterone during the second and third trimesters of pregnancy, coinciding with an increased incidence of the toxoplasmosis infection (Montoya and Remington, 2008; Al-warid and Al-qadhi, 2012). Across the menstrual cycle, there are fluctuations in the levels of these hormones (E2 and Progesterone), which significantly influence immune system cells. This hormonal effect on the immune system could potentially lead to increased susceptibility to toxoplasmosis infection (Roberts *et al.,* 2001). Due to the potential occurrence of progesterone secretion abnormalities during pregnancy, progesterone levels become irregular in the women with toxoplasmosis during that period. Additionally, research has shown that toxoplasmosis-infected sheep experience low progesterone levels throughout pregnancy (Galvan-Ramirez *et al.,* 2014). In response to the potential occurrence of progesterone secretion abnormalities during pregnancy, progesterone levels become irregular in women with toxoplasmosis during that period. Additionally, research has shown that toxoplasmosis-infected sheep experience low progesterone levels throughout pregnancy (Galvan-Ramirez *et al.,* 2014). Moreover, studies conducted on mice have highlighted the significance of sexual hormones, revealing that administering estrogen exacerbated the disease in mice, whereas a gonadectomy improved disease resistance. Similarly, in guinea pigs infected with *T. gondii* and subsequently treated with estrogen, there was an increase in mortality and a deterioration of infection due to a significant decline in cellular immunity caused by high doses of estrogen as compared to untreated control animals (Kittas and Henry, 1979).

Cortisol

A study conducted to assess the impact of *T. gondii* infection on testosterone and cortisol levels as well as psychological stress in patients with *T. gondii* found a notable statistical association. The study revealed that toxoplasmosis patients exhibited elevated levels of testosterone and cortisol in their blood plasma. In addition, they showed elevated levels of stress and anxiety. However, it was observed that only males with toxoplasmosis experienced an increase in depression, as indicated by the study conducted by (Shirbazou *et al.,* 2011). One hypothesis or explanation put forward to understand the high levels of steroid hormones in patients with toxoplasmosis suggests that a combination of weakened cellular immunity and increased steroid hormone levels plays a significant role in enabling the parasite to persist in the infected person's body. The rise in steroid hormones, coupled with a compromised immune system, aids parasite survival in the infected individual. Survival is the primary objective of the parasite, as highlighted in Flegr *et al* research. In 1996 several studies have revealed that latent toxoplasmosis leads to a reduction in corticosterone hormone secretion due to the withdrawal of dendrites from the basolateral amygdala. This reduction significantly contributes to various behavioral abnormalities, as demonstrated in (Mitra *et al.,* 2013).

Thyroid hormones

Since *T. gondii* can infect numerous organs within the human body, such as the brain, eyes, muscles, and various visceral organs, its impact is particularly significant when it infiltrates the brain. In such cases, it can stimulate the hypothalamus nerves, leading to disruption of TSH secretion and abnormal secretion of T3 and T4 hormones. Furthermore, it can cause the thyroid gland to undergo changes, as well as notably elevate thyroid peroxidase levels. This is highlighted by research conducted by (Al-Issawi and Aysir, 2020). A study conducted in the Kurdistan Region of Iraq aimed to explore the link between latent toxoplasmosis and thyroid hormone levels in schizophrenia patients. The investigation indicated that schizophrenia patients had a higher likelihood of contracting toxoplasmosis. Moreover, *T. gondii* infection resulted in elevated levels of serum T3 and T4 hormones in patients with schizophrenia. Consequently, the study suggests that treatment and screening programs for toxoplasmosis should be prioritized among schizophrenia patients (Mohammed and Mageed, 2022). *T. gondii*-infected Nylar female mice eventually developed hypogonadotropic hypogonadism due to the hypothalamic dysfunction. In these animals, *T. gondii* infection lowers serum thyroxine (T4) levels. Infertility can result from the hypogonadotropic hypogonadism, a reproductive system condition. Serum thyroxine insufficiency may play a role in metabolic problems in these animals (Galvan-Ramirez *et al.,* 2014).

