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TOXOPLASMOSIS AND RISK OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND MAJOR DEPRESSIVE DISORDER: A REVIEW ARTICLE

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Abstract

Toxoplasmosis is a worldwide disease caused by *Toxoplasma gondii* which is an obligate intracellular parasite that affects warm-blooded mammals including man. *T. gondii* neurotropic nature made it a potential causative agent for psychiatric and behavioral disorders. *T. gondii* uses a complicated mechanism to gain access to the brain, where it invades different brain cells, including astrocytes and neurons forming cysts. Attention deficit hyperactivity disorder (ADHD) represents a neuropsychiatric alarm-ing concern due to its indefinite etiopathogenesis among children. Depression as major depressive disorder (MDD) is a common and serious psychiatric illness that negatively affects feeling, thinking and acting. Owing to the high prevalence of toxoplasmosis and the increased incidence of ADHD and MDD in recent years, this review studied the relationship between toxoplasmosis and each of ADHD and MDD.

Keywords: *Toxoplasma gondii*, Psychiatric disorders, Mental disorder, Attention deficit hyperactivity disorder, Depression, Major depressive disorder.

Introduction

Toxoplasmosis, a parasitic infection caused by the protozoan *T. gondii*, was identified as a "new disease" in Egypt (Ruge, 1952). Since then, many studies were published indicating its importance in Egypt (Taman and Alhusseiny, 2020). Attention-deficit hyperactivity disorder is a neurodevelopmental disorder, with symptoms such as inattention and hyperactivity (Afsharpaiman *et al,* 2017). Major depressive disorder, also referred to as depression, is often accompanied by loss of interest and decreased self-esteem (Arling *et al,* 2009). Association between *T. gondii* infection, neuropsychiatric disorders, and personality changes was suggested in the early 1990s (Havlícek *et al,* 2001).

Review and Discussion

Toxoplasmosis is found worldwide, and is estimated to have infected up to one-third of the global population (de Bles *et al,* 2021). It is a highly prevalent zoonosis where the definitive host of *T. gondii* is cat, which harbors the sexual parasitic cycle in the feline intestine and spreads infectious oocysts via feces, while the asexual reproduction of the parasite takes place in a broad spectrum of intermediate hosts, including humans who represent dead-end hosts of *T. gondii* (Imam *et al,* 2022). Human infection is often via the ingestion of sporulated oocysts detected on vegetables or in water and soil and eating raw or uncooked meat of infected animals. The nosocomial transmission was associated with blood transfusion, needle-stick injury and hematopoietic stem cell transplantation (Hussein *et al,* 2022). In pregnant women congenital transmission occurred (Al-Agroudi *et al,* 2016). *T. gondii* infection in effective immune response, fast-replicated tachyzoites were cleared, but some parasites are converted into bradyzoites persisted in cysts, predominantly in brain; astrocytes, microglia and neurons, or in muscle tissues (Weiss and Kim, 2000). Acute infection presents as mild flu-like symptoms, largely controlled by a healthy immune system (Kamal *et al,* 2023). Clinically silent or latent infection in immunocompromised patients; AIDS, organ transplantation, and on chemotherapy, toxoplasmosis causes risky reactivated infection (Nissapatorn, 2017). Also, latent infection caused fatal encephalitis (Robert-Gangneux and Darde, 2012).

A fascinating effect of the neurotropic apicomplexan parasite on rodent' behavior was

its ability to cause them to lose their natural aversion to cat odors (Vyas *et al,* 2007), with behavioral showed evidence that latent toxoplasmosis may lead to behavioral changes, the so-called manipulation hypothesis (Webster and McConkey, 2010). There was a less fear by rodents toward cats, which are the only definitive host, and so this cunning intracellular parasite manipulated its host, increasing the parasite's chance to be transmitted by cats (Tyebji *et al,* 2019).

Toxoplasma gondii was one of the causes of mental disorders (Sutterland *et al,* 2015). Its role in developing psychiatric illnesses was directly by affecting neurons, glial cell, and brain structures, or indirectly by causing a specific immune response, releasing proinflammatory cytokines and neurotoxic factors (Del Grande *et al,* 2017). An *in-vivo* study showed that *T. gondii* in mammalian dopaminergic cells repeatedly raised dopamine-dependent potassium secretion (Prandovszky *et al,* 2001). Staining infected rats' brains with dopamine-specific antibodies resulted in strong staining of cysteine-containing regions, and tyrosine hydroxylase, a limited enzyme in dopamine production, was within intracellular cysts. They concluded that *T. gondii* plays an important role in increasing dopamine metabolism in neurons, a process that led to neurologic and psychiatric disorders, such as ADHD (Akaltun *et al,* 2018a).

