REVIEW ARTICLE

Association between exposure to toxoplasmosis and major psychiatric disorders: a systematic review

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Objective: To assess the association between exposure to toxoplasmosis and major psychiatric disorders through a systematic review of the literature.
Methods: The literature review was performed in the MEDLINE, SciELO, and PsycINFO databases. To evaluate the quality of the studies included in the review, the Newcastle-Ottawa Scale was used.
Results: Thirty-one studies were included, and the majority found an association between exposure to toxoplasmosis and schizophrenia or bipolar disorder (58.3 and 54.5% of the included papers, respectively), but not major depressive disorder. We found no significant difference in mean quality scores between studies that corroborated and contradicted the association hypothesis for either schizophrenia or bipolar disorder. All included papers were considered at least satisfactory according to the Newcastle-Ottawa Scale (total scores $\geqslant$ 6 out of 9).
Conclusion: Although there was no association between exposure to toxoplasmosis and major depressive disorder, the results indicate an association with both bipolar disorder and schizophrenia, despite their heterogeneity. Further studies should be performed with more specific variables so that the nature of these relationships can be elucidated.

Keywords: Major depressive disorder; schizophrenia; mood disorders; bipolar disorder; toxoplasmosis

Introduction

Toxoplasma gondii (*T. gondii*) is a protozoan parasite that occurs worldwide and has a high seroprevalence, infecting more than 60% of the population in some countries.[1] Known for its ability to alter the host's behavior to increase the chance of transmission, there is much curiosity about its effects on human health during the latent phase of infection.

T. gondii has three stages of development: tachyzoites, bradyzoites, and oocysts. When attacked by the host's immune system, some of the parasites turn into cystic formations containing bradyzoites, which initiates the chronic or latent phase of the disease. Although a relationship between schizophrenia and toxoplasmosis has been hypothesized since the 1950s,[2] only recently has this and other associations been deeply investigated.[3,4]

In the early 1990s, the association between *T. gondii* infection, neuropsychiatric disorders, and personality changes was also studied.[3,5] Further studies have raised the possibility that exposure to toxoplasmosis (ET) is a risk factor for diseases such as schizophrenia and mood

disorders. Moreover, different authors have reported that mood stabilizers and antipsychotics used in bipolar disorder (BD) treatment can inhibit *T. gondii* replication *in vitro*.[4,6]

This evidence is founded on the fact that the main neurobiological changes caused by latent *T. gondii* infection in humans are consistent with the pathophysiology of neuropsychiatric diseases such as schizophrenia and mood disorders, as was found in a previous review.[7] Furthermore, an experimental study has shown that *T. gondii* infection in mammalian dopaminergic cells repeatedly raises dopamine-dependent K^+ secretion. In the same study, staining the brains of infected rats with dopamine-specific antibodies resulted in strong staining of cysteine-containing regions. Tyrosine hydroxylase, the limiting enzyme in dopamine production, was also found within intracellular cysts. The overall conclusion of this study was that ET plays an important role in increasing dopamine metabolism in neurons.[8]

Indeed, the dopaminergic system plays a significant role in the etiology of mood disorders and schizophrenia. The dopamine hypothesis in BD states that high levels of

dopamine are found in the mania/hypomania phases, while decreasing levels of this neurotransmitter occur in the depressive phase.[9,10]

In fact, a meta-analysis[2] found a higher prevalence of *T. gondii* antibodies in patients with schizophrenia than healthy controls (odds ratio [OR] = 2.73). It should be pointed out that this review collected data from papers published since the 1950s across 17 countries, including countries in Asia and Eastern Europe, which were absent at the time from Western databases such as MEDLINE. However, the authors did not consider age an important confounding factor for ET diagnosis, as emphasized by a later study that same year.[11] In addition, the heterogeneity of strains and their geographical distribution might play a role in disease burden, as previously pointed out.[12] Another meta-analysis replicated the association between schizophrenia and ET (OR = 2.74). Through the Egger test (p = 0.045), these authors also identified a greater trend toward publishing studies in this scope, and their results indicated a significant difference between cases and controls.[13]

Using a more rigorous method, the latest meta-analysis of these disorders,[14] including papers published until 2013, also found an association between ET and schizophrenia (adjusted OR [aOR] = 1.43) and included BD and addiction in the research. When adjusted for the previously outlined publication bias,[13] the study found no significant difference between studies that did and did not adjust for matched age as a confounding variable. Regarding BD, the authors found an overall association with no evidence for publication bias (OR = 1.52), which is consistent with previous studies, and no association was found between major depressive disorder (MDD) and ET.

Therefore, the objective of this review was to evaluate the association between ET and major psychiatric disorders through a systematic review, updating the literature and pointing out its major controversies. We also point out questions that should be answered by future research.

Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] A search was conducted for studies that reported ET frequency (defined by one of the following diagnostic methods: the Sabin-Feldman dye test, immunofluorescence, chemiluminescence, enzyme-linked immunosorbent assay, enzyme immunoassays, or immune hemagglutination) and a diagnosis of schizophrenia, MDD, or BD, according to criteria established by the DSM-IV, DSM-IV-TR or DSM-5, or the ICD-10 and determined through diagnostic structured interviews (the Structured Clinical Interview for the DSM [SCID], the Mini-International Neuropsychiatric Interview-Plus [MINI-PLUS], or the Composite International Diagnostic Interview [CIDI]).

