Does *Toxoplasma. gondii* Cause Schizophrenia? A Narrative Systematic review.

Abstract:

Background: Accumulating evidence associated infectious agents with schizophrenia. Majority of these studies analyzed *Toxoplasma. gondii* association with schizophrenia.

Aims and objectives: To perform systematic search on studies conducted on investigating association between *T. gondii* and schizophrenia using IgG antibodies against *T. gondii.* Secondary objective to discuss possible mechanisms by which *T. gondii* linked to schizophrenia.

Methods: Systematic search performed using Google Scholar, PubMed, Web of Science and University of Manchester databases. Key words Schizo* AND Toxoplasm* used to find articles published from years 2010-2020, used IgG antibodies against *T. gondii,* and patients participated in these studies definitively diagnosed with schizophrenia using DSM-IV or ICD- 10. Studies included *P* value as statistical methods.

Result: Total of 122 articles was identified after duplicated were removed, of these 24 were included in review. Two-third of studies found that schizophrenic patients had significantly higher IgG antibodies versus controls.

Conclusion: These findings suggest that *T. gondii* is associated with schizophrenia and that *T. gondii* might be risk factor for schizophrenia development. If causative link is ascertained, then it would be possible to treat and prevent schizophrenia.

1- Introduction:

Behavioral and psychiatric disorders significant affects public health since they frequently occur and affect 10-16% of community world-wide (Demyttenaere et al, 2004; Wang et al, 2007a). They are not only associated with increased level of individual's distress, premature mortality, and disability, but led to substantial increase of cost related to lost productivity and utilization of health services. These diseases constitute 12% of global disease burden (World Health Organisation,2001).

1.1. Schizophrenia:

1.1.1 : Definition and Burden:

Schizophrenia is serious neuropsychiatric disorders of unknown origin (Cetinkaya et al, 2007), disease affects approximately fifty million individuals worldwide. Disease burden on economy, either directly or indirectly. Direct impact of the disease constitutes 1.5-3% of total national healthcare budget worldwide, which includes hospitalization, medications, procedures, diagnosis and prolonged care services (Nicholl et al, 2010), whereas indirect burden includes increased premature mortality rate as result of suicide and unemployment rate and reduced productivity in work place. Disease's cost indirect burden exceeds those of direct costs by 20% (Goeree et al, 2005; Chang et al, 2008).

1.1.2 : Symptoms and Clinical Manifestation:

Schizophrenia onset time differ between males and females. In females, disease onset usually begins in late adolescence to early adulthood, while in men disease onset usually develops earlier (Hafner et al, 1993). Disease characterized by two types of symptoms: negative and positive. Positive symptoms manifested as hallucination, delusions and unusual motor behaviors with different severity grade, whereas negative symptoms presented as reduction in emotion expression and induction of goal-directed behavior. In addition, alogia and anhedonia present in some patients. Cognitive symptoms occur and grouped as third category. These symptoms include disorganized thought, speech, and potentially attention, eventually debilitating person's capability to communicate (Patel et al, 2014).

1.1.3 Risk Factors:

Unfortunately, until now no causative agent discovered in relation to schizophrenia, however, there are some risk factors that play role in causing disease. These include: abnormalities in neurons development, genetic susceptibility, and environmental associated factors (Fuglewicz et al, 2017). Pathogens as cytomegalovirus, *Herpes simplex* virus, influenza virus, and *Toxoplasma. gondii*, contribute in causation of some behavioral and psychiatric disorders. Many studies focused on schizophrenia association with *T. gondii* infection (Park et al, 2012).

1.2. Toxoplasma. gondii (T. gondii):

1.2.1 Definition and Background:

T. gondii is commonest protozoan parasite that belongs to Apicomplexa phylum, a phylum that contains 5000 species. Only minority of species (e.g. *Plasmodium* spp. and *Cryptosporidium* spp.) responsible for causing disease in humans (Xiao and Yolken, 2015). Parasite is categorized into three major genotypes, which vary in their virulence characteristics and distribution (epidemiology). For instance, type I strain is highly virulent in mice and commonly found in patients with ocular toxoplasmosis (Dalimi and Abdoli, 2012). Both type II and III strains are not virulent in mice, but frequently involved in human infections in Europe and North America, although type III is less frequent than type II (Maubon et al, 2008). Type I and II involved in congenital diseases and HIV patients (Ajzenberg et al, 2002; Khan et al, 2005).

1.2.2. Prevalence:

T. gondii infection is widely distributed and approximately one third of world's population infected with *Toxoplasma* (Fekadu et al, 2010). Disease incidence differs depending on weather, hygienic and nutritional habits and geographical area (Fuglewicz et al, 2017). Antibodies prevalence to *T. gondii* in London was 22%. In New York City prevalence achieved 32% (Esshili et al, 2016). While prevalence in France reached 84% that explained by French people's nutritional habits, as they frequently consume lightly-cooked meat (Hill et al, 2005).

Life cycle of *T. gondii:*

T. gondii life cycle characterized by its complexity and heterogenicity; with members of feline family (e.g. domestic cat) as primary hosts, and all warm-blooded animals including humans acting as secondary hosts (Da- Silva et al, 2009). Parasite has three

infectious stages; resistant and immature form oocyst, which shed in felines feces; bradyzoites; slow replicating form of parasite, which generates during chronic infection and localized in tissue cysts; and finally tachyzoites; rapidly replicating form that occurs during acute infection and excreted in all body fluids (Tenter et al, 2000):

These different stages vary in their resistance to environmental conditions. Tachyzoite is most sensitive form to extreme environmental condition as temperature, high salt and proteolytic enzymes (e.g. pepsin found in GIT of both secondary and primary host). Because of this high sensitivity, they rarely survive outside host and hence, they are of less concern epidemiologically except for vertical transmission (mother to baby) (Tenter et al, 2000). Bradyzoites resist effect of proteolytic enzymes and survive in this environment more than tachyzoites (Dubey et al, 1998). They remain infectious for approximately three weeks even with environmental changes like heating or freezing (Tenter et al, 2000). Regarding oocysts, this stage considered highly resistant as it can survive in dehydration and cold and remain infectious in humid sand or soil for one and half year (Tenter et al, 2000). These three stages linked together in complex life cycle shown in Figure 1, including transmitted mode to human.

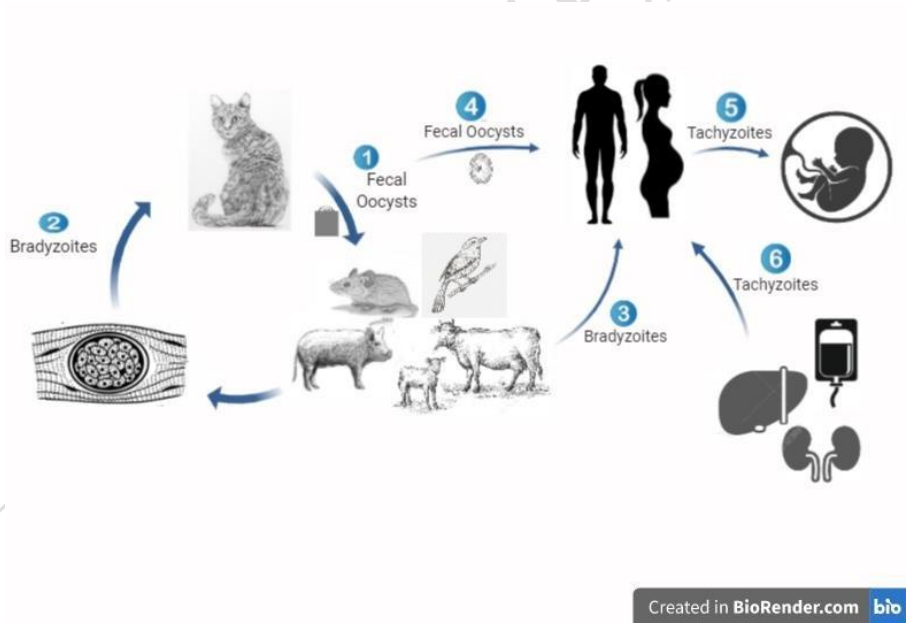

Figure 1. *T. gondii* life cycle and transmission to human.

Definitive hosts of *T. gondii* felines as domestic cats (Jackson and Hutchison, 1989). Parasite reproduce sexually only in felines, who shed infectious oocyte into environment (Yolken et al, 2017). 1) Oocyte contaminates food stuffs e.g. grass of other warm-blooded animal act as intermediate hosts (Tenter, 2000). When intermediate host ingests oocyst, *T. gondii* initiates two stages of asexual reproduction. Primary stage (tachyzoites) replicates rapidly by frequent endogeny

in all body cells. Once immune system starts to suppress infection, final generation of tachyzoites generates second stage of asexual reproduction, which results in tissue cysts generation. In tissue cysts, cystozoites or bradyzoites replicate slowly by endodyogeny (Jackson and Hutchison, 1989; Dubey et al, 1998). Tissue cysts increased tropism to muscular and neural tissues.

They are mainly found in eyes, CNS and skeletal and cardiac muscles; however, they may locate in kidney, lung and liver, but less common (Dubey et al, 1998). Tissue cysts remain infectious and persist for life-span of intermediate hosts (Tenter, 2000). 2) Cats can be infected by eating prey animal whose tissues contain *T. gondii* cysts. Once cat infected by tissue cysts, bradyzoites undergo asexual dissemination which consist of many stages of endopolygeny in feline's small intestine. Final stages of this dissemination create sexual life cycle replication phase. Oocysts and gamogony also formed in small intestine epithelium. Unsporalated oocysts discharged into intestinal lumen and excreted into environment via cat feces. Sporogony happens in environment and result in infectious oocysts formation which possess 2 sporocysts and four sporozoites in each (Jackson and Hutchison, 1989; Dubey et al, 1998). Not only bradyzoites cause infection to cats, but also tachyzoites and oocysts. Successful infection rate is not as high as with bradyzoite cysts (Dubey et al, 1998). While in humans, *T. gondii* infection acquired via four routes: 3) by ingesting meat from cattle, pigs, sheep or poultry whose tissues contain bradyzoites cysts. 4) by ingesting oocysts after handling cat feces or materials contaminated with cat feces. 5) from mother to baby via placenta if mother infected with *T. gondii* during pregnancy (by tachyzoites stage) (Yolken et al, 2017). 6) by organ transplantation where *T. gondii* can be in form of tachyzoites or bradyzoites. *T. gondii* transmission in tachyzoites form occurs during blood transfusion. Infection chances via this route are rare and occur mainly if blood donor has acute infection (Tenter et al, 2000).

1.2.3. Prevalence of different infection routes in human:

Both ingesting sporulated oocysts after handling cat feces and ingesting lightly-cooked meat from cattle and pigs are common infection routes in human. Determining major infection route differs among human population with diverse eating, cultural habits and climate conditions (Cook et al, 2000). In Poland, ingesting lightly-cooked meat containing bradyzoites identified as major infection source, nearly 80% of live stocks reported as *T. gondii* seropositive (Flegr et al, 2014a). In some parts of Brazil, weather conditions (warmth and humidity) enhance long-term oocysts survival and most people life in low-socioeconomic status (Yan et al, 2016), ingesting oocysts largely attributed for most cases (Bahia- Oliveira et al, 2003).

1.2.4. *T. gondii* infection in human:

Primary *T. gondii* infection in healthy individuals is subclinical in >80% of individuals, and in remaining 20%, only transient symptoms seen. However,

infection is more severe in immunocompromised patients who experience neuropsychiatric symptoms (e.g. schizophrenic psychosis, depression, anxiety, and disorientation) (Fabiani et al, 2013).

Chronic infection result in behavioral and personality disorders (Fabiani et al, 2013), decline in psychomotor performance and intelligence quotient (Flegr et al, 2003; Havlicek et al, 2001; Fabiani et al, 2013), and mental health problems development (e.g. parkinsonian manifestations, schizophrenia, schizophrenia-spectrum disorder) in persons with genetic susceptibility to these disorders (Fabiani et al, 2013). Many studies performed to discover etiopathogenetic relationship between these disorders and *T. gondii* (Fabiani et al, 2013). Most common method used higher titers of anti-*T. gondii* antibodies in schizophrenic patients versus controls (Del Grande et al, 2017). Although some investigations revealed association, others did not find. It is still debatable whether *T. gondii* causes schizophrenia or behavioral changes caused by disease favored *T. gondii* acquisition (Sutterland et al, 2015).

Study aim:

Primary objective was to evaluate association between schizophrenia and *T. gondii* by performing systematic search on studies conducted in last ten years (2010-2020). Second objective was to discuss possible mechanisms by which *T. gondii* linked to schizophrenia.

2- Materials and Methods:

2.1 Search strategy:

Studies that investigated association of *T. gondii* with schizophrenia were retrieved using PubMed, Google Scholar, Web of Science, and University of Manchester Library databases. Key words used were Toxoplasm* AND Schizo*. Title and abstract of articles were examined and selection made based on inclusion/ exclusion criteria. Additionally, reference lists of reviews and retrieved articles were screened and relevant articles were cross-referenced.