The attention-deficit hyperactivity disorder (ADHD), as one of the common neurodevelopmental disorders, is a chronic condition with onset before 12 years of age (Afsharpaiman *et al.,* 2017). It is neurodevelopmental disorder that occurs by developed and developing countries and was more common in males than females (Rommelse *et al,* 2017). The clinicians increased recognition of this disorder is more likely today than in before. ADHD affected about 3-7% of school-aged children (Arabgol *et al,* 2009), but the adult ADHD has a worldwide prevalence of 2.8% (Fayyad *et al,* 2017). In Egypt, the incidence was up to 21.8% (Azzam *et al,* 2021). The ADHD clinical presentation was primarily inattentive, primarily hyperactive-impulsive, or both, depending on the symptoms' nature (WHO, 2018). Hyperactive-impulsive symptoms are associated with peer rejection, aggression, impaired concentration, and motor restlessness impairing both academic performance and interpersonal relationships (Rommelse *et al,* 2017).

Pathogenesis of ADHD is considered multifactorial. Population-based registry studies in children and adults suggested that infections were associated with an increased risk of mental disorders by a direct influence on the nervous system, immune activation, or inflammatory mediators. But, studies focused on relationship of infective agents and ADHD were scarce (Shehata *et al,* 2016). A wide range of functional and structural brain anomalies had been found to be associated with the disorder, especially in the dopaminergic system (Dunn *et al,* 2019). Also, for most people with ADHD, many genetic and environmental risk factors could accumulate causing disorder **(**Younis *et al,* 2023). Smoking (Becker *et al,* 2008), obesity (Buss *et al,* 2012), Stress (Bronson and Bale, 2014), and mothers' infection (Terasaki and Schwarz, 2016), could be among the factors that have been mentioned in various studies.

Toxoplasmosis might be associated with an increased risk of developing ADHD (Elzeky *et al,* 2022). Attention disorders, in ADHD, were associated with minimal brain damage and many disturbances in neurotransmitter levels, particularly disturbances in the level of dopamine (Akaltun *et al,* 2018a), which were recorded in toxoplasmosis (Nessim *et al,* 2023). Studies comparing infected and uninfected humans in terms of personality traits, behavior, and psychomotor performance as well as intelligence suggested the applicability of manipulation hypothesis of *T. gondii* to man (Martinez *et al,* 2018). Parasite influenced, deregulated dopamine metabolism and disease susceptibility to host' genes (Prandovszky *et al,* 2011)**.** Dopaminergic neurotransmission pathway was strongly related to ADHD developing (Volkow,

2009). *T. gondii* cysts by settling and damaging brain, as well as performing changes in dopaminergic systems and neurotransmitters, may be involved in ADHD severity (Akaltun *et al,* 2018a). Behavioral changes of *T. gondii*-infected rodents resembled patients' clinical symptoms of ADHD (Carter, 2013). Also, resemblance between toxoplasmosis-induced changes and ADHD showed elevated activity levels (Flegr, 2002), deficits in motor performance (Gulinello *et al,* 2010), less anxiety (Afonso *et al,* 2012), increased novelty-seeking behavior (Donfrancesco *et al,* 2015), and increased injury risk (Lindemann *et al,* 2017).

Alvarado-Esquivel *et al.* (2017) found that children with ADHD were more likely to have been exposed to *T. gondii* than those without ADHD. The study of 151 children with ADHD and 149 healthy controls, measured serum IgG antibodies to *T. gondii* levels, showed children with ADHD had higher levels IgG antibodies than healthy controls, suggesting that they had a higher rate of exposure to the parasite. Alvarado-Esquivel (2019) investigated the relationship between toxoplasmosis and ADHD in 100adults and 100 healthy controls; found that adults with ADHD had higher levels of IgM antibodies to *T. gondii* than healthy controls, indicating that they had a more recent infection with the parasite. They also found that the severity of ADHD symptoms positively correlated with levels of IgM antibodies, suggesting that the parasite may be a contributing factor to the development of ADHD.

No doubt, the immune response to *T. gondii* contributed to ADHD development. Toxoplasmosis activates immune system, led to the cytokines production such as interferon-gamma and other immune molecules. These molecules affected brain function, behavior, and contributed to the ADHD symptoms development (Miman *et al,* 2010). Also, parasite affected the brain neurotransmitters levels, such as dopamine and serotonin (Prandovszky *et al,* 2011), which play a role in the ADHD developing (Del Campo, 2011).

Tryptophan is a precursor for serotonin synthesis, required for *T. gondii* growth decreased the concentration of this amino acid, thus, decreasing serotonin level (Cerávolo *et al,* 1999). Inattention, reduced behavioral inhibition, and increased impulsivity caused by decreased serotonin via tryptophan depletion (Banerjee and Nandagopal, 2015). Also, tryptophan catabolism products play a marked role in increasing brain oxidative stress and apoptosis (Schwarcz *et al,* 2012). The interferon-gamma and tumor necrosis factor-α were important on controlling the tachyzoites proliferation in acute and chronic stages of infection (Suzuki, 2002). The interferon-gamma induced the release of indoleamine 2, 3-dioxygenase, which has a role in tryptophan catabolism (Tan *et al,* 2012). So, concentrated indoleamine 2, 3-dioxygenase increased during *T. gondii* infection leading to decreased serotonin synthesis recorded in ADHD (Banerjee and Nandagopal, 2015). *T. gondii* alters the neurotransmitters levels in animals and possible effects may occur in humans (Kamal *et al,* 2022). Also, *T. gondii* could affect the expression of about 3000 host genes throughout its life cycle (Faraone *et al,* 2015). Remarkably, the expression of 17.7% of 237 ADHD susceptibility genes is affected by the *T. gondii* infection (Carter, 2013). Furthermore, it was clarified that the primary common emphasis in ADHD was on calcium signaling pathway and number of other metabolic pathways, such as tyrosine, tryptophan, and histidine, and number of recovered gene in this pathway was 44 (Liao *et al,* 2010). The calcium-signaling pa-thway is activated by voltage or receptorga- ted ion channels, processes modulating intracellular stores, and phosphatidylinositol signaling system (Deckelbaum and Torrejon, 2012). The calcium channel blockers, calmodulin antagonism, or extracellular calcium reduce cell invasion by *T. gondii* (Song *et al,* 2004), and that calcium signaling being essential for cellular and developmental changes supporting *T. gondii* parasitism (Triana *et al,* 2018).