The MEDLINE/PubMed, SciELO, and PsycINFO databases were searched. The basic research strategy was based on the terms: (toxoplasmic OR toxoplasmosis OR toxoplasma OR neurotoxoplasmosis OR t gondii OR toxopl*) AND ("major mental disorder" OR depression OR "affective disorder" OR "bipolar disorder" OR schizophrenia OR "mood disorder" OR schizophren* OR psychosis).

Additional studies were obtained from the references of the selected articles. The search was limited to articles in English, French, Italian, Portuguese, and Spanish published between 1994 (the year the DSM-IV was published) and October 27, 2019.

The eligibility criteria for the review were human studies evaluating the frequency of ET in adults ($\geqslant$ 18 years of age) of both genders with an established diagnosis of psychiatric disorder according to DSM-IV or later criteria. Clinical trials, cross-sectional studies, and retrospective and prospective studies were included if the frequency of ET in psychiatric patients was compared to healthy controls. Apart from the aforementioned criteria, we also excluded studies that did not control for coinfection of the central nervous system with other pathogens. Additional studies were sought in the references of all reviews on this topic.

To evaluate the quality of the studies included in the review, the Newcastle-Ottawa Scale (original version for cohorts and case-controls, and an adapted version for cross-sectional studies) was used.[16,17] The articles were classified into four quality levels: very good (9 points), good (7 to 8 points), satisfactory (5-6 points), and unsatisfactory ($<$ 5 points). Studies classified as unsatisfactory were excluded. Moreover, to assess potential differences in study quality between papers that corroborate vs. those that contradict the association hypothesis, we used the total Newcastle-Ottawa Scale scores from each paper and performed a two-sample Mann-Whitney *U* test for each diagnosis, where applicable. Full data are available in Table S1 (online-only supplementary material).

Considering the eligibility criteria, two authors (SMF and ARD) reviewed the titles and abstracts of the articles found and selected those suitable for full reading. Differences in the selection of articles were analyzed by a third author (AM-S) and resolved by consensus. We also searched the bibliographic references of the selected articles for studies not detected in the search.

Results

We analyzed the abstracts of 1,304 articles, with subsequent inclusion or exclusion was based on the previously mentioned criteria. Of these, 1,240 were excluded, the most common reasons being the outcome and an incompatible study design. We selected 64 articles for full reading and included 31 in the review, which were analyzed in greater detail. All of the selected articles were in English (Figure 1). According to the quality assessment, none of the studies were classified as unsatisfactory (Table 1). We found no quality difference between studies that corroborated or contradicted the association hypothesis. No papers found an association between MDD and ET, making the test unnecessary. A summary of the included studies is available as online-only supplementary material (Table S1).
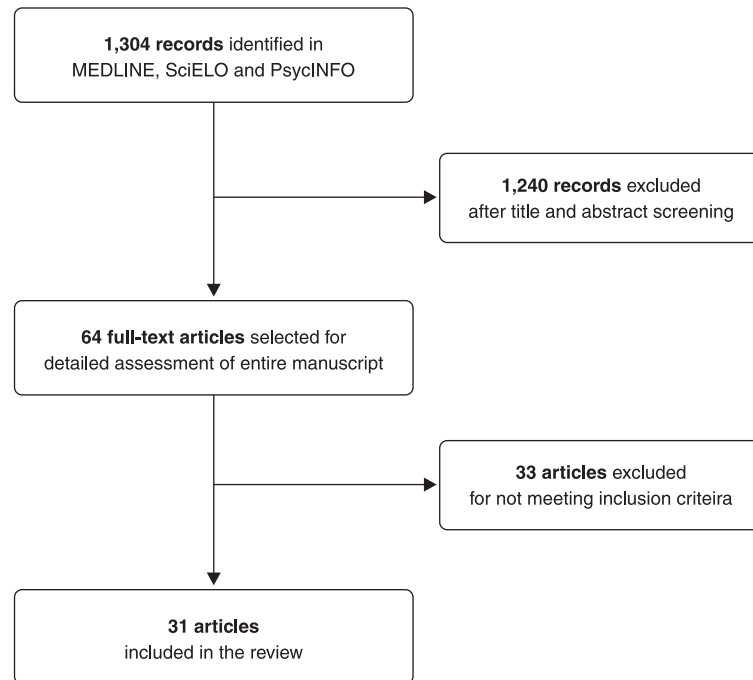
Figure 1 Flowchart of the study selection process.

Table 1 Total Newcastle-Ottawa Scale quality assessment scores for papers investigating the association between schizophrenia and exposure to toxoplasmosis

Corroborates	Total score*	Contradicts*	Total score
Alipour[18]	6	Campos-Carli[19]	7
Alvarado-Esquivel[20]	7	Emelia[21]	6
Ansari-Lari[22]	9	Hamdani[23]	8
Blomström[24]	9	Hinze-Selch[11]	7
Cetinkaya[25]	7	Horacek[26]	7
Chen[27]	8	Karabulut[28]	8
Dogruman-Al[29]	7	Khademvatan[30]	8
Esshili[31]	8	Khademvatan[32]	7
Hamidinejat[33]	6	Pearce[34]	7
Morais[35]	6	Yolken[36]	8
Mortensen[37]	9	-	-
Omar[38]	7	-	-
Tamer[39]	6	-	-
Yuksel[40]	7	-	-
Mean score ($\pm$ SD)	7.28 ($\pm$ 1.13)		7.3 ($\pm$ 0.67)

SD = standard deviation.
* Of a total possible score of 9.