2.2 Inclusion/ exclusion criteria:

Inclusion criteria were;

- Case- control study.

- Primary research.
- Published in English.
- Published in last ten years (2010 to 2020).
- Cases in studies definitely diagnosed by schizophrenia following DSM-IV or ICD-10 criteria. This aimed to eliminate other psychiatric diseases that have schizophrenia like symptoms as schizoaffective and pseudoneurotic schizophrenia (Andreasen and Flaum, 1991).
- Specifically examining association of *T. gondii* with schizophrenia.
- Included measurement of anti- *T. gondii* IgG antibodies titer rather than IgM antibodies as IgM antibodies affected by presence of high IgG level, which leads to false- negative results. Rheumatoid factors existence influences IgM titers, resulting in false-positive results (Filice et al, 1983).
- Presence of statistical comparison between control and schizophrenia.

Exclusion criteria were;

- Review articles.
- Articles that are not completed (e.g. letter to editor).
- Maternal or neonatal studies.
- Animal studies (but these referred to in discussion sections).
- Cohort studies.
- Studies investigating effects of *T. gondii* seropositivity on schizophrenic patients without controls.
- Studies measured risk ratio of schizophrenia development.

2.3 Review process:

PRISMA guidelines; preferred reporting item for systematic review were used (Moher et al, 2009).

3- Results:

Search identified 122 articles after duplicates removed. Of these, 32 were reviews. Title and abstract of remaining 90 articles screened and 49 assessed for eligibility. In total, articles number that met all above- mentioned criteria were 24. Flow chart (PRISMA. http://www.prisma-statement.org/) presenting information through different stages of systematic review was shown in Figure 2.

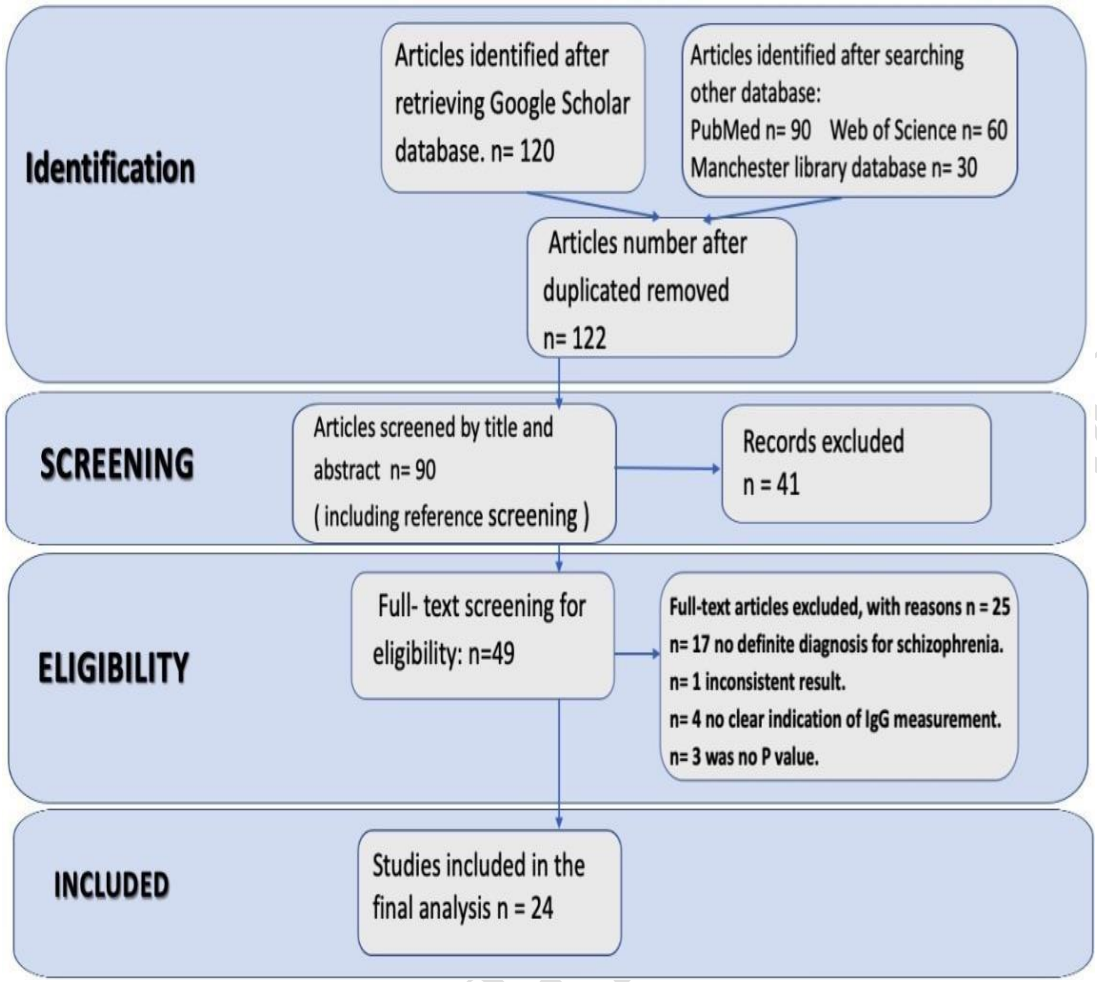

Figure 2. Flow chart Prisma for strategies used for articles selections including list of references screening. adapted from Moher et al (2009).

Twenty four studies included in this report summarized in Table 1. They carried out in different countries with most being in Iran (n=4), Malaysia (n=3), Turkey (n=3), Germany (n=2), Egypt (n=2), Brazil (n= 2), and one for each; Nigeria, Spain, Korea, Saudi Arabia, Tunisia, Mexican, Iraqi Kurdistan and Lebanon.

Table 1. Summary of reviewed studies.

Author/ Year	City	Patients number	Controls number	Mean age of patients	Mean age of controls	Schizophrenia Diagnosis	Patients number with IgG+	Controls number with IgG+
Al- Hussainy et al (2015) *	Saudi Arabia	63	55	NA	NA	DSM-5	20 (31.57 %)	8 (14.55 %)
Esshili et al (2016)*	Tunisia	246	117	40.5	38.6	DSM-5	184 (74. 8%)	63 (53.8 %)
Emelia et al (2012)	Malaysia	144	144	NA	NA	DSM-IV	54 (37.5 %)	49 (34.0 %)
De Campos- Carli et al (2017)	Brazil	40	48	40.21	40.62	DSM-IV	27 (56.25%)	22 (56.41%)
Alvarado- Esquivel et al (2011)*	Mexican	50	150	45.12	45.1	ICD-10	10 (20%)	8 (5.3 %)
Hamidinejat et al	Iran	98	48	33	33	DSM-IV	56 (57.14%)	14 (29.2%)

(2010)*								
Bakre et al (2015)*	Erbil	93	93	34	34	DSM-IV	30 (32.3 %)	4 (4.3%)
El- Sayed et al (2012)*	Egypt	60	30	38	37.76	DSM-IV	34 (56.7 %)	6 (30 %)
Alipour et al (2011)*	Iran	62	62	37.54	37.24	DSM-IV	42 (67.7%)	23 (37.1%)
Juanah et al (2013)*	Malaysia	88	88	39.42	39.42	DSM-IV	45 (51%)	27 (30.7 %)
Park et al (2012)*	Korea	96	50	46.14	44.8	DSM-IV	21 (21.9%)	4 (8.0%)
Yuksel et al (2010)*	Turkey	300	150	42.6	42.6	DSM-IV	182 (60.7 %)	68 (45.3 %)
Karabulut et al (2015)	Turkey	85	60	41.73	40.45	DSM-IV	37 (43.5%)	26 (43.3%)
Omar et al (2015)*	Malaysia	101	55	41.1	45.3	DSM-IV	52 (51.5%)	10 (18.2 %)
Gutierrez- Fernandez et al (2015)*	Spain	143	143	28.69	30.42	ICD-10	56 (39.4 %)	29 (20.4%)
De- Witte et al (2015)	Germany	368	282	30.5	34.5	DSM-IV	68 (18.5 %)	50 (17.7%)
El- Mouhawess et al (2020)	Lebanon	150	150	56	58	DSM-IV	117 (79.1%)	74 (79.6 %)
Ansari- Lari (2017)*	Iran	99	152	40.3	40.6	DSM-IV	42 (42%)	
James et al (2013)*	Neigeria	140	140	28.2	29.1	mini international psychiatric interview based on DSM-IV	43 (30.7 %)	
Morais et al (2019)*	Brazil	34	85	40.6	35.9	DSM-IV	31 (91.18)	
Khademvatan et al (2014)	Iran	100	95	NA	NA	DSM-IV	34 (34%)	
El- Gebaly et al (2019)	Egypt	120	120	35.5	35.5	DSM-IV	54 (45 %)	
Kruase et al (2010)	Germany	31	30	36.7	33.7	DSM-IV	12 (38.70%)	
Cevizci et al (2015)	Turkey	30	60	NA	NA	DSM-IV	10 (33.3 %)	

NA= Not indicated

* P value indicates that difference of antibodies to *T. gondii* between controls and schizophrenic patients is statistically significant. Indicates that study used different method than Elisa for anti- *T. gondii* IgG antibodies detection. i.e. James et al used chromatogram immunoassay while Morais used chemiluminescene method.

4- Discussion:

This review carried to find studies that examined association between schizophrenia and *T. gondii* using IgG antibody titers, aiming to investigate whether there is an association between *T. gondii* and schizophrenia. Further, it aimed if there is an association, to discuss underlies association. As indicated in studies summarized in Table 1 that in most studies, there is an association between schizophrenia and *T. gondii*, with two thirds of studies indicated that schizophrenic patients were more likely to have anti- *T. gondii* IgG antibodies versus controls with statistically significant, *P* value ranging from P=0.00006 to <0.05. This finding of reviewed studies consistent with other meta-analysis examining association between schizophrenia and *T. gondii*, that were out of current research scope, despite having some of studies from these meta-analyses in this review. Torrey et al (2007) reported in their meta-analysis that schizophrenic patients had higher seroprevalence of *T. gondii* seropositivity than

controls with odd ratio 2.73, and 2.54 for first episodes. Meta-analysis contained 38 studies reported odds ratios of 2.71 (95% confidence interval (CI) 1.93-3.78), acknowledging relation between *T. gondii* and schizophrenia disorder (Torrey et al, 2012). Sutterland et al (2015) carried meta-analysis on 42 studies and found significant association between *T. gondii* and schizophrenia with odd ratio 1.81, $P<0.00001$. Taken together, current study and past meta-analyses point clearly to presence of association. Indeed, association between schizophrenia and *T. gondii* observed in many other study types, not only epidemiological studies. Studies summarized in two main categories; first category is association could be explained by *T. gondii* being risk factor for schizophrenia development, or alternatively schizophrenia might favor *T. gondii* acquisition via behavioral changes caused by disease.

4.1 First hypothesis; *T. gondii* might increase schizophrenia risk:

Behavioral changes that *T. gondii* causes in infected individual observed clinically in schizophrenic patients, leading to hypothesis that *T. gondii* might proceed to schizophrenia. It is important to know how *T. gondii* invades cells and reaches brain before explaining pathophysiological changes.

4. 1.1: Entrance of *T. gondii* to body and its lytic cycle in cells:

Immediately after ingestion of tissue cysts or oocysts, parasite can resist stomach acidification and gain access to small intestine (Carruthers, 2002). Once access gained, sporozoites released from oocyst, or bradyzoites obtained from tissue cyst transform to tachyzoites, that invade enterocytes and replicate within these cells (Carruthers, 2002; Hunter and Sibley, 2012). After enterocyte invasion, parasite passes through intestinal epithelium and enters to lamina propria (Hunter and Sibley, 2012). In this location, parasite confronts resident microphages, intraepithelial lymphocytes and dendritic cells. By entering these cells, parasite proliferate into spleen, draining lymph nodes and ultimately all organs (Carruthers, 2002; Hunter and Sibley, 2012). *T. gondii* proliferation occurs due to its proficient framework of motility that enables it to invade host cells (Daher and Soldati- Favre, 2009). Exact mechanism by which *T. gondii* enter and invades cells explained in Figure 3.

4.1.2. Entrance of *T. gondii* to brain:

While invasion and dissemination of parasite occurs, parasite searches for suitable place within body where it hides from immune system and replicate safely and intracellularly. Best place is CNS since immune cells have restricted access to CNS (Randall and Hunter, 2011).

T. gondii passes through Blood Brain Barriers (BBB). Thus, *T. gondii* with its high tropism to CNS has three different mechanisms to reach CNS. An explanation of BBB morphology is shown in Figure 4 and three mechanisms used by *T. gondii* to enter BBB depicted in Figure 5.