Alexandra *et al*. (2020), they investigated the seropositivity, serointensity, and avidity of latent toxoplasmosis in 140 adult ADHD patients and examined the influence of those variables on ADHD symptomatology, 20% were anti-*T. gondii* IgG seropositive without any anti-IgM. Seropositivity was associated with 2.8-fold increase in the ADHD odds in a confounder-adjusted multivariable analysis, which showed a significant association with *T. gondii* positivity, elevated IgG, with stronger anti-*T. gondii* IgG avidity. All severity increased in *Toxoplasma*-seropositive ADHD patients compared to seronegative ones with ADHD. They concluded that there was a high rate of *T. gondii* seropositivity in adults with ADHD, with a clinical impact of latent *T. gondii* on related symptoms in a serointensity- and avidity-dependent manner.

Major depressive disorder (MDD) is a common psychiatric disorders and serious illness (Li *et al,* 2021), and listed as the third largest cause of disease burden by the WHO since 2008, and may rank the first by 2030 (Dadi *et al,* 2020). Globally, an estimated 5% of adults suffer from depression, women were found to be more affected by depression than men (Institute of Health Metrics & Evaluation, 2023). MDD is often associated with loss of interest, decreased self-esteem, cognitive performance, suppressed energy level, feelings of worthlessness, and changes in weight, with attempt for suicide (Pratt and Brody, 2008). It is a mental disorder characterized by at least two weeks of feeling low mood and disappointment (Halonen and Weiss, 2013). Also, it led to a variety of emotional and physical problems and decreased function ability to work and home. MDD is the commonest mental disorder among behavioral disorders, coupled with remarkable morbidity and mortality (American Psychiatric Association, 2013).

No exact pathological theory explained pathogenesis, as MDD is a multifactorial disease caused by social interaction, psychological, and biological aspects (Li *et al,* 2021). Undoubtedly, latent toxoplasmosis caused behavioral disorders in both mice and humans (Elshafey *et al,* 2023). Studies of toxoplasmosis effect on depression were inconsistent *T. gondii* caused chronic brain inflammatory process and contributed to both depression and its' serious complication, suicidal behavior (Hlaváčová *et al,* 2021). Ozkan *et al.* (2020) reported that the MDD patient became better post toxoplasmosis treatment, which caused depression in immune system increasing suicidal behaviors by inducing monoamine neurotransmitters. Toxoplasmosis in mice increased the level of dopamine (Henriquez *et al,* 2009) and decreased serotonin synthesis in brain (Dalimi and Abdoli, 2012). Increase in dopamine release in neuronal cultures showed cysts (Prandovszky *et al,* 2011). T. *gondii* 2 genes encode tyrosine and phenylalanine hydroxylases catalyzed the conversion of phenylalanine to tyrosine, converted into dopa, the first step in dopamine production modified behavior (Gaskell *et al,* 2009).

The MDD and toxoplasmosis showed that depression was associated with microbias as human herpes-virus, HBV, Chlamydiaceae, and Borna disease virus (Wang *et al,* 2014). But, both Chegeni *et al.* (2019) and de Bles *et al.* (2021) didn't find significant relationship between toxoplasmosis and neither of depression nor affective disorders.

Bahceci *et al.* (2021) showed a correlation between anti-*T. gondii* IgG positivity and depression with suicidal thoughts. Also, Liu *et al.* (2022) recorded a high seroprevalence of *T. gondii* infection in psychiatric patients and that age was an influencing factor. But, Fernandes *et al.* (2020) reported that MDD didn't associate with anti-*T. gondii* IgG and IgM. The depressed patients had a lower seroprevalence of *T. gondii* as compared to controls, and they concluded that toxoplasmosis is not a risk factor for depression.