CONCLUSION:

The present study revealed findings that challenge the prevailing consensus regarding toxoplasmosis. It reveals its typical asymptomatic nature or manifestation of flu-like symptoms, and its ability to remain dormant throughout a patient's life. Recent research suggests that it poses a significant risk, particularly to those with compromised immune systems, as it can reactivate later. Moreover, this parasitic infection influences psychological and neurological behavior by impacting the production of specific hormones and neurotransmitters. Notably, the *T. gondii* infection is associated with increased susceptibility to mental health disorders such as schizophrenia, autism, Alzheimer's, and bipolar disorder. In addition, it has been associated with behavioral changes like impulsivity and aggression. It is therefore crucial to fully understand the potential ramifications of this parasite on both physical and mental well-being. Moreover, infection with this parasite can alter the secretion rates of various hormones and neurotransmitters, including the dopamine, thyroid hormones, cortisol, and sex hormones.

ACKNOWLEDGEMENT:

All authors contributed evenly to this study. The researchers have emphasized that they have no source of funding.

CONFLICTS OF INTEREST:

The authors state that they have no conflicts of interest regarding the publication of this study

REFERENCES:

1) Aabasian, L., Damghani, S., & Delpisheh, A. (2013). Hormonal changes in women with breast cancer infected with *Toxoplasma gondii*. *J. Basic Res. Med. Sci*., **3**(1), 16-21.
2) Al-Issawi, T. A. M., & Mohammed, A. S. (2020). Effects of Infection with *Toxoplasma gondii* to the Levels of Thyroid Hormones. *Eur J Mol Clin Med*., **7**(1), 110-114. http://doi.org/10.5334/ejmcm.288
3) Al Malki, J. S., Hussien, N. A., & Al Malki, F. (2021). Maternal toxoplasmosis and the risk of childhood autism: serological and molecular small-scale studies. *BMC Pediatr*., **21**(1), 1-9. https://doi.org/10.1186/s12887-021-02604-4
4) Alvarado-Esquivel, C., Estrada-Martínez, S., & Saenz-Soto, L. (2022). *Toxoplasma gondii* infection and insomnia: A case control seroprevalence study. *PloS one*, **17**(6), e0266214. https://doi.org/10.1371/journal.pone.0266214
5) Al-Warid, H. S., & Al-Qadhi, B. N. (2012). Evaluation of progesterone and estrogen hormonal levels in pregnant women with toxoplasmosis. *Eur J Sci Res*., **91**(4), 515-519.
6) Avelino, M. M., Costa, T. L., & Castro, A. M. (2014). Congenital toxoplasmosis and prenatal care state programs. *BMC Infect. Dis.,* **14**(1), 1-13. https://doi.org/10.1186/1471-2334-14-33
7) Berdoy, M., Webster, J. P., & Macdonald, D. W. (1995). Parasite-altered behavior is the effect of

Toxoplasma gondii on Rattus norvegicus specific. *Parasitol*, **111**(4), 403-409. https://doi.org/10.1017/S0031182000065902