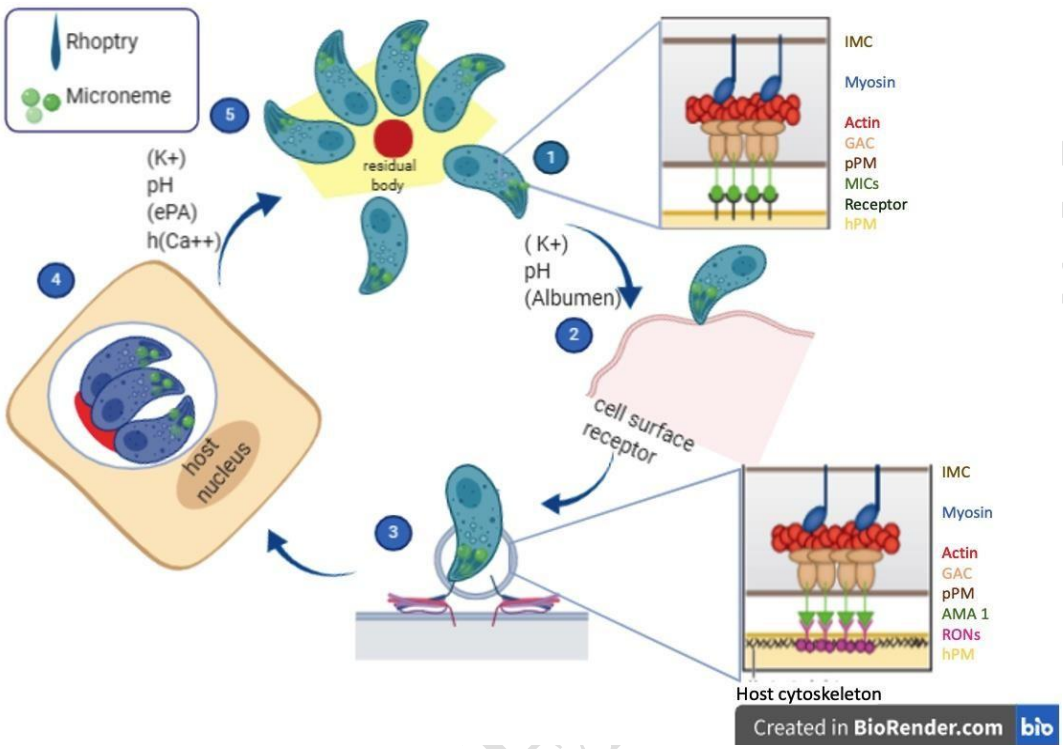

Figure 3. Mechanism of *T. gondii* invasion of host cells

T. gondii lyse host cells via four methods; adherence, invasion, replication and exit. Tachyzoite form move extracellularly utilizing gliding motility. (1) Micronemes (green) located at apical tip of parasite contain secretions that are exocytosed, when parasite fuses with host cell membrane (Carruthers, 2002). Some of secretion (MIC) remains correlated with parasite's apical tip, where they mediate attachment to host plasma membrane (hPM) by binding to host receptors (Bisio and Soldati- Favre, 2019; Carruthers, 2002). After binding, parasite plasma membrane (pPM) moves further towards host cell, as result of rearward translocation of myosin (dark blue) and actin (red) that occur in inner membrane complex-IMC (Bisio and Soldati- Favre, 2019). Actin fibers linked to cytosolic tail of adhesion by glidesome-associated connector (GAC). Presence of serum albumin, pH <7.2, low K+ levels help in enhancing signals for micronemes exocytosis, which result in gliding motility and host cell invasion. (2) When parasite recognizes suitable cell, it translocates to this cell as result of rhomboid protease activity and then attaches and (3) begin invading cells after micronemes and rhoptries secretion (Bottom inset). Reason behind rhoptry signals secretion may aid parasite in identifying host cell receptors via micronemal proteins. This mechanism used for attack and gliding. While rhoptry induction process is taking place, host receptors presented by parasite in hPM (RONs) and then invades cell via (AMA1) adhesin (Bisio and Soldati- Favre, 2019) (4) After *T. gondii* accesses host cell, parasite forms

parasitophorous vacuoles (PV) consisting of host- and rhoptry derived lipids and proteins, which is resistant to acidic effects and lysosome degradation. Within this PV parasite replicates and produce two daughter cells, which connected cytosolically (Black and Boothroyd, 2000). This procedure is reliant on filamentous actin and myosins (Bisio and Soldati- Favre, 2019) (5) Exit from host cell is initiated by presence of low K^+ levels and pH with increased Ca^{++} levels and extracellular phosphatidic acid (ePA) in environment. If this is achieved, parasite gliding movement stimulated and then PV destabilizes resulting in parasite exit (Black and Boothroyd, 2000). Micronemes secretions play role in destabilizing PV by providing pPM with MICs and thus permitting gliding motility. Binary fission of parasite allows separation of basal actin filaments, which render independent parasites able to start new lytic cycle (Bisio and Soldati- Favre, 2019). Figure adapted from Bisio and Soldati- Favre (2019).

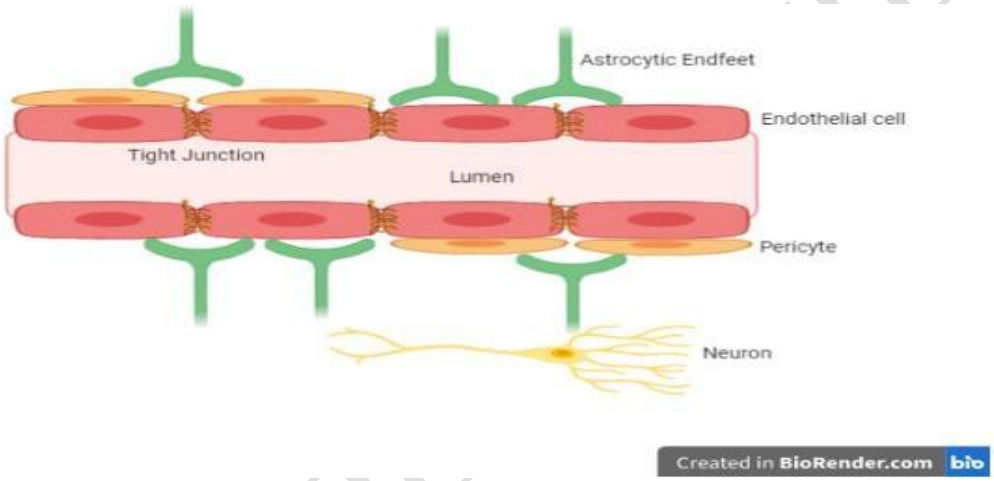

Figure 4. Structure of Blood Brain Barriers.

BBB contains 3 layers that interconnected together to form restricted barriers against pathogens and large molecules. First layer comprises small vessels, which are covered from top and bottom by endothelial cells. Endothelial cells connected with tight junctions. Next layer is pericytes formed above each tight junction for additional protection. Final layer composed of astrocytic Endfeet that act as receptors for molecules to enter. Figure adapted from Mendez and Koshy (2017).

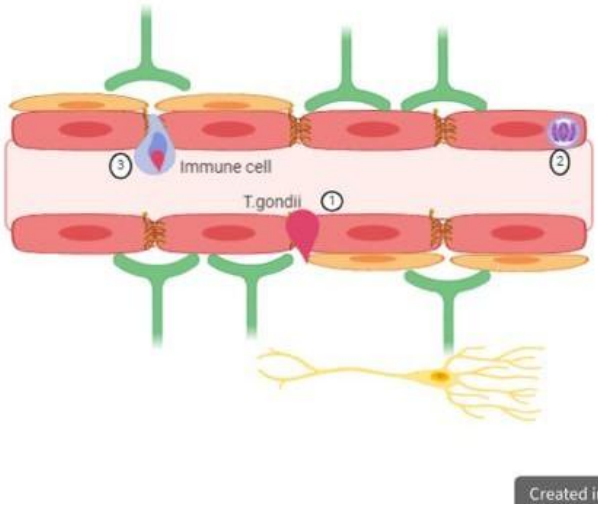

Figure 5. Mechanisms used by *T. gondii* to cross BBB.

Three suggested mechanisms by which *T. gondii* crosses BBB. 1) paracellular penetration is process characterized by intracellular tachyzoites travelling through junctions between endothelial cells (Konradt et al, 2016). 2) transcellular entry; occurs when *T. gondii* invades endothelial cells during its dissemination in blood, thereby it reproduces inside cell and then exits to neural parenchyma 3) "Trojan horse" method; parasite circulates within immune cells and proliferates to all organs including CNS. Once infected immune cell enters CNS, parasite separates itself from cell and settles in brain parenchyma. Figure adapted from Mendez and Koshy (2017).

4.1.3. After *T. gondii* reaches brain:

Once it reaches brain, *T. gondii* invades all nucleated cells and generates activation of resident microglia and astrocytes. First sign of glia activation seen between 7-10 days after infection and recruitment of peripheral T cells and mononuclear cells occurs afterwards (Hunter et al, 1992; Wilson and Hunter, 2004; Del -Grande et al, 2017). Initial activation of astrocyte and microglia associated with local secretions of chemokines and cytokines, which results in immune cells recruitment in periphery. Effective control of parasite replication and disruption of parasitophorous vacuoles relies on both intrinsic and extrinsic cell mechanisms mediated by cytokine signaling (Del- Grande et al, 2017; Parlog et al, 2015). Within weeks or months, tachyzoites vanish, but bradyzoites persist in tissue cysts for lifespan of individual. Studies carried out *in vitro* revealed that parasite initiate cysts in astrocytes and neurons, but another report demonstrated that in dormant infection stage, cysts predominantly found in neurons (Del Grande et al, 2017). Infected neurons lack MHC class I, invading CD8+ T cells cannot recognize them and clear parasite from neurons. Thus, parasite remains protected inside neurons for long time periods (Parlog et al, 2015).

4.1.4. Localization of tissue cysts:

While *T. gondii* localization had important role in manipulating host behaviors (Del Grande et al, 2017), determining tissue cysts localization in brain is point of argument with most studies carried on mice revealed different areas in which tissue cysts persist in brain (Vyas et al, 2007; Dubey et al, 2016; Berenreiterova et al, 2011). Situation is different in humans with few studies carried out in detecting tissue cysts location and describing pathological process, because of difficulty in accessing post- mortem materials (Parlog et al, 2015). Those studies were limited specifically to immuno-deficient patients who suffer from reactivated toxoplasmosis. Lesions in cortex and cerebellum detected in cerebral toxoplasmosis patients using MRI, which resemble studies performed in murine models (Parlog et al, 2015).

4.1.5. Effects of *T. gondii* on dopamine levels:

By persistence of tissue cysts predominately in neurons, parasite triggers multiple changes in brain, some of which observed clinically in schizophrenic patients. One of these changes is known capability of *T. gondii* to upregulate neurotransmission in various pathways particularly dopamine. Increased dopaminergic transmission is seen in both schizophrenic patients and animal models of *Toxoplasma* infected mice and rats (Prandovszky et al, 2011; El- Sayed et al, 2012). Mice infected with *T. gondii* showed increase in dopamine levels by 14% versus control, as infection progressed into its latent stage (Wang et al, 2015). Treating rats with dopamine selective uptake inhibitor changed rats' behavior (Flegr et al, 2003; Wang et al, 2015).

Humans infected with *T. gondii* showed changes in behaviors (Flegr et al, 2003). Patients with latent toxoplasmosis had impaired psychomotor performance versus *T. gondii* noninfected subjects. However, as *T. gondii* antibody levels decreased (e.g. with *T. gondii* infection duration), psychomotor performance become more impaired (Havlicek et al, 2001). Individuals with latent toxoplasmosis convey different behavior in some personality as measured by 16 PF questionnaire (Flegr et al, 2000). People infected with *T. gondii* showed different reaction to cat odor versus non-infected people. Women infected with *T. gondii* were less attracted to cat odor versus non-infected women, whereas men infected with *T. gondii* were more attracted to cat odor versus non-infected men (Flegr et al, 2011). These differences related to increased dopamine levels in ventral midbrain. Elevated dopamine levels in these areas, mesolimbic and mesocortical contributed in schizophrenia evolvement (Flegr et al, 2003).

Examination of *T. gondii* genome provides potential explanation for its effects on dopamine. *T. gondii* genome contains two aromatic amino acid AAH1 and AAH2 hydroxylases that could directly influence dopamine and serotonin biosynthesis (Dalimi & Abdoli 2012). *T. gondii* may therefore openly intensify dopamine creation as organism synthesizes a tyrosine hydroxylase in neurons, which changes amino acid tyrosine to L-dopa, rate- limiting enzyme for dopamine synthesis (Gaskell, 2009). This enzyme observed in *T. gondii* tissue cysts that reside in infected neurons cell. Enzyme secreted out of organism and into cyst for catalytic action adjacent to host cytosol (McConkey et al, 2013). In tissue segments of chronically diseased rats' brains, organism cysts contain dopamine high levels. Therefore, infection causes local impact on dopamine concentration (McConkey et al. 2013).