Schizophrenia

Twenty-four of the included articles involved schizophrenia, 14 (58.3%) corroborating and 10 (41.6%) contradicting the association hypothesis. The quality of the studies ranged from satisfactory to very good (mean score = 7.29, standard deviation [SD] = 0.95; Table 2). We found no significant difference between the mean scores of papers that corroborated or contradicted the association hypothesis (p = 0.805).

Among the studies that corroborated the association hypothesis, one case-control study[37] assessed the serological status of 1,126 individuals (682 healthy controls, 186 patients with schizophrenia, and 258 patients diagnosed with affective disorders, including BD). After adjusting for place and year of birth, gender, and family history of psychiatric disorders, the seroprevalence in the schizophrenia group remained higher than that of healthy controls (OR = 1.79; p = 0.045). This study also found that a family history of psychiatric disorders was not a confounding variable.

Another case-control study[31] assessed the serological status of 246 patients with schizophrenia and 117 healthy controls. Patients diagnosed with schizoaffective or schizophreniform disorders were excluded, and both age and the type and dosage of psychotropic drugs used in treatment were controlled for. The seroprevalence was significantly higher in patient group (OR = 2.55; 95% confidence interval [95%CI] 1.59-4.09; p = 0.00001), as was the serum concentration of antibodies (71.3 $\pm$ 81 international unit

Table 2 Schizophrenia and exposure to toxoplasmosis: assessment of study quality using the Newcastle-Ottawa Scale

Reference	Selection	Comparability	Exposure/outcome	Total	Quality	Hypothesis of association
Alipour[18]	**	**	**	6	Satisfactory	Yes
Alvarado-Esquivel[20]	***	**	**	7	Good	Yes
Ansari-Lari[22]	****	**	***	9	Very good	Yes
Blomström[24]	****	**	***	9	Very good	Yes
Campos-Carli[19]	***	**	**	7	Good	No
Cetinkaya[25]	***	**	**	7	Good	Yes
Chen[27]	****	**	**	8	Good	Yes
Dogruman-Al[29]	****	*	**	7	Good	Yes
Emelia[21]	***	**	*	6	Satisfactory	No
Esshili[31]	****	**	**	8	Good	Yes
Hamdani[23]	****	**	**	8	Good	No
Hamidinejat[33]	**	**	**	6	Satisfactory	Yes
Hinze-Selch[11]	****	*	**	7	Good	No
Horacek[26]	***	**	**	7	Good	No
Karabulut[28]	****	**	**	8	Good	No
Khademvatan[30]	****	**	**	8	Good	No
Khademvatan[32]	***	**	**	7	Good	No
Morais[35]	***	*	**	6	Satisfactory	Yes
Mortensen[37]	****	**	***	9	Very good	Yes
Omar[38]	***	**	**	7	Good	Yes
Pearce[34]	***	**	**	7	Good	No
Tamer[39]	**	**	**	6	Satisfactory	Yes
Yolken[36]	****	**	**	8	Good	No
Yuksel[40]	***	**	**	7	Good	Yes

Higher quality studies are indicated by more stars in each category. The maximum scores in each category are: selection (4), comparability (2), outcome or exposure (3), for a maximum total score of 9.

[IU] [SD $\pm$ 5.19] vs. 52.3 $\pm$ 75 IU [SD = 6.9]; p = 0.03). The same study also pointed out that there was no correlation between serological profile and characteristics such as age, gender, disease duration, or schizophrenia subtype.

A further study assessed the serological status of several neurotropic pathogens (i.e., cytomegalovirus, herpes simplex viruses HSV-1 and HSV-2, and *T. gondii*) in 722 newborns, of whom 198 were diagnosed with schizophrenia later in life and 524 were healthy controls. After controlling for gestational age, place and date of birth, age, and the mother's country of origin, there was a higher seroprevalence of both *T. gondii* and cytomegalovirus in the patient group (OR = 2,1; 95%CI 1,04,5 and OR = 2.2; 95%CI 1.0-5.1, respectively).[24] Moreover, an anti-*T. gondii* antibody level above the 90th percentile is associated with a three-fold higher risk of schizophrenia compared to levels within the reference range (OR = 3.2; 95%CI 1.0-9.8).

Likewise, a case-control study comparing the serological status of 343 patients with schizophrenia, 115 with BD, 61 with MDD, and 681 healthy controls found a higher seroprevalence in the first two groups (OR = 1.921; 95%CI 1.301-2.817; p = 0.001 and OR = 2.281; 95%CI 1.341-3.8; p = 0.003, respectively). Controlling for age and gender, the study and also found a lack of association between ET and MDD, replicating the results of previous studies.[27]

On the other hand, no significant difference in serological status was found in a sample of 277 patients with schizophrenia, 456 with MDD, and 214 healthy controls, when acute or chronic infectious diseases, inflammatory processes, place of origin, and the psychotropic drug use were controlled for.[11] What the study did find was a higher intensity, rather than prevalence, in the

patient groups, notably the schizophrenia group. Moreover, the use of antipsychotics was related to lower antibody titers. This was the first study to emphasize the importance of controlling for age, since it is a major confounder for the seroprevalence of anti-*T. gondii* immunoglobulin G (IgG) antibodies.