8) Berdoy, M., Webster, J. P., & Macdonald, D. W. (2000). Fatal attraction in rats infected with *Toxoplasma gondii*. Proceedings of the Royal Society of London. Series B: *Biol. sci.*, **267**(1452), 1591-1594. https://doi.org/10.1098/rspb.2000.1182
9) Bergner, R. M. (1997). What is psychopathology? And so, what? *Clinical Psychology: Science and Practice*, **4**(3), 235–248. https://doi.org/10.1111/j.1468-2850.1997.tb00112.x
10) Bogitsh, B. J., Carter, C. E., & Oeltmann, T. N. (2018). Human parasitology. *Academic Press*.
11) Brüne, M. (2019). Latent toxoplasmosis: host–parasite interaction & psychopathology. Evolution, *Medicine, and Public Health*, **2019**(1), 212-213. https://doi.org/10.1093/emph/eoz032
12) Brüne, M. (2020). Schizophrenia as parasitic behavior manipulation: can we put together the pieces of an evolutionary puzzle? *World Psychiatry*, **19**(1), 119. https://doi.org/10.1002/wps.20637
13) Campos-Carli, S. M., Salgado, J. V., & Teixeira, A. L. (2017). *Toxoplasma gondii* infection and chronic schizophrenia is there any association. *Arch. Clin. Psychiatry (Sao Paulo).* **44**, 145-148. https://doi.org/10.1590/0101-60830000000140
14) Carruthers, V. B., & Suzuki, Y. (2007). Effects of *Toxoplasma gondii* infection on the brain. *Schizophr. Bull*., **33**(3), 745-751. https://doi.org/10.1093/schbul/sbm008
15) Çelik, T., Akarsu, G. A., Gozukara, H., & Unal, S. (2015). Association between latent toxoplasmosis and clinical course of schizophrenia-continuous course of the disease is characteristic for *Toxoplasma gondii*-infected patients. *Folia Parasitol*, **62**, pii-2015. https://doi.org/10.14411/fp.2015.015
16) Cicchetti, D. (2016). Socioemotional, personality, and biological development: Illustrations from a multilevel developmental psychopathology perspective on child maltreatment. *Annu. Rev. Psychol.,* **67**, 187-211. https://doi.org/10.1146/annurev-psych-122414-033259
17) Del Giudice, M. (2019). Invisible designers: Brain evolution through the lens of parasite manipulation. *Q. Rev. Biol.,* **94**(3), 249-282. https://doi.org/10.1086/705038
18) Del Giudice, M., & Ellis, B. J. (2016). Evolutionary foundations of developmental psychopathology. In D. Cicchetti (Ed.), Developmental psychopathology: *Developmental neuroscience* (pp. 1 - 58). *John Wiley and Sons, Inc*.
19) Del Grande, C., Dell'Osso, L., & Bruschi, F. (2017). Is *Toxoplasma gondii* a trigger of bipolar disorder? *Pathog*, **6**(1), 3. https://doi.org/10.3390/pathogens6010003
20) Demyttenaere, K., Bruffaerts, R., & Chatterji, S. (2004). Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys**.** *J. Am. Med. Assoc*. **291**(21), 2581-2590. https://doi.org/10.1001/jama.291.21.2581
21) Di Carlo, P., Mazzola, A., & Titone, L. (2008). Materno-fetal *Toxoplasma gondii* infection: critical review of available diagnostic methods. *Le Infezioni in Medicina*, **16**(1), 28-32. PMID: 18367880
22) Dickerson, F., Origoni, A., & Yolken, R. (2007). *Toxoplasma gondii* in individuals with schizophrenia: association with clinical and demographic factors and with mortality. *Schizophr. Bull.,* **33**(3), 737-740. https://doi.org/10.1093/schbul/sbm005
23) Dubey, J. P. (2009b). Toxoplasmosis in sheep - the last 20 years. *Vet parasitol*, **163**(1-2), 1-14. https://doi.org/10.1016/j.vetpar.2009.02.026
24) Dubey, J. P., & Beattie, C. P. (1988). Toxoplasmosis of animals and man. *CRC Press*, *Inc*.
25) Dubey, J. P., Lindsay, D. S., & Lappin, M. R. (2009). Toxoplasmosis & other intestinal coccidial infections in cats and dogs. Veterinary Clinics*: J Small Anim Pract*., **39**(6), 1009-1034. https://doi.org/10.1016/j.cvsm.2009.08.001
26) Elsheikha, H. M., Büsselberg, D., & Zhu, X. Q. (2016). The known and missing links between *Toxoplasma gondii* and schizophrenia. *Metab. Brain Dis.,* **31**(4), 749-759. https://doi.org/10.1007/s11011-016-9822-1

27) Elzeky, S. M., Handoussa, A. E., & Hamouda, M. M. (2022). Seroprevalence and Genetic Characterization of *Toxoplasma gondii* among Children with Neurodevelopmental Disorders in Egypt. *J. Trop. Med*., 2022. https://doi.org/10.1155/2022/2343679

28) Fabiani, S., Pinto, B., & Bruschi, F. (2013). Toxoplasmosis and neuropsychiatric diseases: can serological studies establish a clear relationship? *Neurol. Sci.,* **34**(4), 417-425. https://doi.org/10.1007/s10072-012-1197-4

29) Fekadu A, Shibre T, Cleare AJ. (2010). Toxoplasmosis as a cause for behavior disorders-overview of evidence and mechanisms. *Folia Parasitol*., **57**(2), 105. https://doi.org/10.14411/fp.2010.013

30) Fekadu, A., Shibre, T., & Cleare, A. J. (1996). Induction of changes in human behavior by the parasitic protozoan *Toxoplasma gondii*. *Parasitol*, **113**(1), 49-54. https://doi.org/10.1017/S0031182000066269

31) Flegr, J. (2013). Influence of latent *Toxoplasma* infection on human personality, physiology, and morphology: pros and cons of the Toxoplasma–human model in studying the manipulation hypothesis. *J. Exp. Biol.,* **216**(1), 127-133. https://doi.org/10.1242/jeb.073635

32) Flegr, J., & Hrdy, I. (1994). Influence of chronic toxoplasmosis on some human personality factors. *Folia Parasitol.,* **41**(2), 122-126. PMID: 7927062