4.1.6. IFN-γ role in inhibiting parasite growth:

Another mechanism by which parasite cause pathophysiological changes is activation of robust non- specific T- cell- reliant immunity. This later immunity undertakes essential role in inducing parasite- selective T cells proliferation (Dupont et al. 2012). Intrinsic immune reaction to *T. gondii* included capability to detect pathogen and create IL-12, which stimulates natural killer (NK) cells and T cells to form cytokine interferon-gamma (IFN-γ). IFN-γ is chief facilitators of resistance to *T. gondii* and encourages numerous intracellular mechanisms to eradicate organism and deter its reproduction (Elshikha et al, 2016a). IFN-γ suppresses *T. gondii* growth through tryptophan degradation. Tryptophan is amino acid that supports *T. gondii* growth, and its degradation lead to parasite starvation and thus reduces its replication (Flegr, 2013). IFN-γ stimulate indoleamine 2,3 dioxygenase production that convert tryptophan into N-formylkynurenine (MacConkey et al, 2013). Tryptophan degradation decreases serotonin levels in brain, as serotonin is formed from tryptophan (Flegr, 2013). This leads to depression seen in schizophrenic and psychiatric patients (Russo et al, 2005). Moreover, tryptophan degradation also increases kynurenine levels, which is either hydroxylated into quinolinate, a strong NMDA neurotoxic agent, or metabolized to kynurenic acid, NMDA receptors antagonist. These metabolites produce both pro- psychotic (kynurenic acid) and neurotoxic (quinolinate) effects and changes dopamine balance and glutametric neurotransmission (Flegr and Horacek, 2020), both significantly contribute in schizophrenia. Kynurenic acid has been proposed to cause cognitive deficits, and thus as potential mechanism for schizophrenia (Omar et al, 2018).

IFN-γ stimulates expression of vascular cell adhesion molecule- 1 (VCAM-1) in endothelial cells which is responsible for recruitment and entrance of leukocyte and cytotoxic T cells to *T. gondii* infection location (Wang et al, 2007b; El- Sayed et al, 2012). Therefore, overexpression of this molecule by IFN-γ leads to presence of excessive immune cells in brain. These immune cells with excessive cytokine reaction to *T. gondii,* lead to glia disturbance, neuronal apoptosis, morphological alteration and reduction in neurotropic support (Fabiani et al, 2015). Study performed on mice revealed CNS tissue damage, increased apoptosis and demyelination, indicating that infection contribute to exacerbated brain pathology (Elshikha et al, 2016a). These consequences led to reduction in gray matter density (areas containing almost all synaptic connection neuronal cell bodies) of *T. gondii* infected schizophrenic patients versus *T. gondii* non-infected schizophrenic patients (Horacek et al, 2012). Changes in synaptic, axonal and dendritic organization associated with macroscopic features in schizophrenic patient's brain as reduction in cortical volume (Harrison, 1999).

4.1.7. Neural damage:

Besides IFN-γ role, innate immune responses to *T. gondii* infection play important role in eliminating *T. gondii* from infected individual' brains. These immune responses initiated by microglia cells activation. These cells act via kynurenine pathway to induce immune response (Notarangelo et al, 2014). These immune responses or inflammatory mediators stimulate cytotoxic molecules production as reactive oxygen species (ROS) and reactive nitrogen species (RNS) that affect neurons morphologies due to oxidative stress (Fabiani et al, 2015). These molecules result in severe damage to all host cell components including proteins, lipids, and nucleic acids RNA and DNA, leading to host cells apoptosis (Zindler et al, 2010). Damage by ROS is important pathogenic pathway correlated with infection- mediated neuropathy (Gao et al, 2014).

T. gondii induce host inflammatory response via Jak/ STAT pathway, increasing neural RNA expression and stimulating NADPH oxidase (NOX2) enzyme production (Elsheikha et al, 2016a) that lead to increase ROS formation (Sun et al, 2007).

Oxidative stress has been acknowledged to be triggered in schizophrenic patients as a result of NMDA receptor activations, which occur through glutamate. Glutamate is a neurotransmitter that is converted to glutamine after it has been taken up by astrocytes (Elsheikha et al, 2016a; Elsheikha et al, 2016b). As a result of this transformation, neurons'

levels of calcium are increased, leading to neurotransmission abnormalities and excitotoxicity. This, in turn, results in lipid, protein, and DNA damage, and neurotransmission alterations lead to enhancement in the levels of both ROS and RNS. These results suggest that *T. gondii* infection is probably linked with increased levels of neurodegeneration and cognitive impairment (Elsheikha et al, 2016a). This is consistent with the symptoms observed in schizophrenic patients as these patients have impairment in cognitive function; however, they did not have high level of neurodegeneration (Khandaker and Dantzer, 2016).

4.1.8. Host- gene interaction with *T. gondii:*

T. gondii has capability of influencing host- gene expression when enters host cell. Blader et al (2001) studied host gene expression profiles in human fibroblast cells infected with type II *T. gondii* strain. They found that of 22000 known human genes, <1 % was overexpressed by >2-fold in first two hours of infection (Blader et al, 2001). Approximately 50% of those overexpressed genes encoded proteins correlated with immune response, including those involved in chemokines production as (GRO2, GRO1, MCP1, and LIF), which can recruit immune cells. Overexpressed gene were encoding for (IL-6 and IL- 1β) and transcription factors (REL-B, NF-κBp105, and I-κBα), which play role in initiating and regulating additional immune response (Blader et al, 2001). So host cell launches robust response aimed at stimulating and alerting immune system to infection respond (Carruthers and Suzuki, 2007). These genetic interaction and immune activation disrupt AKT1 signaling pathways, which result in dopamine related- behavior alterations (Tan et al, 2008). AKT1 has indirect effect on DA signaling via modulating presynaptic transporters expression that remove DA from extracortical synapses (Wei et al, 2007).

Upregulation of cytokines and chemokines by *T. gondii* infection observed in schizophrenic patients. Increased of pro-inflammatory cytokines levels as IL-1, IL- 6, IL-2, IFN-γ and TNF-α detected in serum and cerebral spinal fluid samples of schizophrenic patients (Elsheikha et al, 2016a). Elevated levels of C-reactive proteins (CRP) in schizophrenic patient's brains observed. CRP is indicator of acute inflammation and immune activation (Dickerson et al, 2013). Circulating CRP level positively associated with serotiters to *T. gondii* (Hinze- Selch et al, 2007), indicating importance of considering immune responses relation between *T. gondii* and schizophrenia.

4.1.9. Proteinases and brain tissue remodeling:

A number of proteins overexpressed due to damage caused by immune activation and tissue remodeling during *T. gondii* infection. One of these proteins is matrix metalloproteinases (MMP) enzymes that govern damage and tissue remodeling during *T. gondii* infection (Tomasik et al, 2016). These enzymes decompose extracellular matrix to promote leukocytes recruitment to brain and help in neurons survival (El- Mouhawess et al, 2020; Clark et al, 2011). Metalloproteinases expression promotes neuroinflammation by microglia activation that enhances cytokine productions. Metalloproteinases expression (specifically MMP-9) results in microglia activation and pro- inflammatory cytokines enhancement in schizophrenia patients and recent onset psychosis (El- Mouhawess et al, 2020). MMP9 has role in neurological disease onset that confirmed by significant increases in serum MMP9 levels in schizophrenic patients (Ali et al, 2017).

Extracellular protein inhibitor TIMP-1 is another protein that induced under inflammatory and non-inflammatory conditions by astrocytes and microglia cells (Clark et al, 2011). These molecules had role in maintaining immune responses balance in brain. CNS inflammation severity increases when these molecules are absent in brain, but pathogen load in brain reduced by their absence (Lee et al, 2005; Thorne et al, 2009). High TIMP-1 levels observed in both animal models infected with *T. gondii* and schizophrenia patients (Okulski et al, 2007) indicate that parasite load in brain increase which affect brain cells. However, this might also indicate presence of less inflammations, but high TIMP-1 levels led to impairment in long-term potentiation (LTP) in prefrontal cortex (Okulski et al, 2007) led to LTP- like plasticity deficit that had role in impairment pathophysiology in schizophrenia patients (Berretta, 2012).

Plasminogen activator inhibitor 1 (PAI-1) increased during *T. gondii* infection. PAI-1 govern MMPs activity and extracellular matrix protein decomposition. These molecules overexpression result in scar and collagen formation (Ghosh and Vaughan, 2012). As these molecules involvement in neurotropic factor maturation in hippocampus, it might eliminate neurotropic support in schizophrenia brain (Mou et al, 2009).

4.1.10. Links to clinical schizophrenia severity:

Infection with *T. gondii* associated with different clinical schizophrenia manifestations in

Toxoplasma infected schizophrenic patients versus non-infected subjects (Flegr, 2015). *Toxoplasma* infected schizophrenic subject's record higher on negative and positive syndrome scale. Progressively extreme positive schizophrenia manifestations noted in studies from three separate research groups (Wang et al, 2006; Yolken et al, 2009; Holub et al, 2013). Another study showed that *Toxoplasma* infected schizophrenic patients requires more time in hospitals than *Toxoplasma* free-subjects (Holub et al, 2013).

4.1.11. Toxoplasmosis symptoms in patients with acute *T. gondii* infection:

Effects of *T. gondii* infection are not only seen in schizophrenic patients, but also in healthy individuals. Acute toxoplasmosis infection in immunocompetent adults induced symptoms similar to positive schizophrenia symptoms (delusion and hallucinations). These symptoms observed in 24 individuals of 114 people with acquired toxoplasmosis (Torrey et al, 2003). First manifestations of toxoplasmosis infection strongly suggested schizophrenia (Fuglewicz et al, 2017).

4.1.12. Therapeutic link:

Antipsychotic drugs effect on *T. gondii* infection level also associates *T. gondii* with schizophrenia (Leweke et al, 2004). Leweke et al (2004) examined *T. gondii* antibodies levels in individuals undergoing antipsychotic treatment and drug- naïve individuals and found significantly lower *T. gondii* antibodies levels in individuals who underwent antipsychotic treatment versus drug- naïve patients.

4.1.13. Additional epidemiological links:

Both toxoplasmosis and schizophrenia are familial. Risk for schizophrenia development increases from 7- 10 folds in individuals had family member with disease, and this is usually interpreted to indicate that this characteristic is of genetic origin (Yolken et al, 2009). *T. gondii* infection affects multiple individuals from same family, either by direct contact with feces of infected cat or by ingesting food containing tissue cysts (Sacks et al, 1982). Animal models of *T. gondii* infection showed genes affect susceptibility of animals to *T. gondii* infection (Johnson et al, 2002). In human, congenital toxoplasmosis observed in offspring of mothers acquired infection from infected men during unprotected sex, indicating that *T. gondii* transmitted sexually (Flegr et al, 2014 b).

Prevalence of both *T. gondii* and schizophrenia is low in areas, where toxoplasmosis does not exist due to feline's absence. Example of this would be highlands of Papua New Guinea, place in which domesticated cats and wild felines rarely found. In this palace, proportion of

individuals with *T. gondii* antibodies was ≤2% (Yolken et al, 2009), while schizophrenia prevalence was lowest (Torrey et al, 1974). Geographic regions with low pervasiveness of *T. gondii* antibodies had low schizophrenia frequency, inverse is not true. People in countries like France, Brazil and Ethiopia showed increased *T. gondii* antibodies level, but schizophrenia was not particularly prevalent in these countries versus world average (Yolken et al, 2009; Torrey et al, 2007). Potential interpretations include differences in route and infection time, variations in *T. gondii* strains neuropathogenicity from area to area and genetics susceptibilities (Yolken et al, 2009; Torrey et al, 2007).

4.1.14. *T. gondii* infection during pregnancy:

T. gondii's causes infection during pregnancy, and afterward stay persistent for several years before turning out to be reactivated (Torrey et al, 2007; El- Gebaly et al, 2019). Infection in this time period results in wide- range of behavior and cognitive disorders in childhood (Khandakr et al, 2013). Individuals exposure to infection by *Toxoplasma*, measles or rubella during prenatal period lead to neurodevelopmental disorders, difficulty in learning, structural brain malformations and intellectual disability in affected individual. Exact mechanism by which *T. gondii* cause these manifestations is unknown (Tenter et al, 2000)

4. 2. Second hypothesis for link; Schizophrenia might favor acquisition of *T. gondii:*

An alternate explanation of this association was that schizophrenia might facilitate acquisitions of *T. gondii* infection in these patients. Schizophrenic patients act in ways that strengthen their probability of contracting infection with *T. gondii*, either before or after disease beginning (Torrey et al, 2007). Daryani et al (2010) reported that schizophrenic patients had increased *T. gondii* antibodies levels because they frequently work in hospital garden, which contains oocyst excreted by hospital's cat's feces. Schizophrenic patients had high tendency to consume unusual things (coprophagia and pica), abnormal behaviors, inadequate self- hygiene and decreased personal care skills (Jafari Modrek et al, 2019). This might suggest that infection occurred after schizophrenia onset. However, Niebuhr et al. (2008) examined serum samples in military personnel in which 180 diagnosed with schizophrenia and 532 healthy controls. Authors found increased *T. gondii* antibodies levels in schizophrenia patients six months before disease onset that continued to be high even after schizophrenia diagnosis. Changes in schizophrenia patients behaviors resulted in acquisitions of *T. gondii* continues is unknown. No expanded risk of schizophrenia seen for different time frames before disease onset (Fabiani et al, 2013).