Studies in rodents and humans have linked *T. gondii* to various neuropsychiatric diseases associated with a dysfunctional dopaminergic system, such as bipolar disorder type I, schizophrenia, depression and Parkinson’s

disease (Fabiani *et al,* 2015), and mood disorders (Torrey and Yolken, 2003). Also, the mood stabilizers and antipsychotics used in bipolar disorder treatment inhibited *T. gondii* replication (Webster *et al,* 2006). Based on the fact that the main neurobiological changes caused by latent toxoplasmosis in man were consistent with the neuropsychiatric disease' pathophysiology as schizophrenia and mood disorders (Fabiani *et al,* 2015). Toxoplasmosis role in developing schizophrenia was proved by a longitudinal study (Niebuhr *et al,* 2007). Changes in brain morphology characterizing schizophrenia, such as gray matter reduction in frontal and temporal cortices, caudate, median cingulate, and thalamus were found typically for *T. gondii*-seropositive schizophrenia patients (Horáček *et al,* 2012). So, *T. gondii*-seropositive patients expressed more prominent positive schizophrenia symptoms (Holub *et al,* 2013), and had a 15-times higher possibility of having a continuous disease course than *T. gondii*-free patients (Celik *et al,* 2015).

T. gondii seropositivity was related to mental illnesses such as schizophrenia, bipolar disorder, generalized anxiety disorder, obsessive-compulsive disorder, suicide, aggression, and impulsivity (Akaltun *et al,* 2018b). But, De Witte *et al*. (2015) didn't find significant relation between psychiatric disorders and toxoplasmosis. Anti- *T. gondii* antibody prevalence of ranged from 10 to 80% (Pan *et al,* 2017). Toxoplasmosis in psychiatric disorders became a heading topic (Hamdani *et al,* 2018).

Chronic *T. gondii* infection led to cortical neurodegeneration and resulted in interaction of complement and microglia, thereby dividing and clearing degenerate neurons (Li *et al,* 2019). Seroprevalence of toxoplasmosis in bipolar disorder patients significantly differed from that in the general population (Chaudhury and Ramana, 2019). However, Şirin *et al.* (2021) reported that bipolar disorder was not associated with toxoplasmosis. *T. gondii* was considered an etiological factor in some schizophrenia cases (Torrey *et al,* 2007). Akgül *et al.* (2021) suggested that toxoplasmosis may be an underlying component of schizophrenia pathophysiology. Liu *et al.* (2022) found that Mania, schizophrenia, bipolar disorder, depression and recurrent depressive disorder were associated with high anti- *T. gondii* antibodies positivity. In a cross-sectional study in (China), they showed that the anti- *T. gondii* IgG and IgM antibodies in psychiatric patients and in the general population were both at low levels, but the positivity rate of anti- *T. gondii* IgG antibody in psychiatric patients was higher than that in general population, indicating that psychiatrist must pay attention to *T. gondii* detection in psychiatric patients. Also, they recorded no significant difference in the positivity rates of anti- *T. gondii* IgM antibody between the general population and psychiatric patients indicating no difference in acute/recent *T. gondii* infection among the general population and psychiatric patients. However, these results disagreed with Chen *et al.* (2019) in China, who showed that anti-*T. gondii* IgG & IgM antibodies were both significantly higher in psychiatric patients than in control. El-Beshbishi *et al.* (2018) in Egypt found high of anti-IgG positivity in neurologically disabled non-syndrome children. Sapmaz *et al.* (2019) reported that toxoplasmosis affected susceptibility and depression severity in children, adolescents and pregnant women.

Conclusion

The relationship between toxoplasmosis and some psychiatric disorders, like ADHD and MDD, must be in consideration. Avoiding *Toxoplasma gondii* infection is a must to manage afflicted patients.

References

Al-Agroudi, MA, Ahmad, GMS, Kondo, MK, Morsy, TA, 2017: An overview of congenital toxoplasmosis: Clinical features, diagnosis, treatment and prevention. JESP 47, 3:523-40.

Afonso, C, Paixao, VB, Costa, RM, 2012: Chronic *Toxoplasma* infection modifes the structure and the risk of host behavior. PLoS One 7, e: 32489. https://doi.org/10.1371/j.pone. 0032489.

Afsharpaiman, S, Khosravi, H, Mahmood, M,

Shirbazoo, S, Amirsalari, S, *et al,* 2017: Assessment of *Toxoplasma* seropositivity in children suffering from anxiety disorders. Iran J. Child Neurol.11, 4:32-7.

Akaltun, I, Kara, T, Ayaydın, H, Alyanak, B, Beka, H, *et al,* 2018a: The relation between serum *Toxoplasma gondii* IgG antibody in childrn and ADHD and its severity. Klin. Psikofarmakol. Bült. 29, 3:326-31.

Akaltun I, Kara SS, Kara T, 2018b: The relationship between *Toxoplasma gondii* IgG antibodies and generalized anxiety disorder and obsessive-compulsive disorder in children and adolescents: A new approach. Nordic. J. Psychiat. 72, 1:57-62.

Akgül, Ö, Demirel, ÖF, Aksoy Poyraz, C, Tanriöver Aydin, E, Uysal, N, *et al,* 2021: *Toxoplasma gondii* infection by serological and molecular methods in schizophrenia patients with and without suicide attempts: An age-sex-matched case-control study. Int. J. Clin. Pract. 75, 8: e14449.