33) Flegr, J., Hůla, M., & Sýkorová, K. (2017). Effects of latent toxoplasmosis on olfactory functions of men and women. *bioRxiv,* 231795. https://doi.org/10.1101/231795

34) Flegr, J., Lenochová, P., Hodný, Z., & Vondrová, M. (2011). Fatal attraction phenomenon in humans – cat odor attractiveness increased for Toxoplasma-infected men while decreased for infected women. *PLOS Negl. Trop. Dis*., **5**(11), e1389. https://doi.org/10.1371/journal.pntd.0001389

35) Flegr, J., Prandota, J., Sovičková, M., & Israili, Z. H. (2014). Toxoplasmosis – a global threat. Correlation of latent toxoplasmosis with specific disease burden in a set of 88 countries. *PloS one,* **9**(3), e90203. https://doi.org/10.1371/journal.pone.0090203

36) Flegr, J., Vitáková, M., & Kodym, P. (2003). Decreased level of psychobiological factor novelty seeking and lower intelligence in men latently infected with the protozoan parasite *Toxoplasma gondii* Dopamine, a missing link between schizophrenia and toxoplasmosis. *Biol. Psychol*., **63**(3), 253-268. https://doi.org/10.1016/S0301-0511(03)00075-9

37) Fond, G., Capdevielle, D., & Boulenger, J. P. (2012). *Toxoplasma gondii*: A potential role in the genesis of psychiatric disorders. *L'encephale, epub-ahead*.; **39**(1), 38-43. https://doi.org/10.1016/j. encep.2012.06.014

38) Frenkel, J. K., Dubey, J. P., & Miller, N. L. (1970). *Toxoplasma gondii* in cats: fecal stages identified as coccidian oocysts. *Science*, **167**(3919), 893-896. https://doi.org/10.1126/science.167.3919.89

39) Galvan-Ramirez, M. D. L. L., Gutiérrez-Maldonado, A. F., Verduzco-Grijalva, F. (2014). The role of hormones on *Toxoplasma gondii* infection: a systematic review. *Front. Microbiol,* **5**, 503. https://doi.org/10.3389/fmicb.2014.00503

40) Gaskell, E. A., Smith, J. E., Pinney, J. W., Westhead, D. R., & McConkey, G. A. (2009). A unique dual activity amino acid hydroxylase in *Toxoplasma gondii*. *PloS one*, **4**(3), e4801. https://doi.org/10.1371/journal.pone.0004801

41) Golbe, L. I., Mark, M. H., & Sage, J. I. (2010). Parkinson's disease handbook. America: *The American Parkinson Disease Association. Inc*.

42) Gonzalez, L. E., Rojnik, B., & Hernandez, L. (2007). *Toxoplasma gondii* infection lower anxiety as measured in the plus-maze and social interaction tests in rats: a behavioral analysis. *Behav. Brain Res*.., **177**(1), 70-79. https://doi.org/10.1016/j.bbr.2006.11.012

43) Gould, S. B., Tham, W. H., Cowman, A. F., McFadden, G. I., & Waller, R. F. (2008). Alveolins, a new family of cortical proteins that define the protist infrakingdom Alveolata. *Mol. Biol. Evo,* **25**(6), 1219-1230. https://doi.org/10.1093/molbev/msn070

44) Gunn, A., & Pitt, S. J. (2012). Helminth parasites. *Parasitology:* an integrated approach, 86-136.

45) Hadiloo N. (2023). Enhancing psychological development in children with disabilities: the power of environment and family, *Eur. J. Med. Health Sci*., **5**(5), 108-117. https://doi.org/10.34104/ejmhs.023.01080117

46) Hamdani, N., Daban-Huard, C., & Leboyer, M. (2013). Relationship between *Toxoplasma gondii* infection and bipolar disorder in a French sample. *J. Affect. Disord.,* **148**(2-3), 444-448. https://doi.org/10.1016/j.jad.2012.11.034

47) Hari Dass, S. A., & Vyas, A. (2014). *Toxoplasma gondii* infection reduces predator aversion in rats through epigenetic modulation in the host medial amygdala. *Mol. Ecol*., **23**(24), 6114-6122. https://doi.org/10.1111/mec.12888

48) Holliman, R. E. (1997). Toxoplasmosis, behavior, and personality. *J. Infect.,* **35**(2), 105-110. https://doi.org/10.1016/S0163-4453(97)91380-3

49) Holub, D., Flegr, J., & Motlová, L. B. (2013). Differences in onset of disease and severity of psychopathology between toxoplasmosis-related and toxoplasmosis-unrelated schizophrenia. *Acta Psychiatr. Scand*.., **127**(3), 227-238. https://doi.org/10.1111/acps.12031

50) Horacek, J., Flegr, J., & Höschl, C. (2012). Latent toxoplasmosis reduces gray matter density in schizophrenia but not in controls: voxel-based-morphometry (VBM) study. *World J. Biol. Psychiatry*., **13**(7), 501-509.