4.3. Studies that did not find link between *T. gondii* and schizophrenia, possible reasons:

In contrast to 66% of studies that link *T. gondii* with schizophrenia, there were eight studies that did not find this association. Association lack noted in studies that performed out of scope for this research. Daryani et al (2010) examined seroprevalence of IgG antibodies to *T. gondii* in 80 schizophrenic patients and 99 controls. Authors found insignificant differences between patients and controls. These differences in results explained by many reasons.

4.3.1 : Differences in seroprevalence of *T. gondii* in countries:

One possible reason for absent association was high seroprevalence of *T. gondii* in these countries. Increased *T. gondii* antibodies prevalence in healthy individuals makes detection of differences difficult to achieve (Sutterland et al, 2015). In Brazil, seroprevalence of *T. gondii* antibodies in controls is high 77.5% (Montazeri et al, 2020). Authors found insignificant differences in *T. gondii* antibodies between schizophrenic patients and controls. While Morais et al (2019) found significant differences in *T. gondii* antibodies between schizophrenia patients and controls in the same country. Possible explanations include relative serological methods insensitivity between two studies, differences in socioeconomic characteristics between patients and controls as living in rural or urban areas or because of study design.

4.3.2. Variation in both individual' genetic susceptibilities and *T. gondii* strains:

There are differences in both *T. gondii* genotypes and individual's tendency to be infected by different microorganisms. Three genotypes of *T. gondii* differ in their prevalence from regions to regions (De Campos- Carli et al, 2017). These strains differ in their effects on brain and neuropathogenicity as indicated in animal studies. Genetic host characterization is specifically crucial in schizophrenia, because of robust association between disease development and genetic aspects (increased risk in siblings and children) (Fuglewicz et al, 2017).

4.3.3 Reason concerned about consent form:

Perhaps an additional reason for not finding positive result is concerned with patients' rights to participate in study. Previously, all cases found in specific hospital were directly enrolled in study (Flegr, 2013). However, changes to ethics procedure now mean that just patients, who are capable and willing to sign informed consent paper enrolled in study (Khademvatan et al, 2014). Infection with *T. gondii* decreased level of conscientious and cooperativeness in infected subjects versus non-infected patients (Lindova et al, 2012). This is also applied for controls, but schizophrenic patients infected with *T. gondii* suffer from severe psychosis

versus *Toxoplasma* free-patients (Holub et al, 2013; Wang et al, 2006). Taking into account disease severity and decreased levels of conscientious and cooperativeness of *Toxoplasma* infected schizophrenic patients, it is possible that many will not enrolled in study (Flegr, 2013; Khademvatan et al, 2014). This result in under- representation of *Toxoplasma* infected patients in schizophrenia groups.

4.3.4: Reasons associated with serological methods sensitivity:

Serological methods usage contributed to variations in findings. Although various studies demonstrated appropriately performed serological test are precise indicators of earlier *Toxoplasma* infection (Innes, 1997; Torrey et al, 2007), they lack sensitivity needed for detection and cannot directly detect *Toxoplasma* organism in body fluids (Torrey et al, 2007; Fuglewicz et al, 2017). Lack of serological methods sensitivity versus parasite detection using PCR was study of Omar et al (2015), in which they examined *T. gondii* presence in 101 schizophrenic patients and 55 controls, using both Elisa (IgG antibodies detection), and Real-time PCR (*T. gondii* DNA detection). Result revealed IgG antibodies presence to *T. gondii* in 52 patients of 101 using Elisa, while of *T. gondii* DNA presence was detected in 33 patients (Omar et al, 2015). Utilization anti- *Toxoplasma* antibodies are not an adequate method for toxoplasmosis diagnosis. As some patients incorrectly diagnosed and undertake unneeded anti-parasitic medication. This indicated necessity of both molecular (PCR) and serological diagnostic approaches utilization for accurate *T. gondii* detection in schizophrenic patients (Ebrahimzadeh et al, 2018).

4.3.5. Variation in time and infection route:

Differences in both time and infection route influence results and possible association. Knowing infection time identified exact relation between *T. gondii* and schizophrenia (whether *T. gondii* infection proceeds to schizophrenia or behavior changes caused by schizophrenia resulted in *T. gondii* acquisition*).* Stage of *T. gondii* life cycle induced schizophrenia (Zhu, 2009). Route of infection contributed in detecting association between *T. gondii* and schizophrenia. Infection with *T. gondii* tissue cysts usually causes mild symptoms, and inflammatory response creation as a result of infection via route is rarely occurring. Detecting association via serological methods may be weak in people infected via tissue cysts. It would be stronger in people infected by oocysts (Ledgerwood et al, 2003).

4.3.6. Bias and confounding factors:

Finally, impacts of confounding factors and publication bias (small participant's number) are

major factors in finding differences in these results (De Witte et al, 2015; Fabiani et al, 2013). Studies that discover link between *T. gondii* and schizophrenia have lower quality than those did not discover this. Combined odds ratio in studies that found an association might be overestimated as indicated by Arias et al (2012). Many investigations were incapable of recognizing *T. gondii* antibodies levels variation between controls and patients (Li et al, 2013; Khademvatan et al, 2014) or presence *T. gondii* antibodies (Khademvatan et al, 2014). An indicator of bias was observed in meta-analysis that made by Sutterland et al (2015), but after editing this bias, significant relation between *T. gondii* and schizophrenia also remained (Sutterland et al, 2015). Importantly, age, social contacts, urbanicity, ethnicity and contact with cats and eating lightly- cooked meat are major risk factors. In many studies, age and sexual orientations incorporated as confounder, yet consideration of others was extremely variable (De Witte et al, 2015). In study included eating lightly- cooked meat and contact with cats as confounder reported that two had major influence on link between *T. gondii* and schizophrenia (Yuksel et al, 2010). Therefore, not including latter risk factors as confounder in most studies resulted in such differences (De Witte et al, 2015).

4.4. Evaluations of association and suggestions for future research:

Schizophrenia is multifactorial disease, and needs combination of both genetic and environmental factors to occur. *T. gondii* is important risk factor for its development in individuals with both genetic and environmental susceptibility (Flegr, 2015), and risk exceeded risk of any other human gene with OR< 1.40, as reported by genome- wide linkage study (Webster et al, 2010).

Improvement in both sensitivity and specificity of results needed to solve these differences. This achieved by conducting studies that uses IgG antibodies and PCR. Only few studies used both methods to investigate association.

Exposure to cats and eating lightly- cooked meat effects investigated only in few studies and significant effect on association was found. Research could be conducted on psychiatric outpatients with healthy controls in same area of residence or carrying out cohort studies using PCR and IgG antibodies to ascertain association.

Another question for future research is determining infection time as this would identify relation between schizophrenia and *T. gondii*. Niebuhr et al (2008) found association before schizophrenia onset, it was difficult to ascertain this association due to nature of military personnel's lifestyles that made them more exposed to *T. gondii* (Gutierrez- Fernandez et al, 2015). It would be interested to examine combination of antimicrobial effects of antipsychotic

drugs with antiparasitic treatment. This might provide possible cure for disease.

Finally, prenatal infection with *T. gondii* results in severe consequences on fetus. Hence, determining exact mechanism by which *T. gondii* cause these consequences is point that needs further research.

5- Limitations:

There are two major limitations. First, review did not include studies that published in languages other than English, which could lessened methodology power. However, exclusion of these studies aimed to construct a replicable systematic search, which is regarded as gold standard. Other limitation was limiting date of included studies to years 2010 to 2020, could also affect methodology power. Nevertheless, this aimed to clearly indicate association between *T. gondii* and schizophrenia, as serological methods sensitivity improved during last ten years.

6- Conclusion:

Many epidemiological studies associated *T. gondii* with schizophrenia. Indeed, association observed in pathophysiological changes (including influence on neurotransmitters, interaction with host gene, overexpression of metalloproteinases proteins and their inhibitor TIMP-1, neural damage via oxidative stress caused by immune response to *T. gondii*), increased schizophrenia symptoms severity in *T. gondii* infected schizophrenic subjects, schizophrenia symptoms development in acutely *T. gondii* infected immunocompetent individuals, antipsychotic medication effect on *T. gondii* growth, and *T. gondii* cause infection during neurodevelopmental stages, which is consistent with schizophrenia disease neurodevelopmental hypothesis. However, other epidemiological studies did not find this association for some reasons include differences in route and infection time, variation in *T. gondii* strains and individual' genetic susceptibilities, serological methods insensitivity and high seroprevalence of *T. gondii* in research country. In addition to risk of bias in these studies and concerns about patients right to participate. So, it was difficult to confirm aetiopathogenesis association between *T. gondii* and schizophrenia. However, given that schizophrenia is multifactorial disease and not all schizophrenic patients infected with *T. gondii*, *T. gondii* identified as an important risk factor for schizophrenia development. Therefore, upcoming research should ascertain association between *T. gondii* and schizophrenia, to open up new perspective in treatment and prevention of this disease. It is vital to continue research on this area, because "any organism that shares our brain with us is

worthy of study" (Bill Hutchinson, quoted in Fabiani et al, 2013).

List of references:

Ajzenberg, D. Cogné, N. Paris, L. Bessières, M. H. Thulliez, P. Filisetti, D. Pelloux, H. Marty, P. Dardé, M. L. (2002). 'Genotype of 86 Toxoplasma gondii Isolates Associated with Human Congenital Toxoplasmosis, and Correlation with Clinical Findings,' *The Journal of Infectious Diseases*, 186, pp. 684-689. doi: 10.1086/342663

Al-Hussainy, N. H. Al-saedi, A. M. Al-lehaibi, J. H. Al-lehaibi, Y. A. Al-Sehli, Y. M. Afifi, M. A. (2015). 'Serological evidences link toxoplasmosis with schizophrenia and major depression disorder,' *Journal of Microscopy and Ultrastructure*. Saudi Society of Microscopes, 3, pp. 148–153. doi: 10.1016/j.jmau.2015.03.006.

Alipour, A. Shojaee, S. Mohebali, M. Tehranidoost, M. Abdi Masoleh, F. Keshavarz, H. (2011). 'Toxoplasma infection in schizophrenia patients: A comparative study with control group,' *Iranian Journal of Parasitology*, 6, pp. 31–37.

Ali, F. T. Abd El-Azeem, E. M. Hamed, M. A. Ali, M. A. M. Abd Al-Kader, N. M. Hassan, E. A. (2017). 'Redox dysregulation, immuno-inflammatory alterations and genetic variants of BDNF and MMP-9 in schizophrenia: Pathophysiological and phenotypic implications,' *Schizophrenia Research*,188, pp. 98–109. doi: 10.1016/j.schres.2017.01.016.

Alvarado-Esquivel, C. Urbina-Álvarez, J. D. Estrada-Martínez, S. Torres-Castorena, A. Molotla-de-León, G. Liesenfeld, O. Dubey, J. P. (2011). 'Toxoplasma gondii infection and schizophrenia: A case control study in a low Toxoplasma seroprevalence Mexican population', *Parasitology International*, 60, pp. 151–155. doi: 10.1016/j.parint.2010.12.003.

Ansari-Lari, M. Farashbandi, H. Mohammadi, F. (2017). 'Association of Toxoplasma gondii infection with schizophrenia and its relationship with suicide attempts in these patients,' *Tropical Medicine and International Health*, 22, pp. 1322–1327. doi: 10.1111/tmi.12933.

Andreasen, N. C. Flaum, M. (1991). 'Schizophrenia: The characteristic symptoms,' *Schizophrenia Bulletin*, 17, pp. 27–49. doi: 10.1093/schbul/17.1.27.

Arias, I. Sorlozano, A. Villegas, E. Luna, J. D. D. McKenney, K. Cervilla, J. Gutierrez, B. Gutierrez, J. (2012). 'Infectious agents associated with schizophrenia: A meta-analysis,' *Schizophrenia Research*, 136, pp. 128–136. doi: 10.1016/j.schres.2011.10.026.

Bakre, H. Hussain, S. Ali, S. (2015). 'Toxoplasma gondii infection in patients with schizophrenia,' *Zanco Journal of Medical Sciences*, 19, pp. 874–879. doi: 10.15218/zjms.2015.0006.

Berenreiterová, M. Flegr, J. Kuběna, A. A. Němec, P. (2011). 'The distribution of Toxoplasma gondii cysts in the brain of a mouse with latent toxoplasmosis: Implications for the behavioral manipulation hypothesis,'*PLoS ONE*, 6. doi: 10.1371/journal.pone.0028925.