Only two studies investigated Brazilian samples. One of them, a cross-sectional study that assessed the serological status of 48 patients with schizophrenia and 40 healthy controls, found similar seroprevalence and titers for both IgG and immunoglobulin M anti-*T. gondii* antibodies in both groups.[19] Another study, on the other hand, compared 34 patients with schizophrenia and 85 healthy controls, finding a seropositivity prevalence of 91.18% (95%CI 77.04-96.95) among the patients, compared to 70.59% (95%CI 60.18-79.21) among controls. The difference was considered significant (p = 0.017).[35] These results, while mostly reinforcing the association hypothesis, are relevant regarding possible biases and confounders in some studies.

Major depressive disorder

Four studies included in this review involved MDD. All of them contradicted the hypothesis that ET and MDD are associated, consistent with previous literature (Table 3). The quality of the studies ranged from good to very good (mean score = 7.5, SD = 0.57).[11,25,27,36] Despite the higher overall serum antibody levels in the patient group (465 individuals with MDD), a case-control study found no significant difference with healthy controls (214 individuals). It should be pointed out that first-episode patients were significantly more likely to have high antibody titers, and not all groups in this study were age matched.[11] In another case-control study with 61 depressive patients,

six (9.8%) were seropositive for *T. gondii* compared to 64 out of 681 (9.4%) controls (OR = 1.052; 95%CI 0.466-2.45; p = 0.810).[27] A case-control study compared 571 healthy controls to 64 patients with MDD, finding no association with ET (6.1 vs. 7.8%, further data not found).[36] In a fourth study, 12 of the 50 (24%) patients with MDD were seropositive for IgG titers vs. 11 of the 50 healthy controls(22%). Again, no association was found, consistent with previous literature on the subject.[25]

Bipolar disorder

Eleven papers included in this review involved BD. Of these, six (54.5%) corroborated the association hypothesis and five (45.4%) contradicted it. The quality of the studies ranged from satisfactory to very good (mean score = 7.45, SD = 0.82; Table 4). We did not find a significant difference in mean quality scores between papers that corroborated or contradicted the association hypothesis (p = 0.279; Table 5). When adjusting for covariates such as age and coinfection, the seroprevalence in the BD group was significantly higher the healthy control group.[23]

This finding has been replicated by several authors, and an association between BD and *T. gondii* seroprevalence (OR = 1.77; 95%CI 1.01-3.10; p = 0,045) was found after excluding patients coinfected with other neurotropic pathogens and a family history of psychiatric disorders.[46] On the other hand, another case-control study found no association between serological markers of prenatal infection and risk of BD.[45]

Overall, the literature is still dubious as to the association between ET and BD. While several studies have corroborated the hypothesis, others have consistently contradicted it based on relevant samples.[37,42,45] Nevertheless, it should be noted that both of the above described studies were based on neonatal blood samples, meaning that the antibodies probably originated from the mother, rather than the newborn's exposure to the parasite.

Table 3 Major depressive disorder and exposure to toxoplasmosis: assessment of study quality using the Newcastle-Ottawa Scale

Reference	Selection	Comparability	Exposure/outcome	Total	Quality
Cetinkaya[24]	***	**	**	7	Good
Chen[21]	****	**	**	8	Good
Hinze-Selch[11]	****	*	**	7	Good
Yolken[25]	****	**	**	8	Good

Higher quality studies are indicated by more stars in each category. The maximum scores in each category are: selection (4), comparability (2), outcome or exposure (3), for a maximum total score of 9.
Hypothesis of association: all studies contradicted it.

Table 4 Bipolar disorder and exposure to toxoplasmosis: assessment of study quality using the Newcastle-Ottawa Scale

Reference	Selection	Comparability	Exposure/outcome	Total	Quality	Hypothesis of association
Afifi[41]	***	**	**	7	Good	Yes
Chen[27]	****	**	**	8	Good	Yes
Frye[42]	****	**	**	8	Good	No
Hamdani[23]	****	**	**	8	Good	Yes
Hamdani[43]	***	*	**	6	Satisfactory	Yes
Hamdani[44]	***	**	**	7	Good	Yes
Mortensen[37]	****	**	***	9	Very Good	No
Mortensen[45]	***	**	**	7	Good	No
Oliveira[46]	***	**	**	7	Good	Yes
Pearce[47]	***	**	**	7	Good	No
Yolken[36]	****	**	**	8	Good	No

Higher quality studies are indicated by more stars in each category. The maximum scores in each category are: selection (4), comparability (2), outcome or exposure (3), for a maximum total score of 9.