51) Hrdá, Š., Votýpka, J., Kodym, P., & Flegr, J. (2000). Transient nature of *Toxoplasma gondii*-induced behavioral changes in mice. *Parasitol*., **86**(4), 657-663. https://doi.org/10.1645/0022-3395(2000)086[0657:TNOTGI]2.0.CO;2

52) Hunt, N. H., Too, L. K., & Ball, H. J. (2017). The kynurenine pathway and parasitic infections that affect CNS function. *Neuropharmacology*, **112**, 389-398. https://doi.org/10.1016/j.neuropharm.2016.02.029

53) Inceboz, M., & Inceboz, T. (2021). Toxoplasmosis and Neuropsychological Effects. *Turkiye Parazitol Derg,* 45(1), 49-55. https://doi.org/10.4274/tpd.galenos.2020.6973

54) Israelski, D. M., & Remington, J. S. (1988). Toxoplasmic encephalitis in patients with AIDS. *Infect. Dis. Clin. N. Am..,* **2**(2), 429-446.

55) Johnson, S. K., Fitza, M. A., & Johnson, P. T. (2018). Risky business: linking Toxoplasma gondii infection and entrepreneurship behaviors across individuals and countries. Proceedings of the Royal Society B: *Biol. sci.*, **285**(1883), 20180822. https://doi.org/10.1098/rspb.2018.0822

56) Jones, J. L., Lopez, A., & Gibbs, R. (2001). Congenital toxoplasmosis: a review. *Obstet Gynecol Surv*., **56**(5), 296-305.

57) Kittas, C., & Henry, L. (1979). Effect of sex hormones on the immune system of Guinea pigs and on the development of Toxoplasmic lesions in non-lymphoid organs. *Clin. Exp. Immunol.,* **36**(1), 16. PMCID: PMC1537697

58) Krause, D. L., & Müller, N. (2012). The relationship between Tourette's syndrome and infections. *Open Neurol. J..,* **6**(1). https://doi.org/10.2174/1874205X01206010124

59) Lachenmaier, S. M., Meissner, M., & Liesenfeld, O. (2011). Intracellular transport of *Toxoplasma gondii* through the blood - brain barrier. *J. Neuroimmunol,* **232**(1-2), 119-130. https://doi.org/10.1016/j.jneuroim.2010.10.029

60) Maddux, J. E., & Winstead, B. A. (Eds.). (2015). Psychopathology: Foundations for a contemporary understanding. *Routledge*.

61) Manning, N. (2019). Sociology, biology, and mechanisms in urban mental health. *Soc. Theory Health.* **17**, 1-22. https://doi.org/10.1057/s41285-018-00085-7

62) McConkey, G. A., Martin, H. L., Bristow, G. C., & Webster, J. P. (2013). *Toxoplasma gondii* infection and behavior - location, location, location? *J. Exp. Biol*.., **216**(1), 113-119. https://doi.org/10.1242/jeb.074153

63) Miman, O., Aktepe, O. C., & Cetinkaya, Z. (2010). The probable relation between *Toxoplasma gondii* and Parkinson's disease. *Neurosci. Lett.,* **475**(3), 129-131. https://doi.org/10.1016/j.neulet.2010.03.057

64) Mitra, R., Sapolsky, R. M., & Vyas, A. (2013). *Toxoplasma gondii* infection induces dendritic retraction in basolateral amygdala accompanied by reduced corticosterone secretion. *Dis Model Mech*, **6**(2), 516-520. https://doi.org/10.1242/dmm.009928

65) Mohammed, A. K., & Mageed, S. N. (2022). Correlation between latent toxoplasmosis and thyroid hormone levels in sera of schizophrenic patients. *GSC Biol. Pharm. Sci..,* **21**(1), 033-041. https://doi.org/10.30574/gscbps.2022.21.1.0364

66) Montoya, J. G., & Contopoulos - Ioannidis, D. (2021). Toxoplasmosis. *Neglected Tropical Diseases - North America*, 69-91.