Bisio, H. Soldati-Favre, D. (2019). 'Signaling cascades governing entry into and exit from host cells by Toxoplasma gondii,' *Annual Review of Microbiology*, 73, pp. 579–599. doi: 10.1146/annurev-micro-020518-120235.

Black, M. W. Boothroyd, J. C. (2000). 'Lytic Cycle of Toxoplasma gondii,' *Microbiology and Molecular Biology Reviews*, 64, pp. 607–623. doi: 10.1128/mmbr.64.3.607-623.2000.

Blader, I. J. Manger, I. D. Boothroyd, J. C. (2001). 'Microarray analysis reveals previously unknown changes in Toxoplasma gondii-infected human cells,' *Journal of Biological Chemistry*, 276, pp. 24223–24231. doi: 10.1074/jbc.M100951200.

Berretta, S. (2012). 'Extracellular matrix abnormalities in schizophrenia,' *Neuropharmacology*, 62, pp. 1584–1597. doi: 10.1016/j.neuropharm.2011.08.010.

Carruthers, V. B. (2002). 'Host cell invasion by the opportunistic pathogen Toxoplasma gondii,' *Acta Tropica*, 81, pp. 111–122. doi: 10.1016/S0001-706X (01)00201-7.

Carruthers, V. B. Suzuki, Y. (2007). 'Effects of Toxoplasma gondii infection on the brain,' *Schizophrenia Bulletin*, 33, pp. 745–751. doi: 10.1093/schbul/sbm008.

Cetinkaya, Z. Yazar, S. Gecici, O. Namli, M. N. (2007). 'Anti-Toxoplasma gondii antibodies in patients with schizophrenia - Preliminary findings in a Turkish sample,' *Schizophrenia Bulletin*, 33, pp. 789–791. doi: 10.1093/schbul/sbm021.

Cevizci, S. Celik, M. Akcali, A. Oyekcin, D. G. Sahin, O. O. Bakar, C. (2015). 'Seroprevalence of anti-Toxoplasma gondii and anti-Borrelia species antibodies in patients with schizophrenia: A case-control study from western Turkey', *World Journal of Biological Psychiatry*, 16, pp. 230–236. doi:10.3109/15622975.2015.1012224

Chang, S. M. Cho, S. J. Jeon, H. J. Hahm, B. J. Lee, H. J. Park, J. I. Cho, M. J. (2008). 'Economic burden of schizophrenia in South Korea,' *The Korean Academy of Medical Sciences*, 23, pp. 167–175. doi: 10.3346/jkms.2008.23.2.167.

Clark, R. T. Philip Nance, J. Noor, S. Wilson, E. H. (2011). 'T-cell production of matrix metalloproteinases and inhibition of parasite clearance by TIMP-1 during chronic Toxoplasma infection in the brain,' *ASN Neuro*, 3, pp. 1–12. doi: 10.1042/AN20100027.

Cook, A. J.C. Gilbert, R. E. Buffolano, W. Zufferey, J. Petersen, E. Jenum, P. A. Foulon, W. Semprini, A. E. Dunn, D. T. (2000). 'Sources of toxoplasma infection in pregnant women: European multicenter case-control study,' *British Medical Journal*, 321, pp. 142–147.
doi: 10.1136/bmj.321.7254.142.

Daher, W. Soldati-Favre, D. (2009). 'Mechanisms controlling glideosome function in apicomplexans,' *Current Opinion in Microbiology*, 12, pp. 408–414. doi:10.1016/j.mib.2009.06.008

Dalimi, A. Abdoli, A. (2012). 'Latent toxoplasmosis and human,' *Iranian Journal of Parasitology*, 7, pp.1-17.

Daryani, A. Sharif, M. Hosseini, S. H. Karimi, S. A. Gholami, Shirzad. (2010). 'Serological survey of Toxoplasma gondii in schizophrenia patients referred to psychiatric hospital, Sari city, Iran,' *Tropical Biomedicine*, 27, pp. 476–482.

Da Silva, R. C. Langoni, H. (2009). 'Toxoplasma gondii: Host-parasite interaction and behavior manipulation,' *Parasitology Research*, 105, pp. 893-898. doi: 10.1007/s00436-009-1526-6.

De Campos-Carli, S. M. Vieira, É. L. M. Rocha, N. P. De Oliveira, K. Guimarães, F. C. Barbosa, I. G. De Barros, J. L. V. M. Okusaga, O. Martins-Filho, O. A. Salgado, J. V. Teixeira, A. L. (2017). 'Toxoplasma gondii infection and chronic schizophrenia: Is there any association?,' *Revista de Psiquiatria Clinica*, 44, pp. 145–148. doi: 10.1590/0101-60830000000140.

Del Grande, C. Galli, L. Schiavi, E. Dell Osso, L. Bruschi, F. (2017). 'Is toxoplasma gondii a trigger of bipolar disorder?,' *Pathogens*, 6, pp. 1–20. doi: 10.3390/pathogens6010003.

Demyttenaere, K. Bruffaerts, R. Posada-Villa, J. Gasquet, I. Kovess, V. Lepine, J. P. Angermeyer, M. C. Bernert, S. de Girolamo, G. Morosini, P. Polidori, G. Kikkawa, T. Kawakami, N. Ono, Y. Takeshima, T. Uda, H. Karam, E. G. Fayyad, J. A. Karam, A. N. Mneimneh, Z. N. WHO World Mental Health Survey Consortium (2004). 'Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys,' *JAMA*, 291, pp. 2581–2590. doi:10.1001/jama.291.21.2581

De Witte, L. D. Van Mierlo, H. C. Litjens, M. Klein, H. C. Bahn, S. Osterhaus, A. D. (2015). 'The association between antibodies to neurotropic pathogens and schizophrenia: A case-control study,' *Npj Schizophrenia*, 1. doi: 10.1038/npjschz.2015.41.

Dickerson, F. Stallings, C. Origoni, A.Vaughan, C. Khushalani, S.Yang, S. Yolken, R. (2013). 'C-reactive protein is elevated in schizophrenia,' *Schizophrenia Research*, 143, pp. 198–202. doi: 10.1016/j.schres.2012.10.041.

Dubey, J. P. Lindsay, D. S. Speer, C. A. (1998). 'Structures of Toxoplasma gondii tachyzoites, bradyzoites, and sporozoites and biology and development of tissue cysts,' *Clinical Microbiology Reviews*, 11, pp. 267–299. doi: 10.1128/cmr.11.2.267.

Dubey, J. P. Ferreira, L. R. Alsaad, M. Verma, S. K. Alves, D. A. Holland, G. N. McConkey, G. A. (2016). 'Experimental toxoplasmosis in rats induced orally with eleven strains of Toxoplasma gondii of seven genotypes: Tissue tropism, tissue cyst size, neural lesions, tissue cyst rupture without reactivation, and ocular lesions,' *PLoS ONE*, 11, pp. 1–26. doi:10.1371/journal.pone.0156255.

Dupont, C. D. Christian, D. A. Hunter, C. A. (2012). 'Immune response and immunopathology during toxoplasmosis,' *Seminars in Immunopathology*, 34, pp. 793-813. doi: 10.1007/s00281-012-0339-3.

Ebrahimzadeh, A. Shahraki, M. and Mohammadi, A. (2018). 'Serological and molecular diagnosis of Toxoplasma gondii in patients with schizophrenia,' . *Journal of Parasitic Diseases*, 42, pp.177-181. https://doi.org/10.1007/s12639-018-0979-x

El-Gebaly, N. Abd-Eltawab, M. Hamed, A. Mahfouz, N. Adel, S. Mahfoz, A. Rehan, M. Elsebaei, E. (2019). 'Insights into the interplay of latent toxoplasmosis, testosterone, cortisol and oxidative stress in screened schizophrenic patients in Egypt,' *Parasitologists United Journal*, 12, pp. 102–109. doi: 10.21608/puj.2019.11819.1040.

Elsheikha, H. M. Zhu, X. Q. (2016). 'Toxoplasma gondii infection and schizophrenia: An inter-kingdom communication perspective,' *Current Opinion in Infectious Diseases*, 29, pp. 311–318. doi: 10.1097/QCO.0000000000000265.

Elsheikha, H. M. Büsselberg, D. Zhu, X. Q. (2016). 'The known and missing links between Toxoplasma gondii and schizophrenia,' *Metabolic Brain Disease*, 31, pp. 749–759. doi: 10.1007/s11011-016-9822-1.

El- Mouhawess, A. Hammoud, A. Zoghbi, M. Hallit, S. Haddad, C. El Haddad, K. El Khoury, S. Tannous, J. Obeid, S. Halabi, M. A. Mammari, N. (2020). 'Erratum: Correction to: Relationship between Toxoplasma gondii

seropositivity and schizophrenia in the Lebanese population: potential implication of genetic polymorphism of MMP-9,' *BMC psychiatry*, 20, p. 330. doi: 10.1186/s12888-020-02727-5.

El-Sayed, N. M. Ismail, K. A. Ahmed, S. A. E. G. Ezz-El-Din, H. M. Ezz-El-Din Azzam, H. M. E. (2012). 'Possible association between Toxoplasma gondii infection and schizophrenia: Egyptian study,' *Infectious Diseases in Clinical Practice*, 20, pp. 394–399. doi: 10.1097/IPC.0b013e31826991aa.

Emelia, O. Amal, R. N. Ruzanna, Z. Z. Shahida, H. Azzubair, Z. Tan, K. S. Noor Aadila, S. Siti, N. A.M. Aisah, M. Y. (2012). 'Seroprevalence of anti-Toxoplasma gondii IgG antibody in patients with schizophrenia,' *Tropical Biomedicine*, 29, pp. 151–159.

Esshili, A. Thabet, S. Jemli, A. Trifa, F. Mechri, A. Zaafrane, F. Gaha, L. Juckel, G. Babba, H. Bel Hadj Jrad, B. (2016). 'Toxoplasma gondii infection in schizophrenia and associated clinical features,' *Psychiatry Research*, 245, pp. 327–332. doi:10.1016/j.psychres.2016.08.056.

Fabiani, S. Pinto, B. Bruschi, F. (2013). 'Toxoplasmosis and neuropsychiatric diseases: Can serological studies establish a clear relationship?,' *Neurological Sciences*, 34, pp. 417–425. doi: 10.1007/s10072-012-1197-4.

Fabiani, S. Pinto, B. Bonuccelli, U. Bruschi, F. (2015). 'Neurobiological studies on the relationship between toxoplasmosis and neuropsychiatric diseases,' *Journal of the Neurological Sciences*, 351, pp. 3–8. doi: 10.1016/j.jns.2015.02.028.

Fekadu, A. Shibre, T. Cleare, A. J. (2010). 'Toxoplasmosis as a cause for behaviour disorders - Overview of evidence and mechanisms,' *Folia Parasitologica*, 57, pp. 105–113.

Filice, G. Meroni, V. Carnevale, G. Olliaro, P. Carosi, G. (1983). 'Comparison of ELISA and indirect immunofluorescence in the detection of IgG and IgM anti-Toxoplasma antibodies,' *Bollettino dell'Istituto sieroterapico milanese*, 62, pp. 445–450.

Flegr, J. Kodym, P. Tolarová, V. (2000). 'Correlation of duration of latent Toxoplasma gondii infection with personality changes in women,' *Biological Psychology*, 53, pp. 57–68. doi: 10.1016/S0301-0511(00)00034-X.

Flegr, J. Preiss, M. Klose, J. Havlíček, 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?,' *Biological Psychology*, 63, pp. 253–268. doi: 10.1016/S0301-0511(03)00075-9.

Flegr, J. Lenochová, P. Hodný, Z. Vondrová, M. (2011). 'Fatal attraction phenomenon in humans- cat odour attractiveness increased for Toxoplasma- infected men while decreased for non- infected women,' *PLos Neglected Tropical Diseases*, 5. doi:10.1371/journal.pntd.0001389

Flegr, J. (2013). 'How and why Toxoplasma makes us crazy,' *Trends in Parasitology*, 29, pp. 156–163. doi: 10.1016/j.pt.2013.01.007.

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. doi: 10.1371/journal.pone.0090203.

Flegr, J. Klapilová, K. Kaňková, S. (2014). 'Toxoplasmosis can be a sexually transmitted infection with serious clinical consequences. Not all routes of infection are created equal,' *Medical Hypotheses*, 83, pp. 286–289. doi: 10.1016/j.mehy.2014.05.019.

Flegr, J. (2015). 'Schizophrenia and Toxoplasma gondii: An undervalued association?,' *Expert Review of Anti-Infective Therapy*, 13, pp. 817–820. doi:10.1586/14787210.2015.1051033.

Flegr, J. Horacek, J. (2020). 'Negative effects of latent Toxoplasmosis on mental health,' *Frontiers in Psychiatry*, 10, pp. 1–8. doi: 10.3389/fpsyt.2019.01012.