Table 5 Total scores using the Newcastle-Ottawa Scale for study quality assessment: Papers that assessed the hypothesis of association between bipolar disorder and exposure to toxoplasmosis

Corroborates	Total score*	Contradicts	Total score*
Afifi[41]	7	Frye[42]	8
Chen[27]	8	Mortensen[37]	9
Hamdani[23]	8	Mortensen[45]	7
Hamdani[43]	6	Pearce[47]	7
Hamdani[44]	7	Yolken[36]	8
Oliveira[46]	7	-	-
Mean score (± SD)	7.16 (± 0.75)		7.8 (± 0.83)

* Of a total possible score of 9.

Discussion

This review describes the main results of studies that evaluated the association between ET and major psychiatric disorders (schizophrenia, BD and MDD), using the criteria and diagnostic interviews summarized in the DSM-IV and later manuals. While there is consensus regarding the lack of association between ET and MDD,[48] there are conflicting findings regarding its association with schizophrenia and BD, since we observed heterogeneity of results. A plausible explanation is the above-mentioned strain hypothesis,[12,14,32] since different regional strains of T. gondii affect different populations and could mediate different neuropsychiatric effects. Furthermore, the virulence and strain-specific effects of the three types of T. gondii, including an increased risk of psychosis in the offspring of pregnant women exposed to the type I parasite, have been previously described.[49]

It has also been pointed out that the patient's disease and treatment phase may play a role in serum antibody levels.[36] Another study reported higher antibody levels in both serum and cerebrospinal fluid in patients subsequent to a first episode of schizophrenia who had not used antipsychotics. Conversely, they found lower antibody levels in patients subsequent to a first episode of schizophrenia who had been treated with antipsychotics than other patients in the same state, both those who had never used antipsychotics and those who formerly, but not currently, used them.[50]

Furthermore, a population-based study[51] indicated that constant exposure to the parasite is necessary to maintain serum immunoglobulin levels specific to it. Moreover, carbamazepine, valproic acid, haloperidol, and risperidone exhibit inhibitory activity against T. gondii replication in vitro, which indicates that patient treatment status should be assessed and adjusted as a bias in forthcoming studies.[6]

Based on these findings, it is possible that the increased seroprevalence found in patients with recent onset psychosis or first episode of schizophrenia falls considerably in patients with chronic schizophrenia or BD, depending on pharmacological treatment and the lack of new exposure to the parasite. In fact, in these studies the majority of patients were being treated with psychotropics such as carbamazepine, lithium, and olanzapine and were in the chronic stage of their respective disorders.[11,19,21,26]

In addition, a recently published French cohort study[52] showed that treatments with anti-toxoplasmic activity were associated with a lower volume of depressive symptoms (aOR = 0.8 [95%CI 0.7-0.9]; p = 0.01), as well as with lower rates of chronic peripheral inflammation (20.9 vs. 48.6%; aOR = 3.5 [95%CI 1.5-7.9]; p = 0.003). This is consistent with the findings of a cross-sectional study on the same drugs.[53] The French cohort study consecutively selected 250 patients with schizophrenia, finding that their seroprevalence of T. gondii was approximately three times higher than that of the general population. Among the seropositive patients, higher scores were found in the negative PANSS subscales (OR = 1.1 [95%CI 1.1-1.1]; p = 0.04) and for excitation (OR = 1.3 [95%CI 1.1-1.6]; p = 0.01), as well as for extrapyramidal symptoms. This was not included

in our review because it did not fit the eligibility criteria (i.e., it did not compare cases and healthy controls).

Despite contradicting the association hypothesis, a cross-sectional study that controlled for sociodemographic variables such as age, gender and place of residence, showed that seropositivity to anti-T. gondii antibodies remained a good predictor of clinically relevant psychotic symptoms (p = 0.001), including hallucinations (incidence rate ratio [IRR] = 1.80; 95%CI 1.14-2.83; p = 0.011) and delusional symptoms (IRR = 1.48; 95%CI 1.13-1.93; p = 0.004). In a logistic regression model, serum antibody levels were also verified as a predictor of clinically relevant psychotic symptoms when the variables "age," "gender," "education level," "residence region," and "cat ownership" were controlled for (OR = 1.35; 95%CI 1.15-1.59; p = 0.001).[54]

Serum antibody levels was also reported to be higher in patients with schizophrenia than healthy controls, and the acoustic startle response was slower in seropositive than seronegative individuals. These data are consistent with the psychomotor retardation observed in individuals seropositive for T. gondii who have not been diagnosed with a psychiatric disorder.[34]

Together, these findings suggest that the literature's ambiguity about the association between ET and schizophrenia is related to methodological flaws and indicates that the statistical analysis in future research should include variables such as disease stage and time since onset, treatment type, patient origin, and seroprevalence at the study site, as well as the participants' age and gender.

In BD the disease phase might play an even greater role in this association. Several studies indicated that chronic T. gondii infection of the central nervous system is associated with increased dopamine levels through previously mentioned mechanisms.[8,55,56] Traditionally, manic or psychotic states have been associated with dopaminergic hyperactivity. Moreover, psychostimulants that increase extracellular levels of dopamine influence behavior in a manner compatible with mania.[57] Thus, in addition to drug use, it would be important for research in this field to provide more information about the patients' mood at the time of data collection, as well as the type and polarity of BD. It is possible that the heterogeneity of the results is due to these factors. None of the studies assessing this association took the above-mentioned variables into account in their statistical analyses.