Alexandra, PL, de Sordi, D, Müller, H**HO, Lam, MC, Carl, A, *et al,* 2020:** Aggravation of symptom severity in adult attention-deficit/hyperactivity disorder by latent *Toxoplasma gondii* infection: A case–control study. Sci. Rept. 10: 14382.

Alvarado-Esquivel, C, Sanchez-Anguiano, L F, Hernandez-Tinoco, J, Perez-Alamos, AR, Rico-Almochantaf, YD, *et al,* 2017: *Toxoplasma gondii* infection and attention deficit hyperactivity disorder: A case-control study. J. Psychiat. Res. 94:1-6.

Alvarado-Esquivel, C, Hernandez-Tinoco, J, Sanchez-Anguiano, LF, Ramos-Nevarez, A, Cerrillo-Soto, SM, *et al*, 2019: *Toxoplasma gondii* infection and ADHD: A case-control study in adults. J. Parasitol. 105, 2:208-12.

American Psychiatric Association, 2013: Diagnostic and Statistical Manual of Mental Disorders. 5th edition American Psychiatric Publishing, Arlington, VA.

Arabgol, F, Panaghi, L, Hebrani, P, 2009: Reboxetine versus methylphenidate in treatment of children and adolescents with attention deficit-hyperactivity disorder. Eur. Child Adolesc. Psychiat. 18, 1:53-9.

Arling, TA, Yolken, RH, Lapidus, M, Langenberg, P, Dickerson, FB, *et al,* 2009: *Toxoplasma gondii* antibody titers and history of suicide attempts in patients with recurrent mood disorders. J. Nerv. Ment. Dis. 3, 12:905-8.

Azzam, H, Hasan, H, Elhabiby, M, El Ghamry, R, Mansour, M, *et al,* 2021: Perceived parenting attitudes in relation to ADHD symptoms and aggressive behaviors in a sample of Egyptian children with ADHD. Mid. East Curr. Psychiat 28, 18. https://doi.org/10.1186/ s43045-021-00088-7

Bahceci, I, Bahceci, B, Senturk, S, Yildiz, I E, Yazici, ZA, 2021: Correlation of suicidal thoughts and toxoplasmosis in patients with depression. Cureus J. Med. Sci. 13, 2:e13369.

Banerjee, E, Nandagopal, K, 2015: Does serotonin deficit mediate susceptibility to ADHD? Neurochem. Int. 82:52-68.

Becker, K, El-Faddagh, M, Schmidt, MH, Esser, G, Laucht, M, 2008: Interaction of dopamine transporter genotype with prenatal smoke exposure on ADHD symptoms. J. Pediatr. 152, 2:263-9.

Bronson, SL, Bale, TL, 2014: Prenatal stress-induced increases in placental inflammation and offspring hyperactivity are male-specific and ameliorated by maternal anti-inflammatory treatment. Endocrinol. 155, 7:2635-46.

Buss, C, Entringer, S, Davis, EP, Hobel, CJ, Swanson, JM, *et al,* 2012: Impaired executive function mediates the association between maternal pre-pregnancy body mass index and child ADHD symptoms. PLoS One 7, 6:e37758.

Carter, CJ, 2013: Toxoplasmosis and polygenic disease susceptibility genes: Extensive *Toxoplasma gondii* host/ pathogen interactome enrichment in nine psychiatric or neurological disorders. J. Pathog. 13:965046.

Celik, T, Kartalci, S, Aytas, O, Akarsu, GA, Gozukara, H, *et al,* 2015: Association between latent toxoplasmosis and clinical course of schizophrenia- continuous course of the disease is characteristic for *Toxoplasma gondii* infected patients. Fol. Parasitol. 62, 1:15. doi: 10.14411/ fp.2015.015.

Cerávolo, IP, Chaves, ACL, Bonjardim, CA, Sibley, D, Romanha, AJ, *et al,* 1999: Replication of *Toxoplasma gondii*, but not *Trypanosoma cruzi,* is regulated in human fibroblasts activated with gamma interferon: requirement of a functional JAK/STAT pathway. Infect. Immun. 67, 5:2233-40.

Chaudhury, A, Ramana, BV, 2019: Schizophrenia and bipolar disorders: The *Toxoplasma* connection. Trop. Parasitol. **9**, 2:71-6.

Chegeni, TN, Sharif, M, Sarvi1, M, Moosazadeh, M, Montazeri, M, *et al,* 2019: Is there any

association between *Toxoplasma gondii* infection and depression? A systematic review and meta-analysis. PLoS One 14, 6:e0218524.

Chen, X, Chen, B, Hou, X, Zheng, C, Yang, X, *et al,* 2019: Association between *Toxoplasma gondii* infection and psychiatric disorders in Zhejiang, Southeastern China. Acta Trop. 192: 82-6.

Dadi, AF, Miller, ER, Bisetegn, TA, Mwanri, L, 2020: Global burden of antenatal depression and its association with adverse birth outcomes: an umbrella review. BMC Pub. Hlth. 20:173-6.