Fuglewicz, A. J., Piotrowski, P. and Stodolak, A. (2017). 'Relationship between toxoplasmosis and schizophrenia: A review,' *Advances in Clinical and Experimental Medicine*, 26, pp. 1033–1038. doi: 10.17219/acem/61435

Gao, H.-M., Zhou, H. Hong, J.-S. (2014). 'Oxidative Stress, Neuroinflammation, and Neurodegeneration,' in Peterson, P. K. and Toborek, M. (eds) *Neuroinflammation and Neurodegeneration*. New York, NY: Springer New York, pp. 81–104.

Garcia Bahia-Oliveira, L. M. Jones, J. L. Azevedo-Silva, J. Alves, C. C.F. Oréfice, F. Addiss, D. G. (2003). 'Highly endemic, waterborne toxoplasmosis in North Rio de Janeiro State, Brazil,' *Emerging Infectious Diseases*, 9, pp. 55–62. doi: 10.3201/eid0901.020160.

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, pp. 1–10. doi: 10.1371/journal.pone.0004801.

Ghosh, A. K. Vaughan, D. E. (2012). 'PAI-1 in tissue fibrosis,' *Journal of Cellular Physiology*, 227, pp. 493–507. doi: 10.1002/jcp.22783.

Goeree, R. Farahati, F. Burke, N. Blackhouse, G. O'Reilly, D. Pyne, J. Tarride, J. E. (2005). 'The economic burden of schizophrenia in Canada in 2004,' *Current Medical Research and Opinion*, 21, pp.2017-2028. doi: 10.1185/030079905X75087.

Gutiérrez-Fernández, J. Del Castillo, J. D. D. L. Mañanes-González, S. Carrillo-Ávila, J. A. Gutiérrez, B. Cervilla, J. A. Sorlózano-Puerto, A. (2015). 'Different presence of Chlamydia pneumoniae, Herpes simplex virus type 1, human herpes virus 6, and Toxoplasma gondii in schizophrenia: Meta-analysis and analytical study,' *Neuropsychiatric Disease and Treatment*, 11, pp. 843–852. doi: 10.2147/NDT.S79285.

Hafner, H. Maurer, K. Loffler, W. Riecher-Rossler, A. (1993). 'The influence of age and sex on the onset of early course of schizophrenia,' *British Journal of Psychiatry*, 162, pp. 80-86. doi: 10.1192/bjp.162.1.80.

Hamidinejat, H. Ghorbanpoor, M. Hosseini, H. Alavi, S. M. Nabavi, L. Jalali, M. H. R. Borojeni, M. P. Jafari, H. Mohammadaligol, S. (2010). 'Toxoplasma gondii infection in first-episode and inpatient individuals with schizophrenia,' *International Journal of Infectious Diseases*, 14, pp. 978–981. doi: 10.1016/j.ijid.2010.05.018.

Harrison, P. J. (1999). 'The neuropathology of schizophrenia. A critical review of the data and their interpretation,' *Brain*, 122, pp. 593–624. doi: 10.1093/brain/122.4.593.

Havlícek, J. Gašová, Z. Smith, A. P. Zvára, K. Flegr, J. (2001). 'Decrease of psychomotor performance in subjects with latent 'asymptomatic' toxoplasmosis,' *Parasitology*, 122, pp. 515–520. doi: 10.1017/S0031182001007624.

Hill, D. E. Chirukandoth, S. Dubey, J. P. (2005). 'Biology and epidemiology of Toxoplasma gondii in man and animals,' *Animal Health Research Reviews*, 6, pp. 41-61. doi: 10.1079/AHR2005100

Hinze- Selch, D. Daubener, W. Eggert, L. Erdag, S. Stoltenberg, R. Wilms, S. (2007). 'A controlled prospective study of Toxoplasma gondii infection in individuals with schizophrenia: Beyond seroprevalence,' *Schizophrenia Bulletin*, 33, pp. 782–788. doi: 10.1093/schbul/sbm010.

Hunter, C. A. Roberts, C. W. Murray, M. Alexander, J. (1992). 'Detection of cytokine mRNA in the brains of mice with toxoplasmic encephalitis,' *Parasite Immunology*, 14, pp. 405–413. doi: 10.1111/j.1365-3024.1992.tb00015.x.

Holub, D. Flegr, J. Dragomirecká, E. Rodriguez, M. Preiss, M. Novák, T. Čermák, J. Horáček, J. Kodym, P. Libiger, J. Höschl, C. Motlová, L. B. (2013). 'Differences in onset of disease and severity of psychopathology between toxoplasmosis-related and toxoplasmosis-unrelated schizophrenia,' *Acta Psychiatrica Scandinavica*, 127, pp. 227–238. doi: 10.1111/acps.12031.

Horacek, J. Flegr, J. Tintera, J. Verebova, K. Spaniel, F. Novak, T. Brunovsky, M. Bubenikova-Valesova, V. Holub, D. Palenicek, T. Höschl, C. (2012). 'Latent toxoplasmosis reduces gray matter density in schizophrenia but not in controls: Voxel-Based-Morphometry (VBM) study,' *World Journal of Biological Psychiatry*, 13, pp. 501–509. doi: 10.3109/15622975.2011.573809.

Hunter, C. A. Sibley, L. D. (2012). 'Modulation of innate immunity by Toxoplasma gondii virulence effectors,' *Nature Reviews Microbiology*. Nature Publishing Group, 10, pp. 766–778. doi:10.1038/nrmicro2858

Innes, E. A. (1997). 'Toxoplasmosis: Comparative species susceptibility and host immune response,' *Comparative Immunology, Microbiology and Infectious Diseases*, 20, pp. 131–138. doi: 10.1016/S0147-9571(96)00038-0.

Jackson, M. H. Hutchison, W. M. (1989). 'The prevalence and source of Toxoplasma infection in the environment,' *Advances in Parasitology*, 28, pp. 55-105. doi: 10.1016/S0065-308X(08)60331-0.

Jafari Modrek, M. Hasanzadeh, R. Foroutan, M. Mirahmadi, H. Rahmati-Balaghaleh, M. Zarean, M. (2019). 'Seroprevalence and molecular evaluation of Toxoplasma gondii in schizophrenic patients hospitalized in Sistan and Baluchestan province, Southeast of Iran,' *Tropical Biomedicine*, 36, pp. 422–429.

James, B. O. Agbonile, I. O. Okolo, M. Lawani, A. O. Omoaregba, J. O. (2013). 'Prevalence of *Toxoplasma gondii* infection among individuals with severe mental illness in Nigeria: a case control study,' *Pathogens and Global Health*, 107, pp. 189- 193. doi:10.1179/2047773213Y.0000000093.

Johnson, J. Suzuki, Y. Mack, D. Mui, E. Estes, R. David, C. Skamene, E. Forman, J. McLeod, R. (2002). 'Genetic analysis of influences on survival following Toxoplasma gondii infection,' *International Journal for Parasitology*, 32, pp. 179–185. doi: 10.1016/S0020-7519(01)00321-6.

Juanah, L. Y. Jalaludin, J. Osman, M. Osman, Z. J. (2013). 'Seroprevalence of Toxoplasma gondii among schizophrenics at hospital Kajang,' *American Journal of Infectious Diseases*, 9, pp. 11–16. doi:10.3844/ajidsp.2013.11.16

Karabulut, N. Bilgiç, S. Gürok, M. G. Karaboğa, F. (2015). 'Is there any role of latent toxoplasmosis in schizophrenia disease?,' *Journal of the Chinese Medical Association*, 78, pp. 533–537. doi: 10.1016/j.jcma.2015.06.007.

Khademvatan, S. Khajeddin, N. Izadi, S. Yousefi, E. (2014). 'Investigation of anti-Toxocara and anti-Toxoplasma antibodies in patients with schizophrenia disorder,' *Schizophrenia Research and Treatment*, 2014, pp. 1–7. doi: 10.1155/2014/230349.

Khan, A. Su, C. German, M. Storch, G. A. Clifford, D. B. Sibley, L. D. (2005). 'Genotyping of Toxoplasma gondii strains from immunocompromised patients reveals high prevalence of type I strains,' *Journal of Clinical Microbiology*, 43, pp. 5881-5887. doi:10.1128/JCM.43.12.5881-5887.2005

Khandaker, G. M. Zimbron, J. Lewis, G. Jones, P. B. (2013). 'Prenatal maternal infection, neurodevelopment and adult schizophrenia: A systematic review of population-based studies,' *Psychological Medicine*, 43, pp. 239–257. doi:10.1017/S0033291712000736.

Khandaker, G. M. Dantzer, R. (2016). 'Is there a role for immune-to-brain communication in schizophrenia?,' *Psychopharmacology*, 233, pp. 1559–1573. doi: 10.1007/s00213-015-3975-1.

Konradt, C. Ueno, N. Christian, D. A. Delong, J. H. Pritchard, G. H. Herz, J. Bzik, D. J. Koshy, A. A. McGavern, D. B. Lodoen, M. B. Hunter, C. A. (2016). 'Endothelial cells are a replicative niche for entry of Toxoplasma gondii to the central nervous system,' *Nature Microbiology*, 1, pp. 1-8. doi: 10.1038/nmicrobiol.2016.1.

Krause, D. Mats, J. Weidinger, E. Wagner, J. Wildenauer, A. Obermeier, M. Riedel, M. Mller, N. (2010). 'The association of infectious agents and schizophrenia,' *World Journal of Biological Psychiatry*, 11, pp. 739–743. doi: 10.3109/15622971003653246.

Ledgerwood, L. G. Ewald, P. W. Cochran, G. M. (2003). 'Genes, germs, and schizophrenia: An evolutionary perspective,' *Perspectives in Biology and Medicine*, 46, pp. 317–348. doi:10.1353/pbm.2003.0038

Lee, M. M. Yoon, B. J. Osiewicz, K. Preston, M. Bundy, B. Van Heeckeren, A. M. Werb, Z. Soloway, P. D. (2005). 'Tissue inhibitor of metalloproteinase 1 regulates resistance to infection,' *Infection and Immunity*, 73, pp. 661–665. doi:10.1128/IAI.73.1.661-665.2005

Leweke, F. M. Gerth, C. W. Koethe, D. Klosterkötter, J. Ruslanova, I. Krivogorsky, B. Torrey, E. F. Yolken, R. H. (2004). 'Antibodies to infectious agents in individuals with recent onset schizophrenia,' *European Archives of Psychiatry and Clinical Neuroscience*, 254, pp. 4–8. doi: 10.1007/s00406-004-0481-6.

Lindová, J. Příplatová, L. Flegr, J. (2012). 'Higher extraversion and lower conscientiousness in humans infected with *Toxoplasma*,' *European Journal of Personality*, 26, pp. 285–291. doi: 10.1002/per.838.

Li, Y. Weber, N. S. Fisher, J. A. Yolken, R. H. Cowan, D. N. Larsen, R. A. Niebuhr, D. W. (2013). 'Association between antibodies to multiple infectious and food antigens and new onset schizophrenia among US military personnel,' *Schizophrenia Research*, 151, pp. 36–42. doi: 10.1016/j.schres.2013.10.004.

Maubon, D. Ajzenberg, D. Brenier-Pinchart, M. P. Dardé, M. L. Pelloux, H. (2008). 'What are the respective host and parasite contributions to toxoplasmosis?,' *Trends in Parasitology*, 24, pp. 299-303. doi:10.1016/j.pt.2008.03.012

McConkey, G. A. Martin, H. L. Bristow, G. C. Webster, J. P. (2013). 'Toxoplasma gondii infection and behavior - location, location, location?,' *The Journal of Experimental Biology*, 216, pp. 113-119. doi:10.1242/jeb.074153

Mendez, O. A. Koshy, A. A. (2017). 'Toxoplasma gondii: entry, association, and physiological influence on the central nervous system,' *PLoS Pathogens*, 13, pp. 1–12. doi: 10.1371/journal.ppat.1006351.

Moher, D. Liberati, A. Tetzlaff, J. Altman, D. G. Altman, D. Antes, G. Atkins, D. Barbour, V. Barrowman, N. Berlin, J. A. Clark, J. Clarke, M. Cook, D. D'Amico, R. Deeks, J. J. Devereaux, P. J. Dickersin, K. Egger, M.

Ernst, E. Gøtzsche, P. C. Grimshaw, J. Guyatt, G. Higgins, J. Ioannidis, J. P. A. Kleijnen, J. Lang, T. Magrini, N. McNamee, D. Moja, L. Mulrow, C. Napoli, M. Oxman, A. Pham, B. Rennie, D. Sampson, M. Schulz, K. F. Shekelle, P. G. Tovey, D. Tugwell, P. (2009). 'Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement,' *PLoS Medicine*, 6. doi:10.1371/journal.pmed1000097

Montazeri, M. Mikaeili Galeh, T. Moosazadeh, M. Sarvi, S. Dodangeh, S. Javidnia, J. Sharif, M. Daryani, A. (2020). 'The global serological prevalence of Toxoplasma gondii in felids during the last five decades (1967-2017): A systematic review and meta-analysis,' *Parasites and Vectors*, 13, pp. 1–10. doi: 10.1186/s13071-020-3954-1.