Concerning the temporal aspects of the infection, a recent case-control study found that the association between ET and schizophrenia (OR = 1.47; 95%CI 1.03-2.09) was even stronger when pathogen exposure preceded the outcome (IRR = 2.78; 95%CI 1.27-6.09).[58] Despite the methodological rigor, this study included patients diagnosed with ICD-8 criteria and, thus, was excluded from the present review.

A major limitation of our review is the use of serological status as a diagnostic tool of latent toxoplasmosis, since it is an indirect measure of T. gondii activity in the organism and does not necessarily indicate the presence of cysts in the central nervous system. Also, as previously discussed, some of the included studies were based on

blood samples from newborns, meaning that the observed antibodies were most likely maternal. Nevertheless, the National Reference Center for Toxoplasmosis highlights the presence of anti-*T. gondii* IgG antibodies as indicative of the chronic presence of the parasite in the body. It also shows that serological studies are the most commonly used tool to identify *T. gondii* infection.[59] Furthermore, the same study indicates that serum levels of IgG antibodies tend to progressively decrease approximately 1 year after primary infection, due to latent cysts in certain areas of the body, such as the muscles, eyes, and brain. This information is in line with previously mentioned studies.[51,60] The body of evidence indicates that, although not the ideal method for detecting *T. gondii* cystic activity in the central nervous system, serological studies are the best diagnostic tool available today.

Moreover, coinfection by cytomegalovirus indicates that there may be a non-specific inflammatory component which acts as a confounding variable in cases where there is an association between ET and major psychiatric disorders.[24] Further research on the topic should also assess inflammatory and serological markers for other known neurotropic infectious agents.

The inclusion of such variables in future studies will help explain the relationship between *T. gondii* and major psychiatric disorders, providing the scientific community with information that can definitively identify both the correlation and a possible causal relationship.

In conclusion, this systematic review has outlined the controversy in the literature about the association between ET and major psychiatric disorders. Although absent in patients with MDD, the majority of the included studies did find an association with schizophrenia and BD. The heterogeneity of the results demonstrates the need for greater attention to detail in future studies, including better-defined samples and refined methods. While updating the state of art on research about the association between ET and major psychiatric disorders, we suggest the inclusion of new variables in future studies: treatment status and serum antibody levels of *T. gondii*; the seroprevalence of other neurotropic pathogens (e.g., human immunodeficiency virus 1 and 2, cytomegalovirus, HSV 1 and 2, and hepatitis A, B, and C); a detailed description of the sample regarding subtypes and different disease phases; and the neutralization of other confounders, such as age, gender, patients origin, and *T. gondii* strain.

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Disclosure

References

1 Neves DP. Parasitologia humana. 11th ed. São Paulo: Atheneu; 2004.

2 Torrey EF, Bartko JJ, Lun ZR, Yolken RH. Antibodies to toxoplasma gondii in patients with schizophrenia: a meta-analysis. Schizophr Bull. 2007;33:729-36.

3 Flegr J, Zitková Š, Kodym P, Frynta D. Induction of changes in human behaviour by the parasitic protozoan toxoplasma gondii. Parasitology. 1996;113:49-54.

4 Webster JP, Lamberton PH, Donnelly CA, Torrey EF. Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood-stabilizer and anti-parasite medication on toxoplasma gondii's ability to alter host behaviour. Proc Biol Sci. 2006;273:1023-30.

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

6 Jones-Brando L, Torrey EF, Yolken R. Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of toxoplasma gondii. Schizophr Res. 2003;62:237-44.

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

8 Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, McConkey GA. The neurotropic parasite toxoplasma gondii increases dopamine metabolism. PLoS One. 2011;6:e23866.

9 Salvadore G, Quiroz JA, Machado-Vieira R, Henter ID, Manji HK, Zarate CA Jr. The neurobiology of the switch process in bipolar disorder: a review. J Clin Psychiatry. 2010;71:1488-501.

10 Berk M, Dodd S, Kauer-Sant'anna M, Malhi GS, Bourin M, Kapczinski F, et al. Dopamine dysregulation syndrome: implications for a dopamine hypothesis of bipolar disorder. Acta Psychiatr Scand Suppl. 2007;(434): 41-9.

11 Hinze-Selch D, Däubener W, Eggert L, Erdag S, Stoltenberg R, Wilms S. A controlled prospective study of toxoplasma gondii infection in individuals with schizophrenia: beyond seroprevalence. Schizophr Bull. 2007;33:782-8.

12 Xiao J, Yolken RH. Strain hypothesis of toxoplasma gondii infection on the outcome of human diseases. Acta Physiol (Oxf). 2015;213: 828-45.

13 Arias I, Sorlozano A, Villegas E, Luna JD, McKenney K, Cervilla J, et alInfectious agents associated with schizophrenia: a meta-analysis. Schizophr Res. 2011;136:128-36.

14 Sutterland AL, Fond G, Kuin A, Koeter MW, Lutter R, van Gool T, et al. Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. Acta Psychiatr Scand. 2015;132:161-79.

15 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.

16 Ottawa Hospital Research Institute. Our research [Internet]. [cited 2020 Aug 2]. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

17 Herzog R, Álvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health. 2013;13:154.

18 Alipour A, Shojaee S, Mohebali M, Tehranidoost M, Abdi Masoleh F, Keshavarz H. Toxoplasma infection in schizophrenia patients: a comparative study with control group. Iran J Parasitol. 2011;6: 31-7.