Dalimi, A, Abdoli, A, 2012: Latent toxoplasmosis and human. Iran. J. Parasitol. 7:1-8.

de Bles, NJ, van der Does, JEH, Kortbeek, L, Hofhuis, A, van Grootheest, G, *et al,* 2021: *Toxoplasma gondii* seropositivity in patients with depressive and anxiety disorders. Brain Behav. Immun. Hlth. 11:100197.

Deckelbaum, RJ, Torrejon, C, 2012: The omega-3 fatty acid nutritional landscape: health benefits and sources. J. Nutr. 142, 3:s587-91.

Del Campo, N, Chamberlain, SR, Sahakian, BJ, Robbins, TW, 2011: The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. Biol. Psychiat. 69:e145-57.

Del Grande, C, Galli, L, Schiavi, E, Dell'osso, L, Bruschi, F, 2017: Is *Toxoplasma gondii* a trigger of bipolar disorder? Pathology 6:3-8.

De Witte, LD, van Mierlo, HC, Litjens, M, Klein, HC, Bahn, S, *et al,* 2015: The association between antibodies to neurotropic pathogens and schizophrenia: A case-control study. NPJ Schizophr. **1**:15041. doi: 10.1038/npjschz.41.

Donfrancesco, R, Di Trani, M, Porfirio, MC, Giana, G, Miano, S, *et al,* 2015: Might the temperament be a bias in clinical study on attention-deficit hyperactivity disorder (ADHD)? Novelty seeking dimension as a core feature of ADHD. Psychiat. Res. 227:333-8.

Dunn, GA, Nigg, JT, Sullivan, EL, 2019: Neuroinflammation as a risk factor for attention deficit hyperactivity disorder. Pharmacol. Biochem. Behav. 182:22-34.

Elshafey, ME, Elbaitar, SA, Zayed, MS, Othman, AA, Abdel Aaty, HE, 2023: Neurotrop- ic parasitic infections associated with psychiatric disorders: A review article. JESP 53, 1:185-97.

El-Beshbishi, SN, El-Tantawy NL, Elzeky, S M, Abdalaziz, KF, Atia, RA, 2018: Sero-prevalence of *Toxoplasma gondii* infection in children with central nervous system disorders in Mansoura, Egypt: A case-control study. Trans. R. Soc. Trop. Med. Hyg. 112, 12:555-60.

Elzeky, SM, Nabih, N, Abdel-Magied, AA, Abdelmagid, DS, Handoussa, AE, *et al,* 2022: Sero-prevalence and genetic characterization of *Toxoplasma gondii* among children with neurodevelopmen-tal disorders in egypt. J. Trop. Med. 27: Article ID 2343679 https://doi.org/10.1155/2022/2343679

Fabiani, S, Pinto, B, Bonuccelli, U, Bruschi, F, 2015: Neurobiological studies on the relationship between toxoplasmosis and neuropsychiatric diseases. J. Neurol Sci. 351:3–8.

Faraone, SV, Larsson, H, 2018: Genetics of attention deficit hyperactivity disorder. Mol. Psyhiat. 24:562-75.

Fayyad, J, Sampson, NA, Hwang, I, Adamowski, T, Aguilar-Gaxiola, S, *et al,* 2017: Descriptive epidemiology of DSM-IV Adult ADHD in the WHO World Mental Health Surveys. Atten. Deficit Hyperact. Disord. 9:47-65.

Fernandes, SM, Dias, AR, Miranda-Scippa A, 2020: Association between exposure to toxoplasmosis and major psychiatric disorders: a systematic review Braz. J. Psychiat. 43, 4:438-45.

Flegr, J, Havlicek, J, Kodym, P, Maly, M, Sm ahel, Z, 2002: Increased risk of traffic accidents in subjects with latent toxoplasmosis: A retrospective case-control study. BMC Infect. Dis. 2: 11-6.

Gaskell, EA, Smith, JE, Pinney, JW, Westhead, DR, Mc-conkey, GA, 2009: A unique dual activity amino acid hydroxylase in *Toxoplasma gondii*. PLoS One 4:e4801.

Gulinello, M, Acquarone, M, Kim, JH, Spray, DC, Barbosa, HS, *et al*, 2010: Acquired infection with *Toxoplasma gondii* in adult mice results in sensorimotor deficits but normal cognitive behavior despite widespread brain pathology. Microb. Infect. 12:528-37.

Halonen, SK, Weiss, LM, 2013: Toxoplasmosis. Handb. Clin. Neurol. 114:125-45.

Hamdani, N, Bengoufa, D, Godin, O, Doukhan, R, Le Guen, E, *et al,* 2018: Immunoglobulin subclass distribution in bipolar disorder and schizophrenia: Potential relationship with latent *Toxoplasma gondii* infection. BMC Psychiat. 18, 1:239. doi: 10.1186/s12888-018-1821-9.

Havlícek, J, Gašová, ZG, Smith, AP, Zvára, K, Flegr, J, 2001: Decrease of psychomotor performance in subjects with latent 'asymptomatic' toxoplasmosis. Parasitology 122:515-20.

Henriquez, SA, Brett, R, Alexander, J, Pratt,

J, Roberts, CW, 2009: Neuropsychiatric disease and *Toxoplasma gondii* infection. Neuroimmunomod. 16:122-6.