Morais, F. B. Arantes, T. E. F. e. Muccioli, C. (2019). 'Seroprevalence and manifestations of ocular toxoplasmosis in patients with schizophrenia,' *Ocular Immunology and Inflammation*, 27, pp. 134–137. doi: 10.1080/09273948.2017.1408843.

Mou, X. Peterson, C. B. Prosser, R. A. (2009). 'Tissue-type plasminogen activator-plasmin-BDNF modulate glutamate-induced phase-shifts of the mouse suprachiasmatic circadian clock in vitro,' *European Journal of Neuroscience*, 30, pp. 1451–1460. doi:10.1111/j.1460-9568.2009.06946.x.

Nicholl, D. Akhras, K.S. Diels, J. Schadrack, J. (2010). 'Burden of schizophrenia in recently diagnosed patients: Healthcare utilisation and cost perspective,' *Current Medical Research and Opinion*, 26, pp. 943–955. doi: 10.1185/03007991003658956.

Niebuhr, D. W. Millikan, A. M. Cowan, D. N. Yolken, R. Li, Y. Weber, N. S. (2008). 'Selected infectious agents and risk of schizophrenia among U.S. military personnel,' *American Journal of Psychiatry*, 165, pp. 99–106. doi: 10.1176/appi.ajp.2007.06081254.

Notarangelo, F. M. Wilson, E. H. Horning, K. J. Thomas, M. A.R. Harris, T. H. Fang, Q. Hunter, C. A. Schwarcz, R. (2014). 'Evaluation of kynurenine pathway metabolism in Toxoplasma gondii-infected mice: Implications for schizophrenia,' *Schizophrenia Research*, 152, pp. 261–267. doi: https://doi.org/10.1016/j.schres.2013.11.011.

Okulski, P. Jay, T. M. Jaworski, J. Duniec, K. Dzwonek, J. Konopacki, F. A. Wilczynski, G. M. Sánchez-Capelo, A. Mallet, J. Kaczmarek, L. (2007). 'TIMP-1 abolishes MMP-9-dependent long-lasting long-term potentiation in the prefrontal cortex,' *Biological Psychiatry*, 62, pp. 359–362. doi: doi: 10.1016/j.biopsych.2006.09.012.

Omar, A. Bakar, O. C. Adam, N. F. Osman, H. Osman, A. Suleiman, A. H. Manaf, M. R. A. Selamat, M. I. (2015). 'Seropositivity and serointensity of Toxoplasma gondii antibodies and DNA among patients with schizophrenia,' *Korean Journal of Parasitology*, 53, pp. 29–34. doi: 10.3347/kjp.2015.53.1.29.

Omar, S. S. C. Moklas, M. A. M. Mohtarrudin, N. Osman, M. (2018). 'Toxoplasma gondii stimulates the behavioural changes of rodents: Updated evidence,' *Journal of Medical Biomedical and Applied Sciences*, 6, pp. 148-153. doi: 10.15520/jmbas.v6i9.152

Park, M. H. Kwon, Y. J. Jeong, H. Y. Lee, H. Y. Hwangbo, Y. Yoon, H. J. Shim, S. H. (2012). 'Association between intracellular infectious agents and schizophrenia,' *Clinical Psychopharmacology and Neuroscience*, 10, pp. 117–123. doi: 10.9758/cpn.2012.10.2.117.

Parlog, A. Schlüter, D. Dunay, I. R. (2015). 'Toxoplasma gondii-induced neuronal alterations,' *Parasite Immunology*, 37, pp. 159–170. doi:10.1111/pim.12157.

Patel, K. R. Cherian, J. Gohil, K. Atkinson, D. (2014). 'Schizophrenia: Overview and treatment options,' *P and T*, 39, pp. 638-645.

Prandovszky, E. Gaskell, E. Martin, H. Dubey, J. P. Webster, J. P. McConkey, G. A. (2011). 'The neurotropic parasite Toxoplasma gondii increases dopamine metabolism,'*PLoS ONE*, 6. doi:10.1371/journal.pone.0023866

Randall, L. M. Hunter, C. A. (2011). 'Parasite dissemination and the pathogenesis of toxoplasmosis,' *European Journal of Microbiology and Immunology*, 1, pp. 3–9. doi: 10.1556/EuJMI.1.2011.1.3

Russo, S. Kema, I. P. Haagsma, E. B. Boon, J. C. Willemse, P. H. B. Den Boer, J. A. De Vries, E. G. E. Korf, J. (2005). 'Irritability rather than depression during interferon treatment is linked to increased tryptophan catabolism,' *Psychosomatic Medicine*, 67, pp. 773–777. doi: 10.1097/01 0000171193.28044.d8.

Sacks, J. J. Roberto, R. R. Brooks, N. F. (1982). 'Toxoplasmosis infection associated with raw goat's milk,' *The Journal of the American Medical Association*, 248, pp. 1728–1732. doi: 10.1001/jama.1982.03330140038029.

Sun, G. Y. Horrocks, L. A. Farooqui, A. A. (2007). 'The roles of NADPH oxidase and phospholipases A2 in oxidative and inflammatory responses in neurodegenerative diseases,' *Journal of Neurochemistry*, 103, pp. 1–16. doi: 10.1111/j.1471-4159.2007.04670.x.

Sutterland, A. L. Fond, G. Kuin, A. Koeter, M. W.J. Lutter, R. van Gool, T. Yolken, R. Szoke, A. Leboyer, M. de Haan, L. (2015). 'Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: Systematic review and meta-analysis,' *Acta Psychiatrica Scandinavica*, 132, pp. 161–179. doi: doi:10.1111/acps.12423.

Tan, H. Y. Nicodemus, K. K. Chen, Q. Li, Z. Brooke, J. K. Honea, R. Kolachana, B. S. Straub, R. E. Meyer-Lindenberg, A. Sei, Y. Mattay, V. S. Callicott, J. H. Weinberger, D. R. (2008). 'Genetic variation in AKT1 is linked to dopamine-associated prefrontal cortical structure and function in humans,' *Journal of Clinical Investigation*, 118, pp. 2200–2208. doi: 10.1172/JCI34725.

Tenter, A. M. Heckeroth, A. R. and Weiss, L. M. (2000). 'Toxoplasma gondii: From animals to humans,' *International Journal for Parasitology*, 30, pp. 1217–1258. doi: https://doi.org/10.1016/S0020-7519(00)00124-7.

Thorne, M. Moore, C. S. Robertson, G. S. (2009). 'Lack of TIMP-1 increases severity of experimental autoimmune encephalomyelitis: Effects of darbepoetin alfa on TIMP-1 null and wild-type mice,' *Journal of Neuroimmunology*, 211, pp. 92–100. doi: 10.1016/j.jneuroim.2009.04.003

Tomasik, J. Schultz, T. L. Kluge, W. Yolken, R. H. Bahn, S. Carruthers, V. B. (2016). 'Shared immune and repair markers during experimental Toxoplasma chronic brain infection and schizophrenia,' *Schizophrenia Bulletin*, 42, pp. 386–395. doi: 10.1093/schbul/sbv134.

Torrey, E. F. Torrey, B. B. Burton Bradley, B. G. (1974). 'The epidemiology of schizophrenia in Papua New Guinea,' *American Journal of Psychiatry*, 131, pp. 567–573. doi: 10.1176/ajp.131.5.567.

Torrey, E. F.Yolken, R. H. (2003). 'Toxoplasma gondii and Schizophrenia,' *Emerging Infectious Diseases*, 9, pp. 1375–1380. doi: 10.3201/eid0911.030143.

Torrey, E. F. Bartko, J. J. Lun, Z. R. Yolken, R. H. (2007). 'Antibodies to Toxoplasma gondii in patients with schizophrenia: A meta-analysis,' *Schizophrenia Bulletin*, 33, pp. 729–736. doi:10.1093/schbul/sbl050

Torrey, E. F. Bartko, J. J. Yolken, R. H. (2012). 'Toxoplasma gondii and other risk factors for schizophrenia: An update,' *Schizophrenia Bulletin*, 38, pp. 642–647. doi:10.1093/schbul/sbs043

Vyas, A. Kim, S. K. Giacomini, N. Boothroyd, J. C. Sapolsky, R. M. (2007). 'Behavioral changes induced by Toxoplasma infection of rodents are highly specific to aversion of cat odors,' *Proceedings of the National Academy of Sciences of the United States of America*, 104, pp. 6442–6447. doi:10.1073/pnas.0608310104

Wang, H. L. Wang, G. H. Li, Q. Y. Shu, C. Jiang, M. S. Guo, Y. (2006). 'Prevalence of Toxoplasma infection in first-episode schizophrenia and comparison between Toxoplasma-seropositive and Toxoplasma-seronegative schizophrenia,' *Acta Psychiatrica Scandinavica*, 114, pp. 40–48. doi:10.1111/j.1600-0447.2006.00780.x

Wang, P. S. Aguilar.G, S. Alonso, J. Angermeyer, M. C. Borges, G. Bromet, E. J. Bruffaerts, R. de Girolamo, G. de Graaf, R. Gureje, O. Haro, J. M. Karam, E. G. Kessler, R. C. Kovess, V. Lane, M. C. Lee, S. Levinson, D. Ono, Y. Petukhova, M. Posada. V, J. Seedat, 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,' *Lancet*, 370, pp. 841–850. doi:10.1016/S0140-6736(07)61414-7.

Wang, X. Michie, S. A. Xu, B. Suzuki, Y. (2007). 'Importance of IFN-γ-mediated expression of endothelial VCAM-1 on recruitment of CD8+ T cells into the brain during chronic infection with *Toxoplasma gondii*,' *Journal of Interferon and Cytokine Research*, 27, pp. 329–338. doi:10.1089/jir.2006.0154.

Wang, Z. T. Harmon, S. O'Malley, K. L. Sibley, L. D. (2015). 'Reassessment of the role of aromatic amino acid hydroxylases and the effect of infection by Toxoplasma gondii on host dopamine,' *Infection and Immunity*, 83, pp. 1039–1047. doi: 10.1128/IAI.02465-14.

Webster, J. P. McConkey, G. A. (2010). 'Toxoplasma gondii-altered host behaviour: clues as to mechanism of action,' *Folia Parasitologica*, 5683, pp. 95–104. doi:10.14411/fp.2010.012.

Wei, Y. Williams, J. M. Dipace, C. Sung, U. Javitch, J. A. Galli, A. Saunders, C. (2007). 'Dopamine transporter activity mediates amphetamine- induced inhibition of Akt through a Ca,' *Molecular Pharmacology*, 71, pp. 835–842. doi: 10.1124/mol.106.026351.

Wilson, E. H. Hunter, C. A. (2004). 'The role of astrocytes in the immunopathogenesis of toxoplasmic encephalitis,' *International Journal for Parasitology*, 34, pp. 543–548. doi: 10.1016/j.ijpara.2003.12.010

World Health Organisation 2001: World Health Report 2001. Mental Health: New Understanding, New Hope. World Health Organisation, Geneva, 178 pp

Xiao, J. Yolken, R. H. (2015). 'Strain hypothesis of Toxoplasma gondii infection on the outcome of human diseases,' *Acta Physiologica,* 213, pp.828-845. doi:10.1111/apha.12458.

Yan, C. Liang, L. J. Zheng, K. Y. Zhu, X. Q. (2016). 'Impact of environmental factors on the emergence, transmission and distribution of Toxoplasma gondii,' *Parasites and Vectors*. Parasites & Vectors, 9, pp. 1–7. doi:10.1186/s13071-016-1432-6

Yolken, R. H. Dickerson, F. B. Fuller Torrey, E. (2009). 'Toxoplasma and schizophrenia,' *Parasite Immunology*, 31, pp. 706–715. doi:10.1111/j.1365-3024.2009.01131.x

Yolken, R., Torrey, E. F. Dickerson, F. (2017). 'Evidence of increased exposure to Toxoplasma gondii in individuals with recent onset psychosis but not with established schizophrenia,' *PLoS Neglected Tropical Diseases*, 11, pp. 1–10. doi: 10.1371/journal.pntd.0006040.

Yuksel, P. Alpay, N. Babur, C. Bayar, R. Saribas, S. Karakose, A. R. Aksoy, C. Asian, M. Mehmetali, S. Kilic, S. Balcioglu, I. Hamanca, O. Dirican, A. Kucukbasmaci, O. Oner, A. Torun, M. M. Kocazeybek, B. (2010). 'The role of latent toxoplasmosis in the aetiopathogenesis of schizophrenia - The risk factor or an indication of a contact with cat?,' *Folia Parasitologica*, 57, pp. 121–128. doi: 10.14411/fp.2010.015

Zhu, S. (2009). 'Psychosis may be associated with toxoplasmosis,' *Medical Hypotheses*, 73, pp. 799–801. doi: https://doi.org/10.1016/j.mehy.2009.04.013.

Zindler, E. Zipp, F. (2010). 'Neuronal injury in chronic CNS inflammation,' *Best Practice and Research: Clinical Anaesthesiology*, 24, pp. 551–562. doi:10.1016/j.bpa.2010.11.001