67) Montoya, J. G., & Remington, J. S. (2008). Management of *Toxoplasma gondii* Infection during Pregnancy. *Clin. Infect. Dis.*, **47**, 554 - 66. https://doi.org/10.1086/590149

68) Mortensen, P. B., Torrey, E. F., & Yolken, R. H. (2007). *Toxoplasma gondii* as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth. *Biol. Psychiatry.*, **61**(5), 688-693. https://doi.org/10.1016/j.biopsych.2006.05.024

69) Nayeri, T., Sharif, M., & Daryani, A. (2021). *Toxoplasma gondii*: A possible etiologic agent for Alzheimer's disease. *Heliyon*, **7**(6), e07151. https://doi.org/10.1016/j.heliyon.2021.e07151

70) Niebuhr, D. W., Li, Y., & Weber, N. (2007, March). Risk of schizophrenia and antibodies to *Toxoplasma gondii* among US military personnel. In Schizophrenia Bulletin, **33**(2), 243-244. GREAT CLARENDON ST, OXFORD OX2 6DP, *ENGLAND: OXFORD UNIV PRESS*.

71) O'Shaughnessy, P. J., & Fowler, P. A. (2014). Development of the human fetal testis. In Annales d'endocrinologie. *Elsevier Masson*, **75**, 48-53. https://doi.org/10.1016/j.ando.2014.03.009

72) Oktenli, C., Doganci, L., & Inal, A. (2004). Transient hypogonadotropic hypogonadism in males with acute toxoplasmosis: suppressive effect of interleukin-1β on the secretion of GnRH. *Hum. Reprod.*, **19**(4), 859 - 866. https://doi.org/10.1093/humrep/deh161

73) Owen, M. J., Sawa, A. & Mortensen, P. B. (2016). Schizophrenia. *Lancet,* **388**(10039), 86 - 97

74) Pappas, G., Roussos, N., & Falagas, M. E. (2009). Toxoplasmosis snapshots: global status of *Toxoplasma gondii* seroprevalence and implications for pregnancy and congenital toxoplasmosis. *Parasitol. Int.*, **39**(12), 1385 - 1394. https://doi.org/10.1016/j.ijpara.2009.04.003

75) Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *Trends Cogn. Sci..*, **9**(2), 60 - 68. https://doi.org/10.1016/j.tics.2004.12.008

76) Pearce, B. D., Hubbard, S., & Duncan, E. (2013). *Toxoplasma gondii* exposure affects neural processing speed as measured by acoustic startle latency in schizophrenia and controls. *Schizophr. Res*, **150**(1), 258-261. https://doi.org/10.1016/j.schres.2013.07.028

77) Poirotte, C., Moussodji, M., & Charpentier, M. J. (2016). Morbid attraction to leopard urine in Toxoplasma-infected chimpanzees. *Curr. Biol..*, **26**(3), R98-R99. https://doi.org/10.1016/j.cub.2015.12.020

78) Poulin, R. (1995). "Adaptive" changes in the behavior of parasitized animals: a critical review. *Parasitol. Int..*, **25**(12), 1371-1383. https://doi.org/10.1016/0020-7519(95)00100-X

79) Prandovszky E, Webster JP, and McConkey GA. (2011). The neurotropic parasite *Toxoplasma gondii* increases dopamine metabolism. *PloS one,* **6**(9), e23866. https://doi.org/10.1371/journal.pone.0023866

80) Prandovszky, S., Knappskog, K. J., & Andreassen, O. A. (2020). Effects of inflammation on dopamine function and psychosis: A review. *Neurosci Biobehav Rev.*, **108**, 1-19. https://doi.org/10.1016/j.neubiorev.2020.01.006

81) Příplatová, L., Šebánková, B., & Flegr, J. (2014). Contrasting effect of prepulse signals on performance of *Toxoplasma*-infected and *Toxoplasma*-free subjects in an acoustic reaction times test. *PLoS One,* **9**(11), e112771. https://doi.org/10.1371/journal.pone.0112771

82) Qayyum, A., C Zai, C., & Kennedy, L. (2015). The role of the catechol-o-methyltransferase (COMT) GeneVal158Met in aggressive behavior, a review of genetic studies. *Curr. Neuropharmacol.*, **13**(6), 802-814. https://doi.org/10.2174/1570159X13666150612225836

83) Rantala, M. J., Krama, T., & Krams, I. (2019). Eating disorders: an evolutionary psychoneuroimmunology approach. *Front. Psychol*, **10**, 2200. https://doi.org/10.3389/fpsyg.2019.02200