Hlaváčová J, Flegr, J, Fiurašková, K, Kaňková, Š, 2021: Relationship between Latent Toxoplasmosis and depression in clients of a center for assisted reproduction. Pathogens 10, 8:1052.

Holub, D, Flegr, J, Dragomirecka, E, Rodriguez, M, Preiss, M, *et al,* 2013: Differences in onset of disease and severity of psychopathology between toxoplasmosis-related and toxoplasmosis-unrelated schizophrenia. Acta Psychiatr. Scand. 127:227-38.

Horáček, J, Flegr, J, Tintera, J, Verebova, K, Spaniel, F, *et al,* 2012: Latent toxoplasmosis reduces gray matter density in schizophrenia but not controls: voxel-based-morphometry (VBM) study. Wld. J. Biol. Psychiatr. 13:501-9.

Hussein, EH, Megahed, LA, El Sadany, RAR, Morsy, TA, 2022: An overview needle sticks or sharps related injuries and blood-borne pathogens. JESP 52, 2:353-62.

Imam, NFA, Ismail, MAM, Bocktor, NZ, 2022: Congenital toxoplasmosis: An overview on transmission, diagnosis and treatment with reference to Egypt. JESP 52, 2:193-206.

Institute of Health Metrics and Evaluation, 2023: Global Health Data Exchange (GHDx). https://vizhub.healthdata.org/gbd-results.

Kamal, AM, Abd El-Fatah, AS, Rizk, MM, Hassan, EE, 2022: Latent toxoplasmosis is associated with depression and suicidal behavior. Arch. Suicide Res. 26, 2:819-30.

Liao, P, Soong, TW, Ca, V, 2010: Channelopathies: From arrhythmias to autism, bipolar disorder, and immunodeficiency. Pflügers Arch. 460, 2:353-9.

Lindemann, C, Langner, I, Banaschewski, T, Garbe, E, Mikolajczyk, RT, 2017: The risk of hospitalizations with injury diagnoses in a matched cohort of children and adolescents with and without attention deficit/hyperactivity disorder in Germany: a database study. Front. Pediatr. 5: 220-5.

Liu, T, Gao, P, Bu, D, Liu, D, 2022: Association between *Toxoplasma gondii* infection and psychiatric disorders: A cross-sectional study in China. Sci. Rep. 12:15092

Li, Y, Severance, EG, Viscidi, RP, Yolken, R H, Xiao, J, 2019: Persistent *toxoplasma* infection of the brain induced neurodegeneration associated with activation of complement and microglia. Infect. Immun. 87, 8:e00139-19.

Li, Z, Ruan, M, Chen, J, and Fang, Y, 2021: Major Depressive Disorder: Advances in Neuroscience Research and Translational Applications. Neurosci. Bull. 37, 6:863-80.

Martinez, VO, de Mendonca Lima, FW, de Carvalho, CF, Menezes-Filho, JA, 2018: *Toxoplasma gondii* infection and behavioral outcomes in humans: a systematic review. Parasitol. Res. 117:3059-65.

Miman, O, Kusbeci, OY, Aktepe, OC, Cetinkaya, Z, Yaman, M, 2010: The probable relation between *Toxoplasma gondii* and Parkinson's disease. Neurosci. Lett. 475, 3:129-31.

Nessim, PJ, Luna-Ramirez, JC, Moreno-Gómez, GA, Galvis-Soto, DM, Gomez, JE, 2023: Estimation of the number people with mental diseases associated with toxoplasmosis and identification of risk factors by continent. Psych. Res. 323:196. https://doi.org/10.1016/j.psychres.115130.

Niebuhr, DW, Cowan, DN, Millikan, AM, Yolken, R, Li, Y, *et al,* 2007: Risk of schizophrenia and antibodies to *Toxoplasma gondii* among US military personnel. Schizoph. Bull 33:243-4.

Nissapatorn, V, 2017: *Toxoplasma gondii* and HIV: A never-ending story. Lancet 4:e146-7.

Ozkan, Y, Sapmaz, SY, Sen, S, Ozturk, M, Kandemir, H, 2020: Treatment-Resistant Depression that Recovered after *Toxoplasma gondii* Treatment: A case report. Psychiatr. Behav. Sci.10, 4:207-9.

Pan, M, Lyu, C, Zhao, J, Shen, B, 2017: Sixty years (1957-2017) of research on toxoplasmosis in China. An overview. Front. Microbiol. 8:825. doi.org/10.3389/fmicb.2017.01825

Pratt, LA, Brody, DJ, 2008: Depression in the United States household population, 2005-2006. NCHS Data Brief 7:1-8.

Prandovszky, E, Gaskell, E, Martin, H, Dubey, JP, Webster, JP, *et al,* 2011: The neurotropic parasite *Toxoplasma gondii* increases dopamine metabolism. PLoS One 6:e23866.

Robert-Gangneux, F, Darde, ML, 2012: Epidemiology of and diagnostic strategies for toxoplasmosis. Clin. Microbiol. Rev. 25, 2:264-96.