19 Campos-Carli SM de, Vieira ÉLM, Rocha NP, de Oliveira K, Guimarães FC, Barbosa IG, et al. Toxoplasma gondii infection and chronic schizophrenia: is there any association? Arch Clin Psychiatry. 2017;44:145-8.

20 Alvarado-Esquivel C, Urbina-Álvarez JD, Estrada-Martínez S, Torres-Castorena A, Molotla-de-León G, Liesenfeld O, et al. Toxoplasma gondii infection and schizophrenia: a case control study in a low toxoplasma seroprevalence Mexican population. Parasitol Int. 2011;60:151-5.

21 Emelia O, Amal RN, Ruzanna ZZ, Shahida H, Azzubair Z, Tan KS, et al. Seroprevalence of anti-toxoplasma gondii IgG antibody in patients with schizophrenia. Trop Biomed. 2012;29:151-9.

22 Ansari-Lari M, Farashbandi H, Mohammadi F. Association of toxoplasma gondii infection with schizophrenia and its relationship with suicide attempts in these patients. Trop Med Int Health. 2017;22: 1322-7.

23 Hamdani N, Bengoufa D, Godin O, Doukhan R, Le Guen E, Daban-Huard C, et al. Immunoglobulin sub-class distribution in bipolar disorder and schizophrenia: potential relationship with latent toxoplasma gondii infection. BMC Psychiatry. 2018;18:239.

24 Blomström Å, Karlsson H, Wicks S, Yang S, Yolken RH, Dalman C. Maternal antibodies to infectious agents and risk for non-affective psychoses in the offspring-a matched case-control study. Schizophr Res. 2012;140:25-30.

25 Cetinkaya Z, Yazar S, Gecici O, Namli MN. Anti-Toxoplasma gondii antibodies in patients with schizophrenia - preliminary findings in a Turkish sample. Schizophr Bull. 2007;33:789-91.

26 Horacek J, Flegr J, Tintera J, Verebova K, Spaniel F, Novak T, et al. Latent toxoplasmosis reduces gray matter density in schizophrenia but not in controls: voxel-based-morphometry (VBM) study. World J Biol Psychiatry. 2012;13:501-9.

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

28 Karabulut N, Bilgiç S, Gürok MG, Karaboğa F. Is there any role of latent toxoplasmosis in schizophrenia disease? J Chin Med Assoc. 2015;78:533-7.

29 Dogruman-Al F, Aslan S, Yalcin S, Kustimur S, Turk S. A possible relationship between toxoplasma gondii and schizophrenia: a seroprevalence study. Int J Psychiatry Clin Pract. 2009;13:82-7.

30 Khademvatan S, Khajeddin N, Izadi S, Yousefi E. Investigation of anti- toxocara and anti- toxoplasma antibodies in patients with schizophrenia disorder. Schizophr Res Treatment. 2014;2014:230349.

31 Esshili A, Thabet S, Jemli A, Trifa F, Mechri A, Zaafrane F, et al. Toxoplasma gondii infection in schizophrenia and associated clinical features. Psychiatry Res. 2016;245:327-32.

32 Khademvatan S, Saki J, Khajeddin N, Izadi-Mazidi M, Beladi R, Shafiee B, et al. Toxoplasma gondii exposure and the risk of schizophrenia. Jundishapur J Microbiol. 2014;7:e12776.

33 Hamidinejat H, Ghorbanpoor M, Hosseini H, Alavi SM, Nabavi L, Jalali MH, et al. Toxoplasma gondii infection in first-episode and inpatient individuals with schizophrenia. Int J Infect Dis. 2010;14:e978-81.

34 Pearce BD, Hubbard S, Rivera HN, Wilkins PP, Fisch MC, Hopkins MH, et al. Toxoplasma gondii exposure affects neural processing speed as measured by acoustic startle latency in schizophrenia and controls. Schizophr Res. 2013;150:258-61.

35 Morais FB, Arantes TE, Muccioli C. Seroprevalence and manifestations of ocular toxoplasmosis in patients with schizophrenia. Ocul Immunol Inflamm. 2019;27:134-7.

36 Yolken R, Torrey EF, Dickerson F. Evidence of increased exposure to toxoplasma gondii in individuals with recent onset psychosis but not with established schizophrenia. PLoS Negl Trop Dis. 2017;11:e0006040.

37 Mortensen PB, Nørgaard-Pedersen B, Waltoft BL, Sørensen TL, Hougaard D, Torrey EF, et al. Toxoplasma gondii as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth. Biol Psychiatry. 2007;61:688-93.

38 Omar A, Bakar OC, Adam NF, Osman H, Osman A, Suleiman AH, et al. Seropositivity and serointensity of toxoplasma gondii antibodies and DNA among patients with schizophrenia. Korean J Parasitol. 2015;53:29-34.

39 Tamer GS, Dundar D, Yalug I, Caliskan S, Yazar S, Aker A. The schizophrenia and toxoplasma gondii connection: Infectious, immune or both? Adv Ther. 2008;25:703-9.