84) Robert-Gangneux, F., & Dardé, M. L. (2012). Epidemiology of and diagnostic strategies for toxoplasmosis. *Clin. Microbiol. Rev.* **25**(2), 264-296. https://doi.org/10.1128/CMR.05013-11

85) Roberts, A., Hedman, K., & Petersen, E. (2001). Multicenter evaluation of strategies for sero-diagnosis of primary infection with *Toxoplasma gondii*. *Eur. J. Clin. Microbiol. Infect. Dis..,* **20**, 467-474. https://doi.org/10.1007/PL00011289

86) Roberts, C. W., Walker, W., & Alexander, J. (2001). Sex-associated hormones and immunity to protozoan parasites. *Clin. Microbiol. Rev*., **14**(3), 476-488. https://doi.org/10.1128/CMR.14.3.476-488.2001

87) Schmidt-Hieber, M., Blau, I. W., & Thiel, E. (2009). Central nervous system infections in immunecompromised patients – update on diagnostics and therapy. *Leuk. Lymphoma.,* **50**(1), 24-36. https://doi.org/10.1080/10428190802517740

88) Shirbazou, S., Abasian, L., & Meymand, F. T. (2011). Effects of *Toxoplasma gondii* infection on plasma testosterone and cortisol level and stress index on patients referred to Sina hospital, Tehran. *Jundishapur J. Microbiol.,* **4**(3), 167-173.

89) Siberry, G. K., Abzug, M. J., & Nesheim, S. (2013). Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *Pediatr. Infect. Dis. J..,* **32**(02), I. https://doi.org/10.1097/01.inf.0000437856.09540.11

90) Silva, N. M., Rodrigues, C. V., & Gazzinelli, R. T. (2002). Expression of indoleamine 2, 3-dioxygenase, tryptophan degradation, and kynurenine formation during in vivo infection with *Toxoplasma gondii:* induction by endogenous gamma interferon and requirement of interferon regulatory factor 1. *Infect. Immun..,* **70**(2), 859-868. https://doi.org/10.1128/IAI.70.2.859-868.2002

91) Singh, D. K., Hari Dass, Sd. A., Abdulai-Saiku, S., & Vyas, A. (2020). Testosterone acts within the medial amyg ala of rats to reduce innate fear to predator odor akin to the effects of *Toxoplasma gondii* infection *Front. Psychiatry*., **11**, 630. https://doi.org/10.3389/fpsyt.2020.00630

92) Skariah, S., McIntyre, M. K., & Mordue, D. G. (2010). *Toxoplasma gondii*: determinants of tachyzoite to bradyzoite conversion. *Parasitol. Res.,* **107**, 253-260. https://doi.org/10.1007/s00436-010-1899-6

93) Stiles, J., & Jernigan, T. L. (2010). The basics of brain development. *Neuropsychol. Rev..,* **20**(4), 327-348. https://doi.org/10.1007/s11065-010-9148-4

94) Sutterland, A. L., Fond, G., & De Haan, L. (2015). Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. *Acta Psychiatr. Scand*., **132**(3), 161-179. https://doi.org/10.1111/acps.12423

95) Tenter, A. M., Heckeroth, A. R., & Weiss, L. M. (2000). *Toxoplasma gondii*: from animals to humans. *Parasitol. Int..,* **30**(12-13), 1217-1258. https://doi.org/10.1016/S0020-7519(00)00124-7

96) Tong, W. H., Abdulai-Saiku, S., & Vyas, A. (2019). Testosterone reduces fear and causes drastic hypomethylation of arginine vasopressin promoter in medial extended amygdala of male mice. *Front. Behav. Neurosci.,* **13**, 33. https://doi.org/10.3389/fnbeh.2019.00033

97) Tong, W. H., Abdulai-Saiku, S., & Vyas, A. (2021). Medial amygdala arginine vasopressin neurons regulate innate aversion to cat odors in male mice. *Neuroendocrinology*, **111**(6), 505-520. https://doi.org/10.1159/000508862

98) Tong, W. H., Pavey, C., O'Handley, R., & Vyas, A. (2021b). Behavioral biology of *Toxoplasma gondii* infection. *Parasit. Vectors.,* **14**(1), 1-6. https://doi.org/10.1186/s13071-020-04528-x

99) Torgerson, P. R., & Macpherson, C. N. (2011). The socioeconomic burden of parasitic zoonoses: global trends. *Vet parasitol*, **182**(1), 79-95. https://doi.org/10.1016/j.vetpar.2011.07.017