Rommelse, N, Antshel, K, Smeets, S, Greven, C, Hoogeveen, L, *et al,* 2017: High intelligence and the risk of ADHD and other psychopathology. Br. J. Psychiat. 211:359-64.

Ruge, H, 1952: Toxoplasmosis; a new disease. J. Egypt. Med. Ass. 35, 5:337-9.

Sapmaz, YS, Sen, S, Ozkan, Y, Kandemir, H, 2019: Relationship between *Toxoplasma gondii*

seropositivity and depression in children and adolescents. Psychiat. Res. 278:263-7.

Schwarcz, R, Bruno, JP, Muchowski, PJ, Wu, HQ, *et al,* 2012: Kynurenines in the mammalian brain: when physiology meets pathology. Nat. Rev. Neurosci. 13, 7:465-77.

Shehata, AI, Hassanein, FI, Abdul-Ghani, R, 2016: Seroprevalence of *Toxoplasma gondii* infection among patients with nonschizophrenic neurodevelopmental disorders in Alexandria, Egypt. Acta Trop. 154:155-9.

Şirin, MC, Kılıç, F, Demirda, A, Arıdoğan, B, Sesli Çetin, E, 2021: An investigation into the association between *Toxoplasma gondii* infection and bipolar disorder. Turki. Parazitol. Derg. 45, 4:241-6.

Song, HO, Ahn, MH, Ryu, JS, Min, DY, Joo, KH, *et al,* 2004: Influence of calcium ion on host cell invasion and intracellular replication by *Toxoplasma gondii.* Korean J. Parasitol. 42, 4: 185-93.

Sutterland, AL, Fond, G, Kuin, A, Koeter, M W, Lutter, R, *et al,* 2015: Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: Systematic review & meta-analysis. Acta Psychiat. Scand. 132:161-6.

Suzuki, Y, 2002: Host resistance in the brain against *Toxoplasma gondii*. J. Infect. Dis. 185, 1:S58-65.

Taman, A, Alhusseiny, S, 2020: Exposure to toxoplasmosis among the Egyptian population: A systematic review. PUJ 13, 1:1-10.

Tan, L, Yu, JT, Tan, L, 2012: The kynurenine pathway in neurodegenerative diseases: mechanistic and therapeutic considerations. J. Neurol. Sci. 323, 1/2:1-8.

Terasaki, LS, Schwarz, JM, 2016: Effects of moderate prenatal alcohol exposure during early gestation in rats on inflammation across the maternal-fetal-immune interface and later-life immune function in the offspring. J. Neuroimmune Pharmacol. 11, 4:680-92.

Torrey, EF, Bartko, JJ, Lun, ZR, Yolken, R H, 2007: Antibodies to *Toxoplasma gondii* in patients with schizophrenia: A meta-analysis. Schizoph. Bull. 33, 3:729-36.

Torrey, EF, Yolken, RH, 2003: *Toxoplasma gondii* and schizophrenia. Emerg. Infect. Dis. 9, 11:1375-80.

Triana, MAH, Márquez-Nogueras, KM, Vella, SA, Moreno, SNJ, 2018: Calcium signaling and the lytic cycle of the Apicomplexan parasite *Toxoplasma gondii*. Biochim. Biophys. Acta Mol. Cell Res. 1865, 11:1846-56.

Tyebji, S, Seizova, S, Hannan, AJ, Tonkin, C J, 2019: Toxoplasmosis: A pathway to neuropsychiatric disorders. Neuros. Biobehav. Rev. J. 96:72-92.

Vyas, A, Kim, S, Giacomini, N, *et al,* 2007: Behavioral changes induced by *Toxoplasma* infection of rodents are highly specific to aversion of cat odors. Nat. Acad. Sci. 104, 15: 6442-7.

Volkow, ND, Wang, GJ, Kollins, SH, Wigal, TL, Newcorn, JH, *et al,* 2009: Evaluating dopamine reward pathway in ADHD: Clinical implications. JAMA 302:1084-91.

Wang, X, Zhang, L, Lei, Y, Liu, X, Zhou, X, *et al,* 2014: Meta-analysis of infectious agents and depression. Sci. Rep. 4:4530-8.

Webster, JP, Lamberton, PH, Donnelly, CA, Torrey, EF, 2006: Parasites as causative agents of human affective disorders? Impact of antipsychotic, mood-stabilizer and anti-parasite medication on *Toxoplasma gondii's* ability to alter host behavior. Proc. Biol. Sci. 273:1023-30.

Webster, JP, Mconkey, GA, 2010: *Toxoplasma gondii*-altered host behaviour: Clues as to mechanism of action. Folia Parasitol. 57:95-104.

Weiss, LM, Kim, K, 2000: Development and biology of bradyzoites of *Toxoplasma gondii.* Front. Biosci. 5:D391-405.

WHO, 2018: International Statistical Classification of Diseases and Related Health Problems.

Younis, EA, Shalaby, SES, Abdo, SAE, 2023: Screening of attention deficit hyperactivity disorder among preschool children Gharbia Governorate, Egypt. BMC Psychiat. 25, 1:285-90.