40 Yuksel P, Alpay N, Babur C, Bayar R, Saribas S, Karakose AR, et al. The role of latent toxoplasmosis in the aetiopathogenesis of schizophrenia - the risk factor or an indication of a contact with cat? Folia Parasitol (Praha). 2010;57:121-8.

41 Afifi M, Jiman-Fatani AA, Al-Rabia MW, Al-Hussainy NH, El Saadany SE, Mayah W. More than an association: latent toxoplasmosis might provoke a local oxidative stress that triggers the development of bipolar disorder. J Microsc Ultrastruct. 2018;6:139-44.

42 Frye MA, Coombes BJ, McElroy SL, Jones-Brando L, Bond DJ, Veldic M, et al. Association of cytomegalovirus and toxoplasma gondii antibody titers with bipolar disorder. JAMA Psychiatry. 2019;76:1285-93.

43 Hamdani N, Daban-Huard C, Lajnef M, Richard JR, Delavest M, Godin O, et al. Relationship between Toxoplasma gondii infection and bipolar disorder in a French sample. J Affect Disord. 2013;148:444-8.

44 Hamdani N, Daban-Huard C, Lajnef M, Gadel R, Le Corvoisier P, Delavest M, et al. Cognitive deterioration among bipolar disorder patients infected by toxoplasma gondii is correlated to interleukin 6 levels. J Affect Disord. 2015;179:161-6.

45 Mortensen PB, Pedersen CB, Mcgrath JJ, Hougaard DM, Nørgaard-Petersen B, Mors O, et al. Neonatal antibodies to infectious agents and risk of bipolar disorder: a population-based case-control study. Bipolar Disord. 2011;13:624-9.

46 Oliveira J, Kazma R, Le Floch E, Bennabi M, Hamdani N, Bengoufa D, et al. Toxoplasma gondii exposure may modulate the influence of TLR2 genetic variation on bipolar disorder: a gene-environment interaction study. Int J Bipolar Disord. 2016;4:11.

47 Alvarado-Esquivel C, Estrada-Martínez S, Pérez-Alamos AR. A case-control seroprevalence study on the association between toxoplasma gondii infection and bipolar disorder. Front Psychiatry. 2019;10:766.

48 Nayeri Chegeni T, Sharif M, Sarvi S, Moosazadeh M, Montazeri M, Aghayan SA, et al. Is there any association between toxoplasma gondii infection and depression? A systematic review and meta-analysis. PLoS One. 2019;14:e0218524.

49 Xiao J, Buka SL, Cannon TD, Suzuki Y, Viscidi RP, Torrey EF, et al. Serological pattern consistent with infection with type I toxoplasma gondii in mothers and risk of psychosis among adult offspring. Microbes Infect. 2009;11:1011-8.

50 Leweke FM, Gerth CW, Koethe D, Klosterkötter J, Ruslanova I, Krivogorsky B, et al. Antibodies to infectious agents in individuals with recent onset schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2004;254:4-8.

51 Rougier S, Montoya JG, Peyron F. Lifelong persistence of toxoplasma cysts: A questionable dogma? Trends Parasitol. 2017;33:93-101.

52 Fond G, Boyer L, Schürhoff F, Berna F, Godin O, Bulzacka E, et al. Latent toxoplasma infection in real-world schizophrenia: results from the national FACE-SZ cohort. Schizophr Res. 2018;201:373-80.

53 Fond G, Boyer L, Gaman A, Laouamri H, Attiba D, Richard JR, et al. Treatment with anti-toxoplasmic activity (TATA) for toxoplasma positive patients with bipolar disorders or schizophrenia: a cross-sectional study. J Psychiatr Res. 2015;63:58-64.

54 Lindgren M, Torniainen-Holm M, Härkänen T, Dickerson F, Yolken RH, Suvisaari J. The association between toxoplasma and the psychosis continuum in a general population setting. Schizophr Res. 2018;193:329-35.

55 Martin HL, Alsaady I, Howell G, Prandovszky E, Peers C, Robinson P, et al. Effect of parasitic infection on dopamine biosynthesis in dopaminergic cells. Neuroscience. 2015;306:50-62.

56 Gaskell EA, Smith JE, Pinney JW, Westhead DR, McConkey GA. A unique dual activity amino acid hydroxylase in toxoplasma gondii. PLoS One. 2009;4:e4801.

57 Park SY, Kang UG. Hypothetical dopamine dynamics in mania and psychosis -- its pharmacokinetic implications. Prog Neuropsychopharmacology Biol Psychiatry. 2013;43:89-95.

58 Burgdorf KS, Trabjerg BB, Pedersen MG, Nissen J, Banasik K, Pedersen OB, et al. Large-scale study of toxoplasma and cytomegalovirus shows an association between infection and serious psychiatric disorders. Brain Behav Immun. 2019;79:152-8.

59 Villard O, Cimon B, L'Ollivier C, Fricker-Hidalgo H, Godineau N, Houze S, et al. Serological diagnosis of toxoplasma gondii infection: recommendations from the French national reference center for toxoplasmosis. Diagn Microbiol Infect Dis. 2016;84:22-33.

60 Konishi E. Annual change in immunoglobulin G and M antibody levels to toxoplasma gondii in human sera. Microbiol Immunol. 1989;33:403-11.