100) Torrey, E. F., Bartko, J. J., & Yolken, R. H. (2012). *Toxoplasma gondii* and other risk factors for schizophrenia: an update. *Schizophr. Bull.,* **38**(3), 642-647. https://doi.org/10.1093/schbul/sbs043

101) Torrey, E. F., & Yolken, R. H. (2019). Schizophrenia as a pseudogenetic disease: A call for more gene-environmental studies. *Psychiatry Res.,* **278**, 146-150. https://doi.org/10.1016/j.psychres.2019.06.006

102) Torrey, E. F., Bartko, J. J., Lun, Z. R., & Yolken, R. H. (2007). Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis. *Schizophr. Bull.,* **33**(3), 729-736. https://doi.org/10.1093/schbul/sbl050

103) Vyas, A. (2015). Mechanisms of host behavioral change in *Toxoplasma gondii* rodent association. *PLoS Pathog*., **11**(7), e1004935. https://doi.org/10.1371/journal.ppat.1004935

104) W.H.O. World Health Organization. (2001). World Health Report 2001. Mental Health: New Understanding, New Hope. *World Health Organization, Geneva*.

105) Wang, H. L., Jiang, M. S., & Guo, Y. (2006). Prevalence of *Toxoplasma* infection in first-episode schizophrenia and comparison between *Toxoplasma*-seropositive & *Toxoplasma*-seronegative schizophrenia. *Acta Psychiatr. Scand*.., **114**(1), 40 - 48. https://doi.org/10.1111/j.1600-0447.2006.00780.x

106) Wang, P. S., Aguilar-Gaxiola, S., & Wells, J. E. (2007). Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. *The Lancet*, **370**(9590), 841 - 850. https://doi.org/10.1016/S0140-6736(07)61414-7

107) Wang, T., Zhou, J., & Yu, L. (2014). *Toxoplasma gondii* induce apoptosis of neural stem cells via endoplasmic reticulum stress pathway. *Parasitol*, **141**(7), 988-995. https://doi.org/10.1017/S0031182014000183

108) Webster, J. P. (1994). The effect of *Toxoplasma gondii* and other parasites on activity levels in wild and hybrid Rattus norvegicus. *Parasitol*, **109**(5), 583-589. https://doi.org/10.1017/S0031182000076460

109) Webster, J. P. (2001). Rats, cats, people, and parasites: the impact of latent toxoplasmosis on behavior. *Microbes Infect.*, **3**(12), 1037-1045. https://doi.org/10.1016/S1286-4579(01)01459-9

110) Webster, J. P., Kaushik, M., & McConkey, G. A. (2013). *Toxoplasma gondii* infection, from predation to schizophrenia: can animal behavior help us understand human behavior*? J. Exp. Biol*.., **216**(1), 99-112. https://doi.org/10.1242/jeb.074716

111) Webster, J. P., Lamberton, P. H. L., & Torrey, E. F. (2006). Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood-stabilizer, and anti-parasite medication on *Toxoplasma gondii's* ability to alter host behavior. Proceedings of the Royal Society B: *Biological Sciences*, **273**(1589), 1023-1030. https://doi.org/10.1098/rspb.2005.3413

112) Willner, P. (1997). The dopamine hypothesis of schizophrenia: current status, future prospects. *Int. Clin. Psychopharmacol*., **12**, 297-308. https://doi.org/10.1097/00004850-199711000-00002

113) Xiao, J., Severance, E. G., & Yolken, R. H. (2018). *Toxoplasma gondii*: biological parameters of the connection to schizophrenia. *Schizophr. Bull*, **44**(5), 983-992. https://doi.org/10.1093/schbul/sby082

114) Yoon, H. S., Grant, J., & Katz, L. A. (2008). Broadly sampled multigene trees of eukaryotes. *BMC Evol. Biol.* **8**(1), 1-12. https://doi.org/10.1186/1471-2148-8-14

115) Yuan, Z., Liu, B., & Hu, R. (2007). *Toxoplasma gondii* antibodies in cancer patients. *Cancers,* **254**(1), 71-74. https://doi.org/10.1016/j.canlet.2007.02.011

Citation: Dardona Z, Amane M, and BOUSSAA S. (2023). Toxoplasmosis-related psychological, behavioral, neurological, and hormonal changes: a literature review, *Eur. J. Med. Health Sci.*, **5**(5), 128-144. https://doi.org/10.34104/ejmhs.023.